

TAG
Treatment Action Group

PIPELINE REPORT 2017: HIV·TB·HCV

DRUGS, DIAGNOSTICS, VACCINES, PREVENTIVE TECHNOLOGIES, CURE RESEARCH,
AND IMMUNE-BASED AND GENE THERAPIES IN DEVELOPMENT



2017 Pipeline Report

HIV, TB & HCV

DRUGS, DIAGNOSTICS, VACCINES, PREVENTIVE
TECHNOLOGIES, CURE RESEARCH, AND IMMUNE-BASED
AND GENE THERAPIES IN DEVELOPMENT

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JULY 2017
TREATMENT ACTION GROUP

ABOUT TAG

Treatment Action Group (TAG) is an independent, activist and community-based research and policy think tank fighting for better treatment, prevention, a vaccine, and a cure for HIV, tuberculosis, and hepatitis C virus.

TAG works to ensure that all people with HIV, TB, or HCV receive lifesaving treatment, care, and information.

We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions.

TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end HIV, TB, and HCV.

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ISBN 978-0-9983966-3-7

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In Memoriam

Mark Arnold Wainberg

Activist, researcher, global AIDS treatment access pioneer

21 April 1945 - 11 April 2017

Phillips Gay, Jr.

The 2017 Pipeline Report is dedicated to Phillips Gay, Jr., beloved father of HCV Project Director, Bryn Gay. Phil was an enthusiastic supporter of TAG's work, particularly its advocacy for affordable, life-saving medications for the most vulnerable groups. He was a committed activist to disability rights, mental health, and affordable housing causes. He lived his life with unmatched integrity, a wry sense of humor and endless patience. He will be deeply missed by his wife of 44 years, three children, two grandchildren, and immense professional network in the bank compliance and anti-money laundering field.

8 October 1949 - 2 May 2017

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2017 Pipeline Report Introduction, Executive Summary and Recommendations

INTRODUCTION

This year marks the 30th year since the U.S. Food and Drug Administration (FDA) granted a license for Burroughs-Wellcome to market AZT (zidovudine, Retrovir), the first approved drug to treat HIV infection, at the then-unprecedented price of \$10,000 per year. The hope instigated by this apparent medical progress mixed with anger at its high price and the growing epidemic to catalyze the foundation, in the same year, of the AIDS Coalition to Unleash Power, or ACT UP/New York.

The hopes that AZT's approval generated were quickly replaced by disappointment that the drug had only modest short-term activity in delaying the progression of advanced HIV, combined with its prohibitive cost, an unnecessarily high dose, and extensive toxicity. Moreover, it wasn't known whether it would benefit most people with HIV if treatment started earlier.

The following decade was one punctuated by momentary bursts of optimism as each new AZT-like drug made its way through the pipeline, followed by recurrent disappointment as they all displayed the same short-term activity, combined with different degrees of toxicity. By 1995, it was clear that the AZT-like drugs alone, even when two were given together, did not substantially slow progression of HIV to AIDS and death. The results of early combination therapy trials, which were poorly designed and usually studied in individuals that were already resistant or intolerant to AZT, even led to a kind of despair, or at least a therapeutic nihilism, as the AIDS diagnosis and death rates climbed to unprecedented highs in the United States (deaths peaking around 50,000/year in 1994–1995) and other developed countries, whereas there was hardly any access to treatment at all in the developing world, where the great majority of HIV infections were occurring.

1996 saw an unexpected turnaround with the sudden advent of combination triple therapy (two AZT-like drugs combined with a potent protease inhibitor or non-nucleoside reverse transcriptase inhibitor, NNRTI). Given to treatment-naive individuals, these regimens were able to drive HIV levels in the blood, as measured by new quantitative viral load assays, to undetectable levels, which in turn prompted—in most individuals—a rebound of the immune system and, in some cases, a reversal of AIDS-related infections and other conditions. The new combination therapies and viral load testing were quickly approved and disseminated in rich countries, leading to a two-thirds or greater drop in AIDS deaths. It remained unknown, however, whether the treatment, if started earlier, could lead to better outcomes, and globally, effective HIV treatment still remained out of reach. Moreover, the combinations were often complicated, requiring multiple and complex administration of many pills, and came with significant side effects.

The 2000 Durban International AIDS conference—to whose chair, Dr. Mark Wainberg of McGill University, this Pipeline Report is dedicated—marked a turning point in the global pandemic, and the beginning of efforts to scale-up HIV treatment in developing nations. At the same time, continuing research investment led to safer, easier to tolerate, often once-daily treatment regimens. Research on when to start antiretroviral treatment was reinvigorated following the results of the Strategic Management of Antiretroviral Treatment (SMART) study, which showed that interrupting HIV treatment, as compared with ongoing virologic suppression, caused an excess not only of AIDS-related illnesses and mortality, but also of end-organ liver, kidney, and cardiovascular disease—endpoints that had previously been thought to be associated with antiretroviral treatment (ART) itself. Meanwhile, in 2011, the HIV Prevention Trials Network (HPTN) study 052 showed that treatment, when started earlier in the HIV-positive member of a serodiscordant couple, reduced onward transmission to HIV-negative sexual partners by 96%.

These advances led National Institute of Allergy and Infectious Diseases (NIAID) Director Anthony S. Fauci to write, in 2011, that “The fact that treatment of HIV-infected adults is also prevention gives us the wherewithal, even in the absence of an effective vaccine, to begin to control and ultimately end the AIDS pandemic.”¹

SMART and HPTN were followed by the Strategic Timing of Antiretroviral Treatment (START) and TEMPRANO studies, both of which were stopped early when their results showed that immediate initiation of ART reduced progression to symptomatic disease.

A series of studies found that tenofovir disoproxil fumarate (TDF) with or without emtricitabine (FTC) used as pre-exposure prophylaxis (PrEP) could prevent HIV infections among gay men and heterosexual men and women.

Thus, by 2016, the world faced a new paradigm in which all people living with HIV were indicated for immediate initiation of ART following diagnosis, while PrEP with TDF or TDF/FTC (marketed in the US as Truvada) could be used to prevent infection among high-risk individuals.

Programs to treat HIV that began in 2001 were now reaching up to 18.5 million of the world’s estimated 37 million HIV-infected individuals, whereas new infections, according to UNAIDS and the World Health Organization (WHO), had dropped by about a third from their peak of three million per year around 2000.

The scientific progress against HIV has been virtually unprecedented in the history of medicine and public health, and has been based on a unique combination of scientific investment, partnership with affected communities and individuals, strong political will, and extensive community mobilization.

Activists in the United States created the campaigns that led to parallel track in 1989 and to the accelerated approvals of antiretroviral (ARV) drugs in the early and mid-1990s that led to the advent of highly active ART in 1996.

Activists around the world led the movement for global treatment access that instigated the foundation of the Global Fund to Fight AIDS, Tuberculosis and Malaria and the President’s Emergency Plan for AIDS Relief (PEPFAR)—and activists from Brazil to South Africa to Thailand and elsewhere led efforts to persuade or force their national governments to provide free HIV treatment in the public sector.

The tremendous gains of the past three decades, however, and our ability to ensure that all those who can benefit from them receive the prevention, treatment, support, information, and care that they need to live long and healthy lives, however, have been under threat for the past decade by the retrenchment and austerity imposed by Western governments on their own people and the flatlining rates of investment in research and global HIV and tuberculosis (TB) prevention and treatment programs.

The story of tuberculosis over those same 30 years is a much more sobering one, although there has been some recent progress. TB has long been one of the leading killer infectious diseases from ancient history well into the early twentieth century, when advances in sanitation, ventilation, and housing led to substantial declines in new TB cases, although TB infection remained prevalent in about one-third of the human population.

The discovery of effective combination chemotherapy for TB in the 1940s and the 1950s led to the ability to cure TB disease, prevent TB infection, and reduce TB rates everywhere the treatments were made available.

Research on TB, however, tailed off in the late 1970s and the early 1980s. At the same time, the spread of HIV—which activates TB and accelerates the transition from infection to disease—reignited new waves of TB everywhere it spread. TB rates rose again in New York in the late 1980s, in the countries of the former Soviet Union in the 1990s, and in sub-Saharan Africa, where HIV was rising exponentially and where TB had never been properly controlled in the first place.

The last decades of the 20th century saw virtually no investment in tuberculosis research and development (R&D). It wasn't until the directly observed therapy, short-course (DOTS) approach promulgated by the WHO in 1993 after the NYC outbreak of multi-drug-resistant (MDR)-TB in the late 80s proved inadequate to control, let alone eliminate, TB that governments and philanthropists realized that investing in new diagnostic tests, drug regimens, and preventive therapies and vaccines would be critical to ultimately eliminate TB.

Yes, since the disease so overwhelmingly affected people in middle-income and poor countries, there was virtually no pharmaceutical company interest in TB R&D. Funders such as the U.S. Public Health Service (PHS), led by the Centers for Disease Control and Prevention (CDC), maintained a small portfolio of TB treatment studies in the 1990s and early 2000s. These efforts were augmented starting in 2001 by greater investments from the U.S. National Institutes of Health (NIH), through philanthropic support by the Bill and Melinda Gates Foundation (BMGF), and international development agencies such as USAID and the U.K. Department for International Development (DFID). These investments in turn led to the establishment of dedicated product-development partnerships such as Aeras and the TB Vaccine Initiative, the Foundation for Innovative New Diagnostics (FIND), and the Global Alliance for TB Drug Development.

A few companies, such as Tibotec/Janssen and Otsuka, discovered new anti-TB drugs that were studied in combination with older drugs to treat drug-resistant forms of the disease. U.S. biodefense investments led to new molecular diagnostic test platforms such as GeneXpert MTB/RIF, which can detect TB DNA in sputum samples within two hours, and can also detect resistance to one of the most common anti-TB drugs, rifampin. GeneXpert was endorsed by the WHO and recommended for global use in 2010, whereas Janssen's bedaquiline was granted accelerated approval by the FDA in 2012 and Otsuka's delamanid by the European Medicines Agency (EMA) in 2014.

But scale-up of existing preventive and treatment approaches for TB lagged considerably behind the great progress made against HIV in the first 15 years of the 21st century. By 2015, tuberculosis, which had been curable since 1950, once again overtook HIV to become the world's leading infectious killer. Investments in TB R&D were just about 1/20 the size of those against HIV, and stalled around \$650 million per year—well behind the annual \$2 billion recommended by the *Global Plan to Stop TB*. Uptake of GeneXpert was slow—half of all tests were conducted in South Africa alone—whereas anemic WHO guidance on bedaquiline and delamanid and slow registration of the latter inhibited uptake of both drugs in drug-resistant TB treatment programs. Follow-on tests to the GeneXpert moved only slowly through the pipeline, whereas there was just a handful of new TB drugs in clinical trials, and TB vaccine R&D (similarly in this case to HIV vaccine R&D) moved back towards early-stage studies due to setbacks in Phase III trials.

Meanwhile, the direct-acting antiviral (DAA) cures for HCV that have been recently discovered and are making their way to markets in various countries, albeit in highly inequitable and incomplete ways, have not yet blunted the ongoing wave of HCV transmission, which is tightly linked in some places to the ongoing opioid injection epidemic.

Combination HCV treatment can cure most cases of the infection with two drugs in as little as 8–12 weeks, yet high prices, weak political will, and poor infrastructure to diagnose and treat the disease have hindered uptake.

The gap between scientific possibility and political reality that has been growing since the great recession of 2008 has the potential now to become a yawning abyss, with the threat of massive, unprecedented cuts to U.S. research, domestic and global prevention, treatment, care, and support programs.

European countries, entangled in the web of their own self-inflicted austerity policies have not been willing to step up investment in R&D or global health, although (mostly) their domestic health and support service safety nets have not yet been shredded as badly as the new U.S. administration threatens to attack our already massively unjust and inequitable health systems.

Middle-income countries where much HIV and most TB and HCV occur are not investing enough in either research or in health.

Poor countries remain dependent on international aid programs whose prognosis is far from clear.

Thus, 30 years after the first approval of AZT, the world faces a recrudescence of the reactionary and exclusionary policies of the 1980s that first enhanced the spread of HIV, caused the resurgence of TB, and, when combined with the failed U.S. global 'war on drugs', continued to promote the spread of HCV.

Unlike 1987, however, we now have the tools to radically reduce new HIV infections, keep people living with HIV alive and healthy for a normal life span, and reduce new transmissions by 99% or more with PrEP or with treatment as prevention.

As this report will show, the investments of the last 15 years in new TB diagnostics and treatments are finally beginning to make a difference in mortality in the places where it matters, such as in South Africa.

The new HCV cures give us a chance, if diagnoses are accelerated and treatment rapidly made available to all, to eliminate HCV (which has no non-human hosts) as an epidemic.

The *2017 Pipeline Report* shows that the investments of the past 30 years have made it possible to save millions of lives, prevent millions of new infections, and save billions of dollars to health systems worldwide; and it shows the amazing potential that ongoing research has to bring the end of the HIV, TB, and HCV pandemics closer than ever.

Just as in 1987, when the founding of ACT UP led to a national, and then to a global, campaign for rights, equity, research, prevention, treatment, housing, care, and support, so now in 2017, only massive community mobilization and political intervention on behalf of our communities can ensure that the promise of the last 30 years of research, and of new R&D on HIV, TB, and HCV, can turn our situation from one of despair to one of lasting health, hope, and life.

2017 PIPELINE REPORT EXECUTIVE SUMMARY

HIV Treatment

Tim Horn's 2017 "The Antiretroviral Pipeline" demonstrates continuing vitality in this area of research. Although combination therapy continues to get safer and more durably effective, there is still considerable room for improvement, especially when we consider that people in their twenties who become newly infected are going to need safe, effective ART for a half-century or more, and that others who are just becoming sexually active or using injectable drugs will need safe and effective PrEP for their seasons of risk.

Horn discusses the likely approval in 2018 of Merck's doravirine, an NNRTI that will be combined with generic TDF and generic 3TC to make up the first triple-therapy regimen with the potential for significant cost savings in high-income countries as a result of its two generic components. Doravirine also appears to be active against HIV that is resistant to other NNRTIs and can be taken once daily.

Gilead is moving from its boosted-integrase inhibitor elvitegravir-based regimens to ones that do not require boosting based on the integrase inhibitor bicitgravir, which has been filed for approval with the FDA.

Several research programs are exploring dolutegravir-based dual therapies such as combinations with 3TC or the NNRTI rilpivirine.

Merck has finally obtained FDA approval for a once-daily, 1,200 mg dose of the first integrase inhibitor (initially approved at 400 mg twice daily in 2007), raltegravir.

ViiV Healthcare is studying the CD4 attachment inhibitor fostemsavir (formerly BMS 663068) in a Phase III program among heavily treatment-experienced individuals.

Long-acting ARVs, such as the integrase inhibitor cabotegravir and the NNRTI rilpivirine, are being studied as maintenance therapy, initial therapy, and as PrEP—although there are significant concerns about the potential for long-acting therapies, which have long half-lives, to promote the emergence of resistance if other drugs are discontinued or, in the case of PrEP, if someone discontinues the LA-PrEP, becomes exposed to HIV resistant to that single drug, and becomes infected.

Horn investigates a trio of monoclonal antibodies against HIV: ibalizumab (in Phase III and submitted to the FDA), PRO 140 (in data, development, and regulatory purgatory with little new to show over the past year beyond a highly questionable string of results from an open-label extension study), and UB-421 (in Phase II and presented as 8- or 16-week maintenance monotherapy at the Conference on Retroviruses and Opportunistic Infections (CROI) 2017). The future of these approaches, let alone their cost or global availability, remains difficult to predict.

China continues to develop its injectable entry inhibitor albuvirtide (48-week data reported at Glasgow 2016), whereas a Russian sponsor reported Phase II data on its NNRTI elsulfavirine at CROI 2017. The company intends to market this compound in the Russian Federation, Belarus, Kazakhstan, and Ukraine, if it ever makes it into (and out of) Phase III.

Drugs from two new ARV drug classes are in Phase I trials: Gilead's capsid inhibitor GS-CA1 and Merck's nucleoside reverse transcriptase translocation inhibitor EFdA (MK-8591).

Horn also reviews two preclinical maturation inhibitors and one preclinical integrase inhibitor from ViiV.

HIV Prevention

In "Preventive Technologies: Antiretroviral and Vaccine Development," Richard Jefferys and Jeremiah Johnson report on the explosively expanding and complex field of HIV preventive technologies research and development, including antiretroviral chemoprophylaxis, novel delivery methods for PrEP and post-exposure prophylaxis (PEP), combination approaches including ART and contraception or sexually transmitted infection prevention, and vaccine development.

The intersection of science, sex, safety, ethics, efficacy, adherence, and access makes the study of HIV prevention interventions a complex one (fewer resources are devoted to studying HIV prevention among drug users).

Oral PrEP

Continuing research is underway to determine how best to target PrEP to those individuals who will benefit from it the most. Long-overdue studies in pregnant and post-partum women are also underway. Differences in past efficacy studies conducted in gay men and heterosexual women have revealed that not only adherence, but also biological differences in drug penetration in different anatomical sites (e.g., blood versus vaginal versus rectal issue) can significantly influence results.

Currently, where PrEP is recommended it is usually given as TDF/FTC (Truvada) in developed countries in which Gilead's patent protections for TDF are beginning to expire, but WHO recommends "tenofovir-containing regimens," which include TDF alone, TDF/FTC, and TDF/3TC (the last of which is available as a generic component of ART in many developing countries).

Gilead is now studying its newly licensed tenofovir prodrug TAF (which has longer patent protection) with FTC to retain an expensive branded combination PrEP product in rich countries, although many, even where critical efficacy studies have already taken place (such as PRIDE in the UK or IPERGAY in France), still have not licensed Truvada PrEP for general use; the company is also looking at its four-drug combination elvitegravir/cobicistat/FTC/TAF (Genvoya) for PrEP.

Injectable PrEP

Two long-acting ARV formulations, ViiV's cabotegravir (an integrase inhibitor) and Janssen's rilpivirine (an NNRTI) are being studied in long-acting formulations for PrEP. Even if these long-acting injectables prove to be safe and effective, there will be several complications as to implementing them, including the need for oral PrEP lead-ins and oral PrEP subsequent to discontinuing LA-PrEP to ensure sufficient drug levels to protect against infection when detectable levels of the injectable drug remain but are too low to protect (but high enough to promote drug resistance). In one study, according to Jefferys and Jeremiah, "to cover the prolonged PK [pharmacokinetic] 'tail' associated with CAB [cabotegravir] LA dosing, all participants will be required to take daily oral TDF/FTC for at least one year, starting no later than eight weeks after the last injection."² Another concern with injectable long-acting agents is that if toxicity emerges there is no way to eliminate the drug rapidly from the body. Thus, delivery approaches that are intended to simplify adherence (and efficacy) demand very high safety profiles and bring with them implementation challenges of their own.

Topical PrEP

Many approaches using vaginal rings, gels, and applicators, or rectal gels, inserts, or suppositories, are in clinical trials, including agents such as tenofovir DF, dapivirine, elvitegravir, IQP-0528, griffithsin, PC-1005, darunavir, maraviroc (MVC), maraviroc/dapivirine, MK-2048/vicriviroc, dapivirine/darunavir, DS003, dapivirine/DS003, and several multi-purpose technologies including tenofovir/levonorgestrel or dapivirine/levonorgestrel (for contraception) and MB66 (a vaginal film containing anti-HIV and anti-herpes simplex virus 2 antibodies). With the exception of the dapivirine ring (reported on in last year's *Pipeline Report* with newer data in this year's chapter), which demonstrated modest efficacy, it's far too early to tell whether these approaches will prove effective.

HIV Vaccines

Clinical trials of candidate HIV vaccines are flourishing, with one study in Phase IIb/III, six in Phase II, four in Phase I/II, and a whopping 40 in Phase I. The most noteworthy study, HIV Vaccine Trials Network (HVTN) study 702, is the first HIV vaccine efficacy trial since HPTN 505 DNA prime/recombinant adenovirus-5 boost study was stopped in 2013 for lack of efficacy.³ HVTN 702 is designed to recapitulate and expand—with significant modifications and in a different population—the results of the RV144 recombinant canarypox vector prime/gp120 protein boost trial, which showed modest (~26% by intention to treat, 31% by modified ITT) efficacy among 16,402 Thai men and women aged 18–30⁴. HVTN 702 uses modified canarypox vector and modified gp12 proteins based on HIV strains that are more prevalent in southern Africa, and a different adjuvant (alum in RV144, MF59 in HVTN 702). 5,400 young South African men and women will be enrolled at 15 sites and will be randomly assigned to placebo or to ALVAC at baseline followed by ALVAC/gp120 boosts every three months for four total immunizations.

By May 2017, HVTN 702 had enrolled about one-tenth of its target. The design allows for use of PrEP and participants are provided information on how to access it; TDF/FTC blood levels will be measured using dried blood spots. The inclusion of (but not requirement for) PrEP reveals a flexible approach to changing approvals, guidelines, and access programs (South Africa approved PrEP in 2015, but it is not yet universally available), but also shows the challenge of conducting HIV prevention research while new interventions with proven safety and efficacy are becoming more available and the evidence for them stronger. This raises scientific, ethical, and implementation issues that will require continuing community participation, oversight, and promotion of scientific and prevention literacy.

Other candidate HIV vaccines are in much earlier phases of development; for details consult Jefferys and Johnson's Table 2, "HIV Vaccines, Passive Immunization, and Antibody Gene Transfer Pipeline, 2017" (see page 51).

Passive Immunization and Gene Transfer

Passive immunization with broadly neutralizing antibodies (bNAbs) to HIV-1 is an approach that is attracting increased attention due to provocative results in non-human primates and encouraging, but preliminary, results in early-phase human studies. These antibodies are copies of a few rare bNAbs that are found in some individuals living with long-term HIV infection and that are capable of neutralizing (blocking) a broad range of HIV-1 isolates. Some of the bNAbs are being studied in both preliminary treatment and prevention trials.

NIH Vaccine Research Center bNAb 01 (VCR01), given intravenously, is in a Phase IIb prevention trial cosponsored by NIAID, the HVTN, and the HPTN, among 2,700 gay men and transgender women who have sex with men in Brazil, Peru, and the United States, and among 1,500 sexually active women in seven countries in sub-Saharan Africa.

Earlier-phase studies are looking at more recently discovered bNAbs with greater breadth and potency, at different routes of administration (e.g., subcutaneous), and at bNAb combinations to preclude or delay the emergence of resistance to a single bNAb.

Another approach, which uses an adeno-associated-virus (AAV) to inject the DNA sequence for the bNAb of interest into muscle tissue, turning the cells into "persistent generators of bNAbs" (in Jefferys' felicitous phrase), is just beginning to enter human trials after a series of promising results in macaques, with the

caveat that one recent macaque study revealed the emergence of host antibodies against the vectored bNAbs, rendering them potentially less effective.

The bNAbs are also being used in some clinical trials of potentially cure-related treatment approaches (see below).

HIV Cure and Immune-Based and Gene Therapies

As Richard Jefferys demonstrates in “Research Toward a Cure and Immune-Based and Gene Therapies,” HIV-1 cure research continues to expand in three ways: institutionally (there are now six Martin Delaney Collaboratorys supported by NIH, up from the initial three), financially (up from \$161 million in 2014 to \$202 million in 2015, according to AVAC), and scientifically (although, as Jefferys cautions, progress here is incremental).

There is still only a single documented case of a successful clinical cure for HIV-1. This year Timothy Ray Brown celebrated his tenth year since being cured via a harrowing series of chemotherapies and stem cell transplants that has yet to be replicated successfully.

There are a few more cases of medium- to longer-term HIV-1 remission (virologic control free of ART).

Research continues on mechanisms of viral persistence under effective ART when there is adherence and no virologic blips, with an emerging focus on cell division/proliferation by infected cells (as opposed to new rounds of replication) as a contributing mechanism.

Debates continue on the role of persistent, low-level HIV replication in sanctuary cells (such as macrophages) or tissue sites (such as lymphoid tissue or the central nervous system), on the size of the HIV reservoir and how best to measure it, and on the causes and potential therapies for excess inflammation, immunosenescence (aging immunity), frailty, and neurologic sequelae associated with long-term survival with HIV under ART.

Some studies have found differences in the HIV reservoir between women and men, and between populations in Maryland and Uganda, but their clinical significance, if any, is not yet clear.

One group of long-term ART virologic responders, those who control HIV, but fail to experience adequate immune reconstitution, appear to be at increased risk of inflammation, frailty, and immunosenescence. These individuals, dubbed immunologic non-responders (INRs), need increased basic and clinical research approaches and interventions to improve their immune and overall health.

However, the dynamism of research in the HIV cure arena is (pardon the term) infectious. New clinical trials are posted regularly by Richard Jefferys at <http://www.treatmentactiongroup.org/cure/trials>.

Tuberculosis Diagnostics

Underlying the resurgence of tuberculosis as the world’s leading killer infectious disease is a shocking failure of political will, health systems integration, and willingness to deploy existing and emerging technologies to better detect, treat, and prevent a disease that has been curable since the introduction of combination chemotherapy in the early 1950s.

As Erica Lessem shows in “The Tuberculosis Diagnostics Pipeline,” 40%, or about four million, of TB cases are not diagnosed each year; this figure rises to 77% among those with drug-resistant disease (although given the enormity of our unknowing, such an exact number can only be an estimate). Those who are eventually diagnosed face lengthy and often expensive diagnostic delays before finally having their TB confirmed, let alone having drug-susceptibility testing (DST) or starting on appropriate treatment.

The apparent ‘standstill’ that we described TB diagnostics R&D as suffering from in the 2014 and 2015 *Pipeline* chapters has begun to give way to sluggish progress.

Notably, Cepheid’s GeneXpert MTB/RIF Ultra, a cartridge-based PCR system that diagnoses TB and rifampin resistance within two hours of sample collection, was endorsed by the WHO in March of this year. The Ultra cartridge can be used on the same equipment as the original GeneXpert cartridge and is provided globally in the public sector at the same \$9.98/unit test negotiated by Unitaid, FIND, and the Stop TB Partnership at the start of this decade. Ultra is more sensitive than the first-generation test.

A new platform from Cepheid, the GeneXpert Omni, is a portable single-cartridge testing unit that can be brought closer to the point of care, but has yet to be launched or evaluated by the WHO.

Still in development is Cepheid’s Xpert XDR cartridge, which will detect resistance to isoniazid, fluoroquinolones, and some second-line injectables.

Several other tests are either on the market and not yet evaluated by the WHO or still in development; among them is a promising blood test for the LAM antigen that could potentially be used to monitor response to therapy.

Uptake of the WHO-recommended urine LAM dipstick, which is especially useful to detect TB among HIV-infected persons who are severely ill and with have CD4 counts (below 100/mm³), has been glacial.

TB grown on solid or liquid culture is still the gold standard for TB diagnosis, and is essential for detailed DST, which should be universally available to guide optimization of treatment for the organism a patient is infected with, but solid culture can take months and liquid culture weeks to yield a read-out. Faster methods for TB culture, such as growing it with drug concentrations in tiny wells using microfluidics, should be explored.

Whole-genome sequencing (WGS) of the TB organism can provide another method to broaden DST and guide optimized therapy. It is already used in the United States and some other developed countries. The cost of sequencing continues to decline, but the difficulties rolling out and integrating even a selective PCR test such the GeneXpert MTB/RIF in health systems in high-burden settings points to the difficulty of integrating modern molecular testing into the clinics and health programs where they are most needed.

The much-needed machine-free, point-of-care test for TB remains as elusive as ever. In the meantime, as Lessem points out, improved sample transport and health systems information management among lab, clinic, and community will be essential to maximize the use of existing tests and speed the transmission of results to providers and patients.

TB Prevention

Mike Frick leads on a deep dive into basic, translational, and clinical research in his comprehensive “The Tuberculosis Prevention Pipeline.” No longer are chemoprophylaxis and TB vaccines studied in distant silos—both areas increasingly overlap as they take clues from basic, animal, and preclinical research to construct more robust and evidence-based approaches to TB prevention.

For several years Frick has been covering the ‘back to basics’ movement in TB prevention research, which is leading to new discoveries about the TB organism, the host response, imaging techniques, outbred mouse models, and other innovative approaches.

Clinical trials of new TB vaccine candidates are exploring a variety of designs, including prevention of infection (POI), prevention of disease (POD), and prevention of recurrence (POR) as primary endpoints. Considerable methodological work remains, such as determining what kind of measurement is optimal for POI and POR trials, given uncertainty in the former as to whether markers such as interferon gamma release assay (IGRA) conversion reflects transient or persistent infection, and in the latter as to whether a new case of TB disease results from reinfection or recurrence.

The 2017 TB vaccine pipeline contains 14 candidates under active clinical development representing three main constructs. Four subunit vaccines pair different combinations of MTB antigens with immune-modifying adjuvants; five viral-vectored vaccines employ weakened viruses to deliver antigen; and five whole-cell vaccines are based on genetically attenuated MTB or closely related mycobacterial species [Frick 2017].

Over the coming year, several Phase IIa or IIb studies are due to be reported out, including GSK’s M72+AS01 in a POD study among 3,500 South Africans without HIV. M72 is a subunit vaccine with two TB antigens and a proprietary GSK adjuvant. H4:IC31 is a POI study with two different TB antigens and an adjuvant from Valneva being studied in a three-arm Phase IIa study comparing two doses of H4:IC31 to placebo and to reboosted BCG. The readout is TB infection as measured by the IGRA QuantiFERON-Gold (QFT-Gold).

Live-cell approaches under study include *M. vaccae*, recombinant BCG, genetically attenuated *M. tuberculosis*, and *M. obuense*.

Additional protein/adjuvant, ‘fragmented MTB’, and viral vectored vaccine approaches are in earlier phase testing.

Nine studies are looking at new approaches to TB chemoprophylaxis with super-short, cyclical, or novel regimens.

ACTG study A5279 is looking at isoniazid/rifampentine for 30 days versus the standard of care of 9 months of daily INH (9H) among people in high-burden countries and those who are positive by tuberculin skin testing (TST) or IGRA.

A Canadian-sponsored study is looking at 4 months of daily rifampin versus 9H among TST/IGRA+ adults, including HIV-positive individuals receiving ART not contraindicated with rifampin.

The WHIP3TB trial, sponsored by KNCV and USAID, will look at whether one or two annual cycles of 3HP (isoniazid and rifampentine taken once weekly for 12 weeks) is more effective than 6 months of daily INH among HIV-positive individuals in high-burden settings.

A South African study is looking at 3HP versus active surveillance and whether an mRNA signature can accurately distinguish between those who develop active TB and those who do not.

The IMPAACT network’s P2001 study is looking at supervised 3HP among HIV-positive or HIV-negative pregnant or postpartum women with latent TB infection.

ACTG study A5365 will look at whether rifapentine daily for 30 days once a year for three years is superior to 3HP once among HIV-positive adults and adolescents in low-to-medium burden settings.

TB Trials Consortium (TBTC) study 37 (ASTERoid) will look at 6 weeks of daily rifapentine versus 3HP, 4 months of daily rifampin, or 3 months of daily INH/rifampin.

Three studies are looking at new regimens to prevent MDR-TB among household contacts of people with MDR-TB disease.

V-QUIN is looking at six months of daily levofloxacin versus placebo in Vietnamese adults, adolescents, and children exposed to MDR-TB in the household.

TB-CHAMP (<http://www.isrctn.com/ISRCTN92634082>) is a cluster-randomized trial looking at 24 weeks of daily levofloxacin versus placebo in children household contacts of people with MDR-TB.

The ACTG and IMPAACT networks are collaborating on the A5300B/PHOENIX/I2003B study of 26 weeks of daily delamanid versus isoniazid in high-risk (HIV-positive, TST/IGRA-positive, and/or ≤ 5 years of age) household contacts of people with MDR-TB. This study will likely open in the second of quarter of 2018, once pediatric doses of delamanid are defined in the youngest age groups.

A significant finding with potential implications for the global rollout of both rifapentine and the HIV integrase inhibitor dolutegravir for people with HIV and at risk for TB disease emerged at CROI 2017 when an NIH PK study of isoniazid/rifapentine/dolutegravir was stopped early after two of four participants developed hypersensitivity. Further data will need to be carefully gathered to study the safety of this combination.

Nonetheless, the renaissance of clinical trials into new preventive interventions to stop TB infection and disease, either with vaccines or with therapy, is heartening.

TB Treatment

In “The Tuberculosis Treatment Pipeline: A Breakthrough Year for the Treatment of XDR-TB,” by Marcus Low, *Spotlight* Editor and former Head of Policy of South Africa’s Treatment Action Campaign, we can see how, for the first time, a new TB drug is saving lives where it most matters—in programmatic settings in places with a high burden of all forms of TB—and a new TB regimen is achieving significant cure rates in extensively drug-resistant (XDR) and pre-XDR TB. Bedaquiline, a diarylquinoline anti-TB drug first appearing in the literature in 2004⁵ and granted accelerated approval by the U.S. FDA in 2012 based on two small Phase II studies in persons with drug-resistant TB, showed 89% smear conversion and 91% culture conversion in an observational retrospective study of 428 patients with DR-TB in 15 countries. Over 8,000 patients have now received the drug, and previous concerns about potential QTc prolongation seen in the Phase II studies and associated with excess mortality do not appear to be borne out by the emerging programmatic data.

Meanwhile, preliminary results were presented at CROI 2017 on the TB Alliance’s Nix-TB trial, combining bedaquiline with linezolid (an approved antibiotic that is not indicated for TB) and pretomanid (another drug from a new class, the nitroimidazole, like Otsuka’s delamanid), given to persons with XDR, pre-XDR, and drug-intolerant MDR-TB. The study is non-randomized and individuals receive the three drugs for six months, with dose reductions or interruptions of linezolid if dose-limiting neutropenia or peripheral neuropathy occurs. By the time of the conference, in February 2017, as Low reports:

Of the 72 patients enrolled in the study, 40 had at that point finished treatment and 31 had finished six months of follow-up. Four patients died—all in the first eight weeks. Of the 31 who finished six months of follow-up, only two had relapsed or been reinfected... Remarkably, all surviving patients were culture negative at four months—74% were already negative at eight weeks.

Previous outcomes for XDR-TB have been miserable, with high mortality (73% at five years, higher in people with HIV) and low cure rates.

The TB Alliance plans a follow-up, four-arm study in 180 persons using the same regimen, but comparing different linezolid dosing and duration.

USAID's ongoing STREAM-II trial compares bedaquiline plus the old 24-month MDR-TB regimen to that regimen alone, whereas other ongoing studies with bedaquiline include NEXT-5001, TB-PRACTECAL, and endTB (see Low's Table 3).

The TB Alliance intends to follow-up promising results from the four-drug NC-005 study of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (BPaMZ), also presented at CROI 2017. The follow-up study, NC-008, will look at BpaMZ, which appears to be more potent than their previous Phase IIb/III regimen, PaMZ, studied in the STAND trial, which has now stopped enrolling.

The ACTG is conducting A5343, a long-overdue drug-drug interaction study of bedaquiline, delamanid, and both drugs together on a DR-TB background regimen. The study will determine whether the two drugs' QTc-prolonging effects allow or prohibit their co-administration. The drugs' sponsors, Janssen and Otsuka, first agreed to this approach back at bedaquiline's FDA approval hearing in 2012, but it has taken five years to get off the ground due to various bureaucratic and legalistic hurdles.

Otsuka's Phase III registrational study of delamanid is expected to be presented at the October 2017 Union conference in Guadalajara, Mexico, and will shed more light on how and whether this new drug for DR-TB, granted conditional approval by the EMA in 2014, actually works.

Delamanid will also be studied in the groundbreaking ACTG/IMPAACT PHOENIX A5300B/I2003B study of 6 months' delamanid versus isoniazid among high-risk household contacts (HIV positive, TST, or IGRA positive, and/or ≤ 5 years of age) of persons with MDR-TB.

The TB Alliance's similar compound, pretomanid, will be studied as noted above in follow-up to the Nix-TB and NC005 studies. Given the results of Nix, there will be pressure on the Alliance to work with other stakeholders to figure out some kind of access program for pretomanid before regulatory approval is granted.

Sutezolid, similar to linezolid and oxazolidinone, was first discovered at Pharmacia and Upjohn in the 1990s, passed to Pfizer when that company absorbed P&U, sat on the shelf for over a decade, was evaluated in early bactericidal activity (EBA) and then licensed to and Sequella, has now been sitting on the shelf again for the past five years. The drug's intellectual property, partially held by Johns Hopkins University and recently licensed to the Medicines Patent Pool (MPP), may allow other sponsors to finally evaluate the drug, although neither Pfizer nor Sequella is willing to provide access to the existing preclinical toxicology and PK data.

A handful of other compounds are in Phase I or early Phase II, including Qurient's Q203, Sequella's SQ109 (already dumped in a PanACEA trial for lack of activity, but licensed Russia), Nearmedic's DprE1 inhibitor PBTZ169, LegoChem Biosciences' oxazolidinone LCB01-0371, and Otsuka's new carbostyryl compound OPC-167832. Several of these are new to the clinic, and will be welcomed.

Low proceeds to examine clinical research underway to optimize and/or repurpose existing TB drugs, including isoniazid, the rifamycins (rifampin and rifapentine), the fluoroquinolones, the approved anti-leprosy drug clofazimine, linezolid, nitazoxanide, and the carbapenems (see Low table 2). Most of these are included in complex combination studies for various forms of DR-TB, and some for drug-sensitive forms of the disease.

The Tuberculosis Diagnostics and Treatment Pipeline for Children

Lindsay McKenna's "The Tuberculosis Diagnostics and Treatment Pipeline for Children" addresses research underway to close the unacceptable diagnostic and treatment gaps that cause excess TB morbidity and mortality in children. TB diagnosis rates are bad enough in adults, but in children just an estimated 38.4% (384,300 of an estimated one million annual cases) are reported to national authorities each year.

The pace of pediatric TB research is picking up and there is a need for expanded and accelerated investment.

Neither Xpert MTB/RIF nor TB culture, let alone smear microscopy, is as sensitive in children as in adults, deepening the diagnostic gap. McKenna reports on a number of recent studies which tried to optimize Xpert among children.

As in adults, a variety of approaches are being studied to look at gene signatures, biomarker-based blood and skin tests. In the meantime, scaling up and decentralizing existing diagnostic approaches for children will be essential.

Six TB preventive therapy trials are underway or planned for children, including the already discussed P4v9, TB-CHAMP, ACTG 5003B/PHOENIX/IMA ACT P1003, and V-QUIN. In addition, the Titi study in HIV-positive and HIV-negative infant and child contacts ≤ 5 years old, cosponsored by Expertise-France and the Union, is looking at three months of isoniazid/rifampin versus six months of rifampin. TBTC 35 is a pharmacokinetic and safety study of a fixed-dose combination (FDA) of isoniazid and rifapentine in HIV-positive and HIV-negative infants, children, and adolescents 0–12 years old with LTBI, cosponsored by the drug's maker, Sanofi.

Five combination studies are underway in drug-sensitive pediatric TB disease looking at various combinations, including the 2010 WHO dosing guideline-recommended first-line regimens, dose optimization of rifampin, and for TB meningitis, high-dose rifampin with or without levofloxacin (see McKenna's Table 1).

Nine drug-drug interaction studies of TB drugs in combination with ARVs are enrolling, complete and due to report, or planned. ARV drugs in these studies include lopinavir/ritonavir, nevirapine, efavirenz, raltegravir, and dolutegravir.

Seven studies are enrolling, complete and due to report, or planned for pediatric MDR-TB. Two are pharmacokinetic and safety studies of older second-line drugs, three of delamanid with an optimized background regimen (OBR), and two of bedaquiline with an OBR. Delamanid is ahead of bedaquiline in pediatric studies because the EMA, unlike the U.S. FDA, requires a pediatric investigational plan (PIP) as part of the registrational package.

In Table 2, McKenna reviews the pediatric formulations in development or new to market.

Two prevention trials and four treatment trials (including the TB pregnancy registry) are underway in pregnant women.

HCV Pipeline Update

In the “HCV Pipeline: DAAs and Diagnostics in the Pangenotypic Era,” Annette Gaudino gives a high-level review of recent developments in the rapidly changing HCV diagnosis, treatment, research, and access landscape.

The years since 2014 have seen the rapid evolution of HCV treatment approvals and guidelines for the use of DAAs to treat HCV. Rates for 8–12 week sustained virologic responses (SVRs) are often extremely high in most populations, sometimes lower with cirrhosis. More recently approved combinations may sometimes treat all genotypes of HCV (pangenotypic), thereby skipping the need for genotype testing.

Unfortunately, cost has severely constrained uptake of the new DAAs in both developed and developing countries. In many cases, programmatic choices are based on price. Sometimes a sponsor will refuse to negotiate with a given jurisdiction, thereby excluding those with HCV there from receiving what may be the best therapy.

HCV rates are rising in many parts of the world, driven in part by the ongoing opioid epidemic. Punitive drug laws and outdated approaches to opioid addiction and its prevention and treatment are driving new rounds of HCV transmission, often in places and populations that are not familiar with existing harm reduction and syringe exchange approaches that have proved so effective in reducing HIV rates among injecting drug users.

Gaudino’s Table 1 shows the current panoply of multi- and pangenotypic treatment regimens, which in some cases cure in as quickly as six to eight weeks and which may involve two to five drugs (sometimes including ribavirin).

Further discussion addresses the need for and thus far limited extent of regulatory approval of and programmatic access to generic DAAs.

Some countries and jurisdictions are beginning to develop and launch HCV elimination plans, although the United States is not among them.

New research and programmatic approaches, including rapid and point-of-care diagnostics, are needed to define the efficacy and epidemiologic impact of HCV treatment as prevention.

Since HCV has no non-human hosts, and can be completely cured in the vast majority of those infected, elimination is an achievable goal.

The experience of the last 75 years with tuberculosis shows, however, the dangers of abandoning research once a first- or second-generation cure has been developed and brought to scale. Table 2 abstracts the target product profiles for HCV diagnostics.

Gaudino concludes by examining the emergent pipeline of potential HCV vaccines.

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The Antiretroviral Pipeline

By Tim Horn

INTRODUCTION

The antiretroviral (ARV) pipeline remains robust, with several drugs, coformulations, and biologics currently in Phase II and III stages of development. The trends are clear: maximizing the safety and efficacy of standard three-drug regimens; validating two-drug regimens as durable maintenance therapy and, potentially, for people living with HIV starting treatment for the first time; advancing long-acting and extended release products; and, no less importantly, developing new drugs and biologics to address the needs of people with HIV resistant to multiple drugs and classes.

Another notable trend is the development of drugs and single-tablet regimens (STRs) that could potentially address treatment-cost-related concerns that continue to threaten drug access in middle- and high-income countries. The first STR to be approved by the U.S. Food and Drug Administration (FDA), Atripla (efavirenz/tenofovir DF/emtricitabine), debuted in 2006 with a wholesale acquisition cost (WAC) price of \$13,811. The most recent, Genvoya (elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine), debuted at \$37,118 just nine years later. In the context of public payer systems already stretched to the brink and facing an uncertain future under the current White House administration; commercial health insurance plans defraying spending on high-cost drugs by increasing annual premiums and consumer cost sharing, and placing these drugs on unaffordable formulary tiers; and the fact that the number of U.S. residents living with HIV with suppressed viral loads needs to more than double to meet the 2020 goals of the National HIV/AIDS Strategy, it becomes clear that cost—in addition to safety, efficacy, and dosing—is a factor that must be considered.

With several ARVs still widely considered to be components of first-line therapy losing their U.S. patent protection this year, at least one innovator product—Merck's doravirine coformulated with tenofovir disoproxil fumarate (TDF) and lamivudine (3TC)—has the potential to buck the decade-long trend of manufacturers launching STRs at prices that are, at best, comparable with that of their competition. Another regimen in late-stage development that carries the potential for significant cost savings is dolutegravir (DTG) combined with just one other drug, 3TC. ViiV Healthcare is developing a coformulated version, with stand-alone DTG plus generic 3TC being another potential option.

This year's ARV pipeline review features two drug products that may meet affordable HIV treatment needs in middle-income countries: Frontier Technologies' albuvirtide and Viriom's elsulfavirine. Although several middle-income countries, such as India and several African nations, are paying low prices for first-line and many second-line treatment regimens—comparable to those paid by low-income countries—others, including those in Eastern Europe, Latin America, and China, are paying relatively high prices for first-line and, often, second-line options.¹ The introduction of innovator drugs developed exclusively for middle-income countries, particularly those with strict national patent laws that prevent the importation of low-cost generics and that are likely to be affected by the diminishment of support from the Global Fund, is essential to the UNAIDS 90-90-90 global treatment target to help end HIV as an epidemic.

For all of the optimism and hope behind global, national, and regional efforts to end HIV as an epidemic, HIV remains a significant health challenge in all countries. Safe, effective, easy-to-use—and affordable—ARV options are a cornerstone of every plan to dramatically reduce new HIV infections and minimize HIV-related mortality.

SUMMARY OF PIPELINE PROGRESS

A summary of key developments since the 2016 *Pipeline Report* is included in Table 1, which is organized alphabetically by development status. Study details, references, and timelines for compounds with significant advances over the past year are discussed in greater detail below.

Table 1. Summary of pipeline compounds in 2017

Compound	Class/Type	Company	Status	Comments
DRUGS AND COFORMULATIONS				
Raltegravir (once-daily formulation)*	INSTI	Merck	FDA approved	Approved by FDA May 30, 2017. 48-week data from Phase III ONCEMRK study presented at 2016 IAC and submitted for publication.
Albuvirtide*	Fusion inhibitor	Frontier Biotechnologies	Phase III	48-week data from Phase III TALENT study reported at Glasgow 2016. Primarily developed for China's national Free Antiretroviral Treatment Program.
	INSTI	Gilead	Phase III	To be coformulated with TAF and FTC. 24- and 48-week data from Phase II study reported at CROI 2017 and published in <i>The Lancet HIV</i> . Phase III trials under way. NDA filed in June with FDA; EMA filing expected this summer.
Darunavir plus cobicistat plus tenofovir alafenmaide fumarate plus emtricitabine (coformulation)	PI plus PK booster plus NtRTI plus NRTI	Janssen Therapeutics	Phase III	Currently in two Phase III studies: AMBER and EMERALD. Preliminary results from at least one Phase III trial expected to be reported at IAS 2017. FDA approval anticipated mid-2018.
Dolutegravir plus lamivudine (coformulation)*	INSTI plus NRTI	ViiV Healthcare/ GSK	Phase III	ANRS evaluation as maintenance therapy reported at CROI 2017. Currently in Phase II and III trials involving treatment-naïve participants. FDA approval expected in late 2018.
Dolutegravir plus rilpivirine (coformulation)*	INSTI plus NNRTI	ViiV Healthcare/ GSK, Janssen	Phase III	48-week data from Phase III SWORD-1 and SWORD-2 studies presented at CROI 2017. FDA and EMA applications filed; approvals expected in early 2018.
Doravirine (MK-1439)*	NNRTI	Merck	Phase III	48-week data from Phase III DRIVE study presented at CROI 2017. To be coformulated with TDF and 3TC.
Fostemsavir (GSK3684934; formerly BMS 663068)*	CD4 attachment inhibitor	ViiV Healthcare/ GSK	Phase III	Currently in Phase III evaluation involving heavily treatment-experienced volunteers.
Elsulfavirine*	NNRTI	Viriom	Phase II	48-week data from Phase IIb study reported at CROI 2017. No known Phase III trial. To be commercialized in Russia, Ukraine, Belarus, and Kazakhstan.
GS-CA1	Capsid inhibitor	Gilead Sciences	Phase I	Preclinical data reported at CROI 2017. Highly potent inhibitor of HIV in PBMCs and active against all major clades.
MK-8591 (EFdA)	NRTTI	Merck	Phase I	Preclinical and Phase I data suggest potential for long-acting administration for HIV treatment and PrEP. CROI 2017 animal data suggest high lymphoid, rectal, and vaginal concentrations.

Compound	Class/Type	Company	Status	Comments
GS-9131	NtRTI	Gilead Sciences	Preclinical	Preclinical data reported at CROI 2017. Active against HIV resistant to available NRTIs.
GS-PI1	PI	Gilead Sciences	Preclinical	First PI from Gilead. Preclinical data reported at CROI suggest high barrier to resistance and potential for unboosted once-daily dosing.
GSK1264	INSTI	ViiV Healthcare/ GSK	Preclinical	Allosteric inhibitor of HIV integrase.
GSK3640254	Maturation inhibitor	ViiV Healthcare/ GSK	Preclinical	Third generation follow-up compound to BMS-955176.
BMS-955176	Maturation inhibitor	ViiV Healthcare	DISCONTINUED	Discontinued in Phase II due to gastrointestinal adverse events and emergent drug resistance.
BIOLOGICS				
Ibalizumab*	Entry inhibitor	TaiMed Biologics	BLA submitted/Phase III	24-week Phase III TMB-301 study in treatment-experienced patients presented at CROI 2017. Orphan Drug/priority review BLA filed with FDA in May 2017. Currently requires biweekly intravenous infusions; intramuscular formulation in development.
PRO 140*	CCR5 antagonist	CytoDyn	Phase II/III	Additional follow-up data from small open-label Phase II extension reported at ASM Microbe 2016 and CROI 2017. Additional Phase II and III trials under way.
UB-421*	CD4 attachment inhibitor	BioPharma	Phase II	Eight-dose (weekly and biweekly) Phase II study data presented at CROI 2017.
Combinectin (GSK3732394)	Adnectins and fusion inhibitor peptide	ViiV Healthcare	Preclinical	Preclinical data presented at CROI 2016, 2017; Phase I and additional preclinical studies planned.

*New data summarized below.

ASM: American Society for Microbiology; BLA: biologics license application; BMS: Bristol-Myers Squibb; CROI: Conference on Retroviruses and Opportunistic Infections; FDA: Food and Drug Administration (U.S.); FDC: fixed-dose combination; Glasgow: International Congress of Drug Therapy in HIV Infection; IAC: International AIDS Conference; INSTI: integrase strand transfer inhibitor (integrase inhibitor); NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NRTTI: nucleoside reverse transcriptase translocation inhibitor; NtRTI: nucleotide reverse transcriptase inhibitor; PBMCs: peripheral blood mononuclear cells; PI: protease inhibitor; TDF: tenofovir disoproxil fumarate; 3TC: lamivudine.

APPROVALS SINCE JULY 2016

Once-Daily Raltegravir

The FDA has approved Merck's supplementation new drug application (sNDA) for a once-daily formulation of its integrase strand transfer inhibitor (INSTI) Isentress (raltegravir; RAL) for people living with HIV who are naive to ARV therapy or patients whose virus remains suppressed after treatment with a regimen containing 400 mg RAL used twice daily.² An application for licensure filed with the European Medicines Agency (EMA) has been recommended for approval by the Committee for Medicinal Products for Human Use (CHMP).³

Once-daily dosing of RAL was initially rejected by the FDA after the QDMRK trial, which failed to show that once-daily dosing of raltegravir (800 mg) using its current formulation was non-inferior to twice-daily dosing (400 mg) for first-line therapy.⁴ Formulation development work at Merck has since yielded a 600

mg version (total daily dose 1,200 mg) that was evaluated in a Phase III randomized, double-blind non-inferiority study (ONCEMRK) in comparison with the original twice-daily formulation in treatment-naive participants. Primary endpoint results at 48 weeks from this 96-week study were first presented at the 2016 International AIDS Conference (AIDS 2016) in Durban and have been submitted for publication.^{5,6}

The trial randomized 802 treatment-naive volunteers 2:1 to receive RAL 1,200 mg QD (new formulation) or 400 mg BID (original formulation), each combined with TDF/emtricitabine (FTC). Most participants were male (83% and 88% in the QD and BID groups, respectively) and white (57% and 65%). The median age at baseline was approximately 34 years and the median baseline viral load and CD4 count were 30,000 copies/mL (approximately 28% entered with HIV RNA > 100,000 copies/mL) and roughly 400 cells/mm³ (approximately 13% entered with CD4 counts < 200 cells/mm³).

At week 48, the study's primary endpoint, the rates of HIV RNA < 40 copies/mL were 88.9% in the QD group, as compared with 88.3% in the BID group (difference: 0.5%; 95% confidence interval [CI]: -4.2 to 5.2). Among those with baseline HIV RNA > 100,000 copies/mL, virologic suppression rates at week 48 were 86.7% and 83.8%, respectively (difference: 2.9%; 95% CI: -6.5 to 14.1). CD4 count gains were comparable: 232 cells/mm³ in the QD group versus 234 cells/mm³ in the BID group (difference: 2%; 95% CI: -31 to 27).

Protocol-defined virologic failure rates were also similar in both groups: 3.4% receiving QD and BID RAL were non-responders (i.e., did not achieve HIV RNA < 40 copies/mL by week 24) and 3.4% each experienced virologic rebound (i.e., two consecutive HIV RNA measurements ≥ 40 copies/mL at least one week apart after an initial HIV RNA < 40 copies/mL result). Genotypic testing was conducted on samples from 14 subjects with virologic failure in the QD group—nine had no resistance (or had inconclusive results) and five had documented resistance, including RAL resistance in four.

Drug-related adverse events were reported in approximately 25% of participants in both groups; less than 1% of which were serious and there were slightly more discontinuations due to adverse events in the BID group (2.3% versus 0.8%). The most common side effects were gastrointestinal in nature, with central nervous system (CNS)-related adverse events occurring in less than 2% of all study participants.

SELECT DRUGS AND COFORMULATIONS: PHASE III TRIAL RESULTS

Albuvirtide

Frontier Biotechnologies (based in Nanjing, China) is currently seeking accelerated approval for its peptide-based fusion inhibitor, albuvirtide (ABT), from the China Food and Drug Administration.⁷ The drug, which currently requires once-weekly intravenous infusions (the potential for a subcutaneously administered formulation is being considered by the manufacturer), has been developed to fill a need for low-cost treatment options for a growing number of people in China requiring second- or third-line therapy options. China's National Free Antiretroviral Treatment Program offers only ritonavir-boosted lopinavir (LPV/r), efavirenz (EFV), nevirapine (NVP), zidovudine (AZT), abacavir (ABC), TDF, and 3TC, with few alternatives for patients experiencing treatment failure.

Interim results from an ongoing Phase III non-inferiority trial, the TALENT study, were reported by the manufacturer at the 2016 International Congress of Drug Therapy in HIV Infection in Glasgow (Glasgow 2016). Previously, safety and antiviral activity data from a Phase Ia proof-of-concept study and a limited 12-person Phase IIa evaluation were presented at the 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy in 2012, and a seven-week, open-label, 20-person Phase IIb trial combining ABT with LPV/r was published last year in *AIDS Research and Therapy*.^{8,9}

TALENT randomized 389 treatment-experienced volunteers, all of whom had experienced virologic failure on a first-line regimen, to receive twice-daily LPV/r plus either once-weekly ABT or an optimized nucleoside reverse transcriptase inhibitor (NRTI) backbone regimen (3TC plus AZT, ABC, or TDF). The interim analysis presented at Glasgow 2016 included only the 83 patients in the ABT group and the 92 patients in the NRTI group who had completed 48 weeks of follow up.

The median age at baseline was approximately 40 years; 27% were female. The median viral load at baseline was 63,000 copies/mL, with roughly 12% entering the trial with HIV RNA > 100,000 copies/mL. Median baseline CD4 counts were roughly 235 cells/mm³, with approximately 16% entering the trial with fewer than 100 CD4 cells/mm³. The average time on first-line therapy was approximately 27 months, with 71% and 26% having used either TDF or AZT, respectively, in combination with 3TC in their previous regimen. Baseline drug resistance was confirmed in approximately 82% of all of the participants included in the interim analysis, with genotypic resistance to 3TC (61% in the ABT group, 73% in the NRTI group), AZT (16% and 18%), and TDF (44% and 49%) being the most common.

At week 48, 80.4% in the ABT group, compared with 66% in the NRTI group, had HIV RNA < 50 copies/mL (difference: 14.4%; 95% CI: -3.0 to 31.9), demonstrating non-inferiority. Data pertaining to changes in CD4 counts were not presented.

There were no treatment-emergent mutations in gp41 genes in five patients with HIV RNA ≥ 400 copies/mL at 24 or 48 weeks in the ABT group; one patient in each group developed resistance to LPV/r.

With respect to safety, 5.6% in the ABT group, compared with 3% in the NRTI group, experienced severe adverse events, although only one event—gastroenteritis in the NRTI group—was believed to be drug related. The most common adverse events were diarrhea, gastroenteritis, rash, headache, dizziness, and hematuria. The most common laboratory abnormalities were hypercholesterolemia and hypertriglyceridemia, although specific data were not presented. No injection site reactions were observed.

Dolutegravir and Rilpivirine

Oral DTG combined with rilpivirine (RPV) is on course to be the first two-drug regimen approved as HIV maintenance therapy; FDA and EMA approval applications have been filed, with launches of a coformulated tablet expected in the first half of 2018. Forty-eight-week data from the identical Phase III SWORD 1 and SWORD 2 switch studies were reported at the 2017 Conference on Retroviruses and Opportunistic Infections (CROI 2017).¹⁰

The open-label trials randomized 513 participants to switch from their current integrase strand transfer inhibitor (INSTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or protease inhibitor (PI)-based therapy to DTG 50 mg plus RPV 25 mg; 511 were randomized to continue their current ARV therapy. All of the volunteers entered the trials while on their first or second ARV therapy regimen with HIV RNA < 50 copies/mL, without a history of virologic failure on their current or previous regimens, or genotypic evidence of transmitted or acquired drug resistance. The mean age at baseline was 43 years in both groups; approximately 22% were female, 20% non-white, and most (~70%) entered the trial with CD4 counts > 500 cells/mm³.

At week 48, 95% of participants in both groups maintained virologic suppression < 50 copies/mL in the pooled study analysis. Virologic non-responses did not exceed 1% in either group. The adjusted treatment difference was -0.2% (95% CI: -3.0 to 2.5), slightly favoring the control group in the pooled analysis.

Approximately 3% of participants in the DTG + RPV groups in both trials discontinued the treatment as a result of adverse events or death, as compared with less than 1% in the control groups in both studies. Among the two deaths reported, one was due to Kaposi's sarcoma in the DTG + RPV groups and the other due to lung cancer in the control groups.

Two subjects in each of the pooled groups experienced an HIV RNA rebound (≥ 200 copies/mL), meeting virologic withdrawal criteria. One participant on DTG + RPV meeting these criteria had an emergent NNRTI-resistance associated mutation (K101K/E, conferring a limited 1.2-fold change to RPV sensitivity) following an HIV RNA rebound to ~ 1 million copies/mL between weeks 24 and 36, consistent with a treatment interruption. The study participant restarted DTV/RPV on week 36 and had resuppressed virus by week 45. No INSTI-resistance-associated mutations were documented in any of the study participants.

Although adverse event rates were comparable in both groups (77% among those receiving DTG/RPV, compared with 71% of those in the studies' control groups), adverse events leading to withdrawal were higher in the DTG + RPV group (4% versus $< 1\%$). Discontinuations as a result of adverse events are not uncommon in switch studies, particularly those involving participants who have remained stable on their previous regimens for prolonged periods and are then switched to new medications. The median duration of ARV therapy prior to entering the study was approximately 52 months.

What remains unclear is the clinical benefit of this two-drug maintenance therapy over standard three-drug options. Although efficacy was comparable in SWORD-1 and SWORD-2, there were no adverse event advantages to two-drug versus three-drug therapy (particularly those involving tenofovir alafenamide fumarate [TAF], with its more favorable renal and bone safety profile over TDF). In addition, strict entry criteria for both studies, favoring participants with treatment histories unencumbered by drug resistance, prevent extrapolation of these results to many treatment-experienced patients. Rilpivirine must also be taken with a full meal—not a snack. Cost, however, may be an important advantage, in both U.S. and global markets.

Doravirine (MK-1439)

Doravirine (DOR) is Merck's once-daily NNRTI. It has a unique resistance profile, with activity against the most prevalent NNRTI-resistance mutations (K103N, Y181C, G190A, K103N/Y181C, and E138K). It can be taken with or without food and has limited potential for drug-drug interactions, as DOR is neither an inducer nor an inhibitor of CYP3A4. Forty-eight-week data from a Phase II clinical trial showing comparable efficacy and improved safety versus efavirenz (EFV) were presented last year.¹¹

Preliminary results from the Phase III DRIVE-FORWARD trial, demonstrating DOR's non-inferior efficacy to ritonavir-boosted darunavir (DRV/r), were reported at CROI 2017.¹² The trial randomized 769 treatment-naive patients 1:1 to receive double-blinded DOR 100 mg or DRV/r plus 2 NRTIs, either TDF/FTC (87%) or ABC/3TC (13%). The mean age at baseline was approximately 35 years; most were men (approximately 84%). The mean viral load at baseline was approximately 25,000 copies/mL, with 22% and 19% participants, respectively, in the DOR and DRV/r groups entering the trial with viral loads in excess of 100,000 copies/mL.

DOR was non-inferior to DRV/r at week 48, the primary endpoint, with 83.8% and 79.9%, respectively, achieving HIV RNA < 50 copies/mL (difference 3.9%; 95% CI: -1.6 to 9.4). Of note, virologic suppression rates in both groups were lower than those commonly observed in Phase III trials of INSTIs.

Among those initiating treatment with viral loads $> 100,000$ copies/mL, 81% in the DOR group, versus 76.4% in the DRV/r group, had HIV RNA < 50 copies/mL at week 48 (difference: 3%; 95% CI: -11.2

to 17.1). CD4 count gains were similar between the two groups: 193 cells/mm³ in the DOR group, as compared with 186 cells/mm³ in the DRV/r group.

Discontinuation rates were 7% and 9% in the DOR versus DRV/r, respectively, and were mostly a result of the high bill burden in the trial—four tablets, including placebos, needed to be taken once daily in both groups.

One out of the 383 participants in the DOR group participants discontinued because of noncompliance at week 24, with evidence of DOR resistance (V106I, H221Y, and F227, with a >90-fold increased IC50) and FTC resistance (M184V). None of the 383 participants receiving DRV/r developed PI resistance.

Rates of adverse events believed to be drug related were similar in both groups: 31% in the DOR group versus 32% in the DRV/r group. Serious adverse events occurred in 5% and 6%, respectively, with 1% and 3.1% discontinuing treatment as a result. Rates of nausea, nasopharyngitis, headache, rash, and CNS events were comparable and ranged from 8% to 14%, with diarrhea being slightly more common in the DRV/r group (22% versus 14%). Changes in laboratory values were also comparable, with the only statistically significant difference being decreases in LDL cholesterol and non-HDL cholesterol in the DOR group (−4.5 and −5.3 mg/dL, respectively), as compared with increases in the DRV/r group (+9.9 and +13.8 mg/dL, respectively).

DOR is also being evaluated in several ongoing studies as an STR with 3TC and TDF (DOR/3TC/TDF). Phase II clinical trials include DRIVE-BEYOND, an evaluation of DOR/3TC/TDF in treatment-naive participants with transmitted resistance to NNRTIs, and an evaluation of switching from EFV due to intolerance.^{13,14} Phase III studies include DRIVE-AHEAD, a trial comparing DOR/TDF/3TC with EFV/TDF/FTC in treatment-naive participants, and DRIVE-SHIFT, a trial evaluating a switch to DOR/3TC/TDF in people who are currently virologically suppressed on another ARV regimen.^{15,16}

Coformulated DOR/TDF/3TC is expected to be approved in mid-2018. Because it contains two nonproprietary drugs—3TC has been off patent for several years and TDF's patent protection ends this year—the STR is expected to debut with a WAC that is significantly lower than that of other commonly prescribed STRs for treatment-naive people living with HIV, including Stribild, Genvoya, Triumeq, Complera, and Odefsey (see Table 2).

Long-acting nanoformulations of DOR have been evaluated in a Phase I clinical trial, the data from which have not yet been reported.¹⁷

Table 2. U.S. ARV WAC Prices

Company	Product	Launch Date	Annual WAC at Launch	Annual WAC Current Price	Total Change Since Launch
Abbvie	Norvir	Jul-99	\$3,205	\$18,517	478%
	Kaletra	Sep-00	\$6,500	\$11,605	79%
BMS	Sustiva	Dec-98	\$3,784	\$11,767	211%
	Reyataz	Dec-03	\$7,949	\$17,559	121%
	Evotaz	Feb-15	\$16,844	\$19,266	14%
Gilead	Viread	Nov-01	\$3,917	\$12,799	227%
	Truvada	Aug-04	\$7,810	\$18,811	141%
	Atripla	Jul-06	\$13,811	\$30,579	121%
	Complera	Aug-11	\$20,455	\$30,093	47%

Company	Product	Launch Date	Annual WAC at Launch	Annual WAC Current Price	Total Change Since Launch
	Stribild	Aug-12	\$28,110	\$34,686	23%
	Genvoya	Nov-15	\$37,118	\$39,679	7%
	Odefsey	Mar-16	\$28,150	\$30,093	7%
	Descovy	Apr-16	\$17,597	\$18,811	7%
Janssen	Prezista	Jul-06	\$9,000	\$16,291	81%
	Intelence	Jan-08	\$7,848	\$13,081	67%
	Prezcobix	Feb-15	\$17,258	\$18,621	8%
Merck	Isentress	Oct-07	\$9,720	\$16,675	72%
ViiV	Epzicom	Aug-04	\$7,459	\$15,500	108%
	Selzentry	Aug-07	\$10,440	\$16,797	61%
	Tivicay	Aug-13	\$14,105	\$18,428	31%
	Triumeq	Aug-14	\$26,488	\$31,185	18%

Source: Fair Pricing Coalition

SELECT DRUGS AND COFORMULATIONS: PHASE II TRIAL RESULTS

Bictegravir (GS-9883)

Bictegravir (BIC) is a once-daily INSTI being developed by Gilead Sciences that, unlike its FDA-approved predecessor elvitegravir (EVG; available as a component of Stribild and Genvoya), does not require boosting. It has demonstrated activity against several HIV-1 subtypes, as well as HIV-2. BIC is not being developed as a stand-alone ARV, but instead exclusively as a component of an STR that also contains TAF and FTC. A new drug application (NDA) requesting FDA approval was submitted by Gilead in June; an EMA filing is anticipated this summer.

In vitro evaluations have demonstrated that BIC maintains improved activity against patient-derived HIV isolates with resistance to RAL, EVG, and DTG, with one study finding 13 of 47 isolates with high-level INSTI resistance exhibiting a greater than twofold lower resistance to BIC versus DTG.¹⁸ BIC also has a high barrier to resistance emergence, similar to that of DTG.

Clinical pharmacology evaluations indicate that BIC is well absorbed (>70%); highly bound to plasma proteins (>99%); results in plasma trough concentrations that are roughly 20-fold higher than the drug's established IC₉₅; and, similar to other INSTIs, are affected by cation-containing antacids (therefore requiring staggered administration).¹⁹ Given that BIC is a substrate of CYP3A4 and UGT1A1—inhibition or induction of both is needed for substantial pharmacokinetic changes—significant drug-drug interactions are expected to be limited. Co-administration with the CYP3A4 and UGT1A1 inhibitor atazanavir (ATV) results in a 310% increase in BIC AUC, whereas rifampin and rifabutin—both inducers of CYP3A4 and UGT1A1—are associated with BIC AUC decreases of 75% and 38%, respectively.

In a 10-day Phase I monotherapy study, BIC monotherapy demonstrated a median half-life of approximately 18 hours, with rapid, dose-dependent mean HIV RNA declines ranging from $-1.45 \log^{10}$ copies/mL in the lowest 5-mg dosing group to $-2.43 \log^{10}$ copies/mL in the highest 100-mg dosing group.²⁰ No primary integrase resistance mutations were observed in the study.

Results from a randomized, double-blind, and active-controlled Phase II clinical trial of BIC versus DTG have been reported, with 24-week primary endpoint and 48-week follow-up data reported at CROI 2017

and published in *The Lancet HIV*.^{21,22} The study randomized 98 treatment-naïve volunteers 2:1 to BIC or DTG, each combined with TAF/FTC, for 48 weeks, with all patients offered open-label BIC/TAF/FTC thereafter. Although a 75-mg BIC dose was employed in the Phase II study, a 50-mg dose is being used in the STR conformation with TAF/FTC.

The median age at baseline was 30 years in the BIC group, as compared with 36 years in the DTG group. The majority of study volunteers were male (>90% in both arms) and white (58% and 55%, respectively). Median baseline HIV RNA and CD4 counts were 25,000 copies/mL and 441 cells/mm³ in the BIC group, respectively, and 32,000 copies/mL and 455 cells/mm³ in the DTG group. Approximately 9% in the BIC group and 18% in the DTG group had viral loads above 100,000 copies/mL at baseline.

At week 24, according to the FDA-defined snapshot algorithm for the primary endpoint of virologic suppression, 97% in the BIC group had HIV RNA < 50 copies/mL, as compared with 94% in the DTG group (difference: 2.9%; 95% CI: -8.5 to 14.2). At week 48, 97% versus 91%, respectively, had HIV RNA < 50 copies/mL (difference: 6.4%; 95% CI: -6.0 to 18.8). Using a low-level viremia threshold (HIV RNA < 20 copies/mL), the regimens were also comparable: 90.8% in the BIC group, as compared with 87.9% in the DTG group (difference: 2.8%; 95% CI: -11.9 to 17.5%). Viral response was rapid, with a more than 2.5 log¹⁰ copies/mL decrease in HIV RNA in both groups by week 4.

Adherence by pill count was high in both groups through week 48: 97% among those receiving BIC, as compared with 96% among those receiving DTG. No participants discontinued treatment because of loss of efficacy and only one volunteer, in the DTG group, had HIV RNA > 50 copies/mL at week 48 and discontinued because of non-compliance. Of three participants meeting protocol-defined criteria for drug-resistance testing, an integrase mutation associated with INSTI resistance (T97A) was documented in one volunteer randomized to receive DTG. Mean increases in CD4 counts through week 48 were 258 cells/mm³ in the BIC group, as compared with 192 cells/mm³ in the DTG group.

The most common treatment-related adverse event was diarrhea (12% in both groups), followed by nausea, arthralgia, fatigue, and headache. The overall incidence of grade 2–4 laboratory abnormalities was similar in both groups (44% in the BIC group, versus 47% in the DTG group), although the rate of hyperglycemia was slightly higher in the DTG group (13% versus 8%), whereas rates of grade 2–4 AST and ALT increases were slightly higher in the BIC group (9% versus 3% and 6% versus 0%, respectively). The study also noted smaller decreases in eGFR over 48 weeks in the BIC group compared with the DTG group (-7.0 versus -11.3 mL/min), with the difference likely being a result of more pronounced inhibition of the renal transporter OCT2 and potentially MATE1 among those taking DTG versus BIC, which can lead to mild serum creatinine elevations that are not associated with progressive renal impairment.²³

Phase III trials of BIC/TAF/FTC include two head-to-head comparisons with DTG plus TAF/FTC in treatment-naïve adults, with each study enrolling 600 participants in the U.S., Canada, Belgium, France, Italy, Germany, United Kingdom, Spain, Australia, and the Dominican Republic.^{24,25} Three Phase III switch studies are also under way: one evaluating the safety and efficacy of switching from DTG plus ABC/3TC to BIC/TAF/FTC, the second evaluating a switch from boosted ATV or DRV plus either TDF/FTC or ABC/3TC, and the third evaluating a switch in a cohort comprised of HIV-positive women—all in virologically suppressed participants.^{26,27,28}

Bictegravir (GS-9883)

Long-acting formulations of ARVs have the potential to improve clinical outcomes, particularly for individuals for whom adherence continues to be difficult or infrequent injectable dosing is preferable to daily pills. These slow-release formulations might also have better tolerability and have fewer gastrointestinal-related adverse effects. In addition, they may be cheaper than oral formulations to

produce, given that they use less active pharmaceutical ingredient (API) and packaging, generate fewer distribution costs, and could potentially help overcome a lingering concern of stock-outs in low-income countries.

Downsides include injection site reactions and the fact that once a drug is administered, it cannot be removed, meaning that if drug toxicity occurs then it could be a substantial problem. In addition, a long-acting formulation can produce a subtherapeutic 'tail' that could facilitate the emergence of drug resistance if doses are not given on schedule or are discontinued without starting a new fully active regimen.

Furthest along in development are parenteral nanosuspensions of the INSTI cabotegravir (CAB) and the NNRTI RPV. As a two-drug maintenance therapy, co-administered oral versions of both drugs have comparable efficacy to three-drug therapy.²⁹

Forty-eight-week follow-up results from LATTE-2, a Phase IIb trial evaluating the long-acting versions of CAB and RPV as maintenance therapy, were presented at AIDS 2016 last July.³⁰ The study began with oral CAB plus ABC/3TC treatment for 20 weeks, with oral RPV being used for the last four weeks of the induction phase to safeguard against NNRTI hypersensitivity before administering the long-acting formulation. The study enrolled 309 treatment-naïve patients; 91% had undetectable viral loads at week 20 and were randomized 2:2:1 to one of three open-label arms: intramuscular (IM) CAB 400 mg plus RPV 600 mg every four weeks (Q4W), CAB 600 mg plus RPV 900 mg IM every eight weeks (Q8W), or oral CAB 30 mg plus ABC/3TC.

Median baseline CD4 and viral load were 489 cells/mm³ and 20,000 copies/mL (with 18% > 100,000 copies/mL). Only 8% of participants were women and 15% were black/African American.

At week 48 of the trial's maintenance period, viral suppression was documented in 92% (difference versus the oral regimen: 2.9%; 95% CI: -6.6 to +12.4), 91% (difference: 2.0%; 95% CI: -7.6 to +11.6), and 89% of participants in the Q8W, Q4W, and oral groups, respectively. Virologic non-response rates were lower in the Q4W group (<1% versus 7% in the Q8W groups), with lower non-virologic reasons (e.g., adverse events) for discontinuation in the Q8W arm (<1% versus 8% in the Q4W group and 9% in the oral CAB group).

There were three protocol-defined virologic failures (confirmed viral load > 200 copies/mL): two in the Q8W group and one in the oral CAB group, with evidence of INSTI (Q148R) and NNRTI (K103N, E138G, and K238T) resistance being documented in one Q8W CAB recipient.

Excluding injection site reactions (ISRs), tolerability was good, but higher rates of fever (3-4%) and flu-like illness (2%) were observed in the injection groups. None of the grade 3-4 side effects were judged to be related to the study drug, including a single death that was related to epilepsy.

Reports of ISRs were common, but decreased over the 48-week follow-up period: 84-86% in the IM groups at day 1, as compared with 28-30% at week 48. Most ISRs were grade 1 (82%) or grade 2 (17%), with 90% resolving within seven days. The most common ISR manifestations were pain (67%), swelling (6%), and nodules (7%). Only two participants stopped as a result of ISRs, both in the Q8W group.

In a patient satisfaction survey, between 85% and 88% of patients in the IM groups said they would be "very satisfied" to continue their present form of treatment, as compared with 55% of those in the oral CAB group.

Q4W dosing has been advanced for registration safety and efficacy evaluation in two Phase III trials, which are now under way. In the FLAIR study, treatment-naïve patients will take coformulated DTG/ABC/3TC for 20 weeks (participants who are HLA-B*5701 positive may receive DTG plus a non-ABC NRTI backbone combination), followed by randomization to either remain on their oral DTG-based regimen or switch to four weeks of oral CAB/RPV followed by 44 weeks of long-acting CAB/RPV administered every four weeks.³¹ In the ATLAS study, people living with HIV with suppressed viral loads while taking an INSTI-, PI-, or NNRTI-based regimen will be randomized to either remain on their current regimen or switch to four weeks of oral CAB/RPV followed by Q4W injections of long-acting CAB/RPV.³² Both studies are now fully enrolled at clinical trial sites throughout Africa, the Americas, Asia, and Europe.

Dolutegravir and Lamivudine

Last year's *Pipeline Report* chapter reviewing ARVs in development highlighting a number of small studies, suggesting that DTG may be sufficiently potent and resistance-averse as monotherapy—primarily as stand-alone maintenance therapy—has since given way to data indicating there is an appreciable risk of virologic rebound, with INSTI resistance, associated with using ViiV's INSTI without other ARVs.^{33,34}

The 2016 *Pipeline Report* also highlighted encouraging results from a number of small studies evaluating DTG combined with 3TC, a two-drug combination that recently yielded encouraging results in the two-phase open-label ANRS 167 LAMIDOL switch trial reported at CROI 2017.³⁵

In the first phase of LAMIDOL, 110 participants received DTG plus two NRTIs for eight weeks. In the second phase, 104 participants with HIV RNA < 50 copies/mL—three of the original 110 did not meet virologic criteria for enrolling in phase 2; three discontinued at week 8 due to adverse events—were switched to DTG plus 3TC for 40 weeks of maintenance therapy.

At baseline, the average age was 45 years and 87% were male. The average length of infection at enrollment was 6.3 years, with an average time on ARV therapy of 6.3 years. Approximately 21% of the study participants had been on an INSTI at the time of enrollment.

At week 48, 101/104 (97%) participants who entered the second phase of the study remained virologically suppressed. One of the remaining three participants was lost to follow up; a second was switched to a three-drug regimen by a study investigator, with HIV-RNA <50 copies/mL at week 40. The third experienced low-level virologic rebound at week 12 (84 copies/mL, with low-level viremia continuing after switching to DTG/ABC/3TC at week 16 and then RAL plus etravirine at week 40).

The only adverse events believed to be related to study treatment were a single case of suicide ideation in the first phase of the study and single cases of grade 4 creatine kinase and grade 4 depression in the second phase of the study.

The investigators concluded that “longer follow-up and comparative trials are needed to evaluate more precisely the role of the attractive maintenance strategy in HIV care.”

The potential for dual-drug treatment with DTG and 3TC isn't limited to maintenance therapy. The AIDS Clinical Trials Group is currently conducting a phase II study evaluating DTG and 3TC in 123 treatment-naïve volunteers entering the study with HIV RNA between 1,000 and 500,000 copies/mL, with two phase III trials of DTG and 3TC involving 1,400 first-time treatment takers in Europe, Central and South America, North America, South Africa, and Asia.^{36,37,38}

As with the continued development of DTG and RPV as dual-drug maintenance therapy, the clinical value of DTG combined with 3TC for treatment-naive patients or used as maintenance therapy, compared with that of standard three-drug therapy, remains to be determined.

The potential cost-savings implications cannot be understated, however, particularly given that generic 3TC is available globally. Investigators, under the direction of Harvard Medical School's fair HIV drug pricing champion Rochelle Walensky, MD, MPH, recently evaluated the cost-effectiveness and budget impact of DTG plus generic 3TC in place of Triumeq (with an average wholesale price of US\$31,800), either as first-line therapy or as a switch regimen.^{39,40} After applying hypothetical discounts to both the generic-inclusive combination and the innovator STR, annual costs were calculated to be US\$15,200 and US\$24,500, respectively—a \$9,300 price reduction associated with the removal of ABC and the use of generic 3TC. With additional sensitivity analyses that factored in known virologic suppression and failure rates, as well as Medicaid rebates, the investigators concluded that the incremental cost-effectiveness ratio was US\$22,500 per quality-adjusted life year (QALY) for DTG + 3TC maintenance therapy, as compared with >\$500,000 per QALY for Triumeq.

Should half of all treatment-naive people living with HIV in the U.S. initiate therapy with DTG + 3TC, cost savings would total \$550 million for induction-maintenance therapy within five years, with savings of more than \$3 billion if 25% of U.S. residents living with HIV and suppressed viral loads were switched to DTG + 3TC maintenance therapy.

Elsulfavirine (VM1500)

Elsulfavirine (ESV) is an orally bioavailable prodrug of VM-1500A, an NNRTI being developed by Viriom, a member of the Khimski, Russia-based ChemRar pharmaceutical and biotechnology conglomerate. In 2009, Roche agreed to provide Viriom with pre-clinical candidates in the NNRTI class, with the signing of a licensing agreement granting Viriom development and commercialization rights for people living with HIV in Russia, Ukraine, Belarus, and Kazakhstan.⁴¹ Viriom expects to obtain its first market registration for ESV in 2017, with development of a once-weekly oral and long-acting parenteral formulation under way.

Forty-eight-week data from a 120-person Phase IIb trial were reported at CROI 2017. Treatment-naive participants were randomized 1:1 to receive ESV (20 mg QD) or EFV plus TDF/FTC. Median baseline viral load and CD4 counts in the ESV (n = 60) and EFV (n = 60) arms were 50,000 and 63,000 copies/mL and 349 and 379 cells/mm³, respectively. Approximately 92% (n = 55) of participants completed 48 weeks of treatment in the ESV group, as compared with 78.3% (n = 47) in the EFV group (P = 0.041).

In the on-treatment analysis that included only those who completed 48 weeks of follow up, 81% had HIV RNA < 400 copies/mL in the ESV group, versus 73.7% in the EFV group—comparable, but lackluster, results. Among participants with baseline viral loads >100,000 copies (18 volunteers in the ESV group and 22 in the EFV group), 77.7% and 68.2% had HIV RNA < 400 at week 48 in the on-treatment analysis.

CD4 changes from baseline averaged 179 cells/mm³ in the ESV group and 182 cells/mm³ in the EFV group.

There were significantly more drug-associated adverse events in the EFV group in the analysis including almost all randomized participants: 77.6% versus 36.7% (P < 0.0001). Adverse events most often associated with NNRTIs, notably CNS disorders and rash, occurred in 31.7% of participants in the ESV group, versus 62.1% in the EFV group (P = 0.008). The most frequent side effects were headache (15%

and 24.1%, respectively), dizziness (6.7% and 27.6%), or sleep disorders (5% and 20.7%). Only those in the EFV group had abnormal dreams, skin rash, or pruritis.

Fostemsavir (GSK3684934)

Fostemsavir (GSK3684934, formerly BMS-663068) is an oral prodrug of the HIV attachment inhibitor temsavir (GSK2616713, formerly BMS-626529), which prevents HIV attachment to host CD4 cells by binding to gp120 and has activity against most HIV-1 subtypes, with the exceptions of AE and group O. It is currently in a Phase III clinical development program that is focused on heavily treatment-experienced patients and is one of several compounds included in ViiV Healthcare's acquisition of BMS's HIV portfolio of HIV research and development assets.⁴²

Ninety-six-week follow-up data from an international Phase IIb dose-ranging study were reported at CROI 2016, with a *post hoc* subgroup analyses reported at Glasgow 2016.^{43,44} These data follow a 24-week primary endpoint analysis published in 2015 and 48-week follow-up results published online late last year.^{45,46}

The trial randomized 254 treatment-experienced participants, all of whom had virus susceptible to RAL, TDF, and ATV, to receive fostemsavir at doses of 400 mg twice daily, 800 mg twice daily, 600 mg once daily, or 1,200 mg once daily, as compared with ritonavir-boosted ATV (ATV/r), all in combination with RAL and TDF. Sensitivity to temsavir was also an entry requirement (IC₅₀ < 100 nM).

The median age at baseline was 39 years, 60% of the participants were male, and 38% were white. The median pretreatment viral load was 4.85 log copies/mL (43% had viral loads > 100,000 copies/mL) and CD4 count was 230 cells/mm³ (38% with < 200 CD4 cells/mm³).

Given that fostemsavir 1,200 mg once daily was selected as the open-label continuation dose after week 48, the results reported at Glasgow 2016 were the pooled efficacy and safety data through week 96 (n = 200).

In the modified intent-to-treat analysis, 61% in the fostemsavir group, as compared with 53% in the ATV/r group, had viral loads < 50 copies/mL at week 96, with comparable efficacy regardless of baseline temsavir sensitivity (<0.1 nM versus ≥0.1 nM, <1 nM versus ≥1 nM, and <10 nM versus ≥10 nM). Reasons for not achieving HIV RNA < 50 copies/mL included a sizeable number of discontinuations due to lack of efficacy (32% and 41%, respectively); 11 patients (3% in the fostemsavir group, 10% in the ATV/r group) discontinued as a result of adverse events.

Virologic response rates were generally similar in fostemsavir- and ATV/r-treated patients at week 96 regardless of gender, age (<40 versus ≥40 years of age), or race (black versus white) in the observed analysis (with 90% of all subjects in both groups maintaining HIV RNA < 50 copies/mL). Response rates were also similar among patients entering with high viral loads (≥100,000 versus <100,000 copies/mL) and low CD4 counts (<200 versus ≥200 cells/mm³). The authors caution, however, that the study was not designed to detect differences in these study groups, and the analyses should therefore be interpreted with caution.

A Phase III trial of fostemsavir in treatment-experienced patients was started in February 2015 (study AI438-047) and is fully accrued.⁴⁷ Approximately 410 participants are enrolled. Entry criteria include detectable viral load > 400 copies/mL on current ARV therapy and resistance, intolerance, or contraindications to drugs in at least three classes. Participants had to be taking at least one, but no more than two, active approved drugs to be eligible for the randomized, placebo-controlled eight-

day monotherapy arm of the study. Optimized background therapy was added after day 8, with all participants receiving open-label fostemsavir (600 mg twice daily) for at least 48 weeks.

Participants without any remaining fully active approved ARVs could enroll in an open-label cohort. This arm includes the option of using the investigational monoclonal antibody ibalizumab (see below) to prevent functional monotherapy, although ibalizumab has to be procured by the individual participant and is not provided as part of the study.

The difficulty in enrolling such an experienced patient group has led to this international study having 168 trial sites in multiple countries.

SELECT DRUGS AND COFORMULATIONS: PHASE II TRIAL RESULTS

A number of biologic agents are being studied for their potential in treatment, prevention, and cure research. These are gene- and cellular-based products that are composed of sugars, proteins, and/or nucleic acids that differ from conventional ARV drugs. Notable HIV treatment candidates include the humanized monoclonal antibodies ibalizumab, PRO 140, and UB-42, and the Adnectins-based entry inhibitor BMS-986197. The broadly neutralizing antibody (bNAB) VRC01 is currently undergoing extensive clinical evaluation for primary HIV prevention (see Preventive Technologies, page 37) and as a potential strategy for controlling HIV without ARVs, along with other bNABs, including 3BNC117 and 10-1074 (see Research Toward a Cure, page 69).

Ibalizumab (TMB-355)

Ibalizumab (IBA) is an anti-CD4 IgG4 monoclonal antibody that binds to the second domain of the CD4 receptor and is not associated with known immune system effects. Developed by TaiMed Biologics and to be commercialized by Montreal-based Theratechnologies, it is expected to be the first biologic approved for the treatment of HIV infection. A Biologics License Application was filed with the FDA in May 2017 and it is currently undergoing priority review as an Orphan Drug due its limited, but extremely important, potential as a regimen component for people with multi-drug-resistant HIV. FDA approval of the intravenous (IV) formulation is expected sometime this year; an intramuscular (IM) formulation is being developed by TaiMed.

For treatment-experienced patients requiring IBA to construct a viable or tolerable ARV regimen, two open-label Phase III trials have been initiated by TaiMed to help satisfy FDA registration requirements (Cohort 2 of the second referenced Phase III trial [TMB-311] is serving as a pre-approval expanded access program for the biologic).^{48,49}

Preliminary 24-week data from the first referenced Phase III trial, TMB-301, were reported at CROI 2017.⁵⁰ Following a seven-day control period, during which 40 treatment-experienced patients were monitored on their current failing regimen, a 2,000-mg IV loading dose of IBA was administered. On day 14, the primary endpoint defined by an FDA-suggested protocol design for treatment-experienced patients that limits monotherapy and the risk of developing resistance, the percentage of study volunteers achieving a $\geq 0.5 \log^{10}$ copies/mL reduction in viral load was assessed and an optimized background regimen initiated. On day 21, an 800-mg IV maintenance dose of IBA was started and continued every two weeks through week 24.

The mean age at baseline was 51 years; 85% were male and 45% non-white. Mean duration of HIV infection at the time of study entry was approximately 21 years. The mean baseline viral load was 100,000 copies/mL; the mean baseline CD4 count was 150 cells/mm³ (17 patients had CD4 counts < 50 cells/mm³, 12 of whom had CD4 counts < 10 cells/mm³).

Phenotypic and genotypic resistance to NRTIs, NNRTIs, and PIs were common (88% to 93%), with resistance to INSTIs documented in 68% of the study participants. Thirty-five percent of participants had resistance to four classes of ARVs, with 15% having exhausted all commercially available ARV options. Approximately 43% required access to fostemsavir to improve the potency and durability of the background regimens initiative on day 14.

At the study's primary endpoint, 83% and 60% had HIV RNA reductions of at least $0.5 \log^{10}$ and $1 \log^{10}$ copies/mL, versus no more than 3% experiencing similar virologic improvements during the study's control period. At week 24, the mean viral load reduction was $1.6 \log^{10}$ copies/mL from baseline, with 55%, 48%, and 43% experiencing $\geq 1 \log^{10}$, $\geq 2 \log^{10}$, and HIV RNA < 50 copies/mL, respectively.

Virologic response rates were lower among those entering with CD4 counts < 50 cells/mm³: less than 20% had HIV RNA < 50 copies/mL, versus approximately 60% in the 50–200 and >200 baseline CD4 count strata. Mean HIV RNA reductions were also less pronounced among those with mean baseline CD4 counts < 50 cells/mm³: less than $1 \log^{10}$ copies/mL, as compared with mean reductions of $>2 \log^{10}$ copies/mL in the 50–200 and >200 baseline CD4 count strata.

Most treatment-emergent adverse events were mild to moderate in intensity, with 17 serious adverse events being reported in nine patients (one case of immune reconstitution and inflammatory syndrome [IRIS] led to treatment discontinuation). There were nine total discontinuations, eight of which occurred among those with baseline CD4 counts < 50 cells/mm³ (there were four deaths in this group—one from liver failure, one from Kaposi's sarcoma, one from 'end-stage AIDS', and one from lymphoma).

Anti-IBA antibodies were not detected in any of the patients.

Data from a Phase I monotherapy evaluation of IM IBA were also presented at CROI 2017.⁵¹ The study, conducted in Taiwan, randomized eight patients to receive 800-mg biweekly IM injections of IBA for eight weeks and six patients to receive 2,000-mg monthly IM injections for 10 weeks.

The PK profiles of biweekly IM 800-mg and monthly IM 2,000-mg IBA were comparable with profiles from a Phase II trial (TMB-202) evaluating IV IBA in treatment-experienced patients also receiving an optimized background regimen. An elevation in CD4 receptor occupancy (RO) was generally associated with increased IBA concentrations. In the 800-mg IM dosing group, the mean RO was $>85\%$ during dosing period. In the 2,000-mg IM dosing group, the mean RO was $<85\%$, but the median RO was 98% on day 28 post dose.

The maximum HIV RNA reduction ($-1.2 \log^{10}$ copies/mL in the 800-mg dosing group and $-0.8 \log^{10}$ copies/mL in the 2,000-mg dosing group) occurred on day 7 post dose and rebounded to near baseline levels after one to two weeks, with the rebounds likely a result of monotherapy-associated resistance to IBA.

No serious adverse events, discontinuations, ISRs, or anti-IBA antibodies were reported.

PRO 140

PRO 140, originally developed by Progenics and now owned by CytoDyn, is a humanized IgG4 monoclonal antibody targeting CCR5. Although PRO 140 has long been eyed as an emerging option for people with multi-drug-resistant HIV, its lack of activity against CXCR4- and mixed-tropic virus—both of which are more common in treatment-experienced patients—limits its potential in this population. CytoDyn

appears to be most interested in developing PRO 140 as a stand-alone long-acting maintenance therapy product. In July, the company requested that the FDA designate PRO 140 as an Orphan Drug “for the use in treatment-naïve adults while they are awaiting drug resistance assay results to construct a subsequent regimen.”⁵² The FDA rightfully rejected this claim, noting that it would likely exceed the 200,000-patient threshold required for an Orphan Drug designation.⁵³

Few results from clinical evaluations of PRO 140 have been published or presented in recent years. Data that have been made available over the past year—follow-up results from an extension stage of a Phase IIb study (CD01)—suggest that PRO 140’s potential as maintenance monotherapy may, in fact, be limited.

CD01 originally involved three small cohorts totaling 42 study participants on daily oral ARV therapy to assess the safety and efficacy of switching to once-weekly subcutaneous (SC) injections of 350-mg PRO 140 monotherapy. The initial extension stage data presentation at ASM Microbe 2016 in June in Boston focused on 15 of 39 participants enrolled in the first two cohorts of CD01.⁵⁴ Little more than half of the participants (21/40; 52.5%) completed 14 weeks of monotherapy without virologic failure. Of the 19 participants who did not successfully complete the CD01 follow-up period, 15 (37.5% of the original 40) experienced virologic failure. Of the remaining four who did not successfully complete 14 weeks of monotherapy in CD01, one was disqualified early in the study, three had HIV misclassified as CCR5 tropic, and, curiously, one experienced a virologic rebound after receiving Tdap immunization.

Fifteen of the 21 in the first two cohorts of CD01 who successfully completed 14 weeks of PRO 140 monotherapy entered the extension phase. Of these, four additional participants experienced virologic failure (26%); one withdrew consent. Extension phase data involving patients from all three cohorts of CD01 (an additional three patients) were presented at CROI 2017, although this only contributed one additional patient to the data set in the form of an additional virologic failure (5 of 16, or 31.25%).⁵⁵ Ten of the 16 (62.5%) extension phase participants have maintained HIV RNA < 40 copies/mL for longer than two years.

Considering the relatively high rates of virologic failure in both the initial 14-week study and the extension phase, additional data from a larger clinical trial are necessary to better understand PRO 140’s potential as stand-alone maintenance therapy. A single-arm Phase II/III trial was launched in October 2016.⁵⁶ It will shift 300 people who are virologically suppressed using a standard oral regimen to maintenance monotherapy of PRO 140 350-mg subcutaneous injections administered once a week. The primary objective is the proportion of participants without virologic failure at week 48.

Additional Phase II and III trials include CD02, a Phase IIb/III two-part study evaluating the safety and efficacy of PRO 140 used in conjunction with a failing regimen for one week in treatment-experienced patients with CCR5-tropic virus, followed by PRO 140 combined with an optimized background regimen for 24 weeks.⁵⁷ Data from this study will be used to support an initial indication for treatment-experienced individuals, potentially through the FDA’s accelerated approval mechanism.

UB-421

UB-421, an IgG1 monoclonal antibody that binds to the first domain of the CD4 receptor (with the theoretical potential to interfere with its function), is being developed by Taiwan-based United BioPharma. Unpublished data reported by the developer indicate UB-421 was associated with a mean maximum HIV RNA reduction of 1.6 log¹⁰ copies/mL in a single-dose Phase I study and mean maximum HIV RNA reductions of 2.27 and 2.45 log¹⁰ copies/mL in an eight-week Phase IIa trial of 10 mg/kg and 25 mg/kg administered intravenously every week or every other week, respectively.

Reported at CROI 2017 were data from United BioPharma's Phase II evaluation of UB-421 as maintenance monotherapy in 29 study participants with HIV RNA < 50 copies/mL while taking a standard oral regimen.⁵⁸ The study volunteers, all Taiwanese adults, were allotted to 10 mg/kg/weekly and 25 mg/kg/biweekly for a total of eight doses (eight weeks in the 10 mg/kg group; 16 weeks in the 25 mg/kg group).

At baseline, the median age was approximate 32 years, the duration of infection was approximately 5.7 years, and the CD4 count was approximately 650 cells/mm³.

Twenty-seven of the 29 study participants (93%) completed all doses with no virologic failure. Two participants in the 25 mg/kg group did not complete the study—one was lost to follow up; the other withdrew due to skin rash—but had undetectable HIV RNA for all trial visits.

Twenty-two participants resumed oral ARV therapy at the end of the UB-421 dosing period, all of whom maintained viral suppression. Five participants—three in the 10 mg/kg group, 2 in the 25 mg/kg—opted not to resume oral ARV therapy as defined by the protocol, with virologic rebound detected in all five 35 to 62 days after the last UB-421 infusion (all five eventually resumed oral therapy).

At the end of study for both arms, CD4 cell counts remained stable, whereas CD8 cell counts increased ($P < 0.05$). All subjects' CD4 T-regulatory (Treg) cell percentages were significantly reduced during the treatment period. The clinical relevance of this finding remains unknown; the investigators suggest that it demonstrates an enhancement of host immunity. Treg percentages returned to baseline following completion of UB-421.

The study presenters concluded that further study of UB-421 as maintenance monotherapy is warranted.

CONCLUSION

A number of compounds with potentially significant clinical value to people living with HIV continue to make their way through the development pipeline. The global HIV response, however, cannot thrive on scientific ingenuity alone. As ARV treatment and virologic suppression targets have been expanded globally—90% of all people diagnosed with HIV infection receiving ARV therapy by 2020, and 90% of whom having viral suppression—in the face of increasingly vulnerable domestic and international funding streams, the cost of ARV therapy remains a factor with which we must all contend. Several ARV products in development exemplify awareness of this need by the pharmaceutical industry, an encouraging sign of what will hopefully mean a reversal in drug-pricing trends that are now far beyond what markets can reasonably bear.

RECOMMENDATIONS

- Manufacturers must commit to the drug prices required to achieve cost-contained HIV care and service delivery in high-income countries.
- National and regional treatment guidelines, particularly those in the U.S., must start considering ARV prices and net costs across payer systems when refining first-line therapy recommendations. Not only is this essential to ensure that the societal benefits of affordable care are achieved, including efforts to essentially double the number of people living with HIV who are on therapy with suppressed viral loads where financial resources are finite and politically vulnerable, but also to prevent payer overreach in applying cost-containment measures where they are either unnecessary or dangerous.

- Developers and manufacturers of innovator drug products should follow the lead of companies investing in research and development to meet the HIV treatment needs in middle-income countries. These countries will be home to 70% of people living with HIV before the end of this decade and are facing both funding losses from donor agencies as well as crippling intellectual property rules that will block access to affordable generics.
- Manufacturers developing new oral drugs are strongly encouraged to follow the emerging trend of evaluating coformulations with historically potent and safe generic ARVs, notably TDF and 3TC. However, these fixed-dose combinations must be priced accordingly.
- Long-acting drug formulations and technologies carry unique structural and behavioral opportunities and challenges. Manufacturers, working in collaboration with government, academic, civil society, and community stakeholders, should commit to the health systems research and implementation science required to ensure effective scale-up.
- The development of new drugs for the treatment of multi-drug-resistant HIV should remain a priority. It is very encouraging to see progress in this area. For drugs with limited indications, including those without clear marketing potential for treatment-naïve individuals, the Orphan Drug Designation program should be explored and engaged.
- Manufacturers should continue to closely collaborate with, and invest heavily in, evidence-based research, implementation science, policy advocacy, and service delivery aimed at improving HIV diagnosis and clinical care engagement rates. Their efforts should aim to maximize the virologic suppression rates required to improve disease-free mortality and prevent ongoing transmission of the virus.

The author wishes to thank Melanie Thompson, MD, of the AIDS Research Consortium of Atlanta, and Roy M. Gulick, MD, of Weill Cornell Medicine and the TAG Board of Directors for their review of this chapter.

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Preventive Technologies: Antiretroviral and Vaccine Development

By Jeremiah Johnson and Richard Jefferys

INTRODUCTION

Recent advances in the research, development, and implementation of biomedical HIV prevention—primarily in the form of treatment as prevention (TasP) and tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) as pre-exposure prophylaxis (PrEP)—already appear to be bearing fruit in addressing complex HIV epidemics. At this year's Conference on Retroviruses and Opportunistic Infections (CROI), the Centers for Disease Control and Prevention (CDC) presented their first HIV incidence estimates in six years, showing declines in new infections overall, including among white men who have sex with men (MSM).¹ Last year, a *Lancet* article looking at incidence in Danish MSM found that, thanks to very high levels of viral suppression among HIV-positive MSM, new infections have been declining since 1996, nearly reaching the World Health Organization (WHO) elimination threshold by 2013.² A 42 percent decline in HIV diagnoses among MSM in London's Dean Street STI clinic, which diagnoses one in four of London's HIV infections, also seems strongly linked to increased testing, treatment, and community advocacy to connect men to PrEP in spite of National Health Service England's ongoing refusal to cover PrEP.³ Given the persistence of HIV epidemics among MSM, these successes indicate that we may at last have prevention tools that can end some of the most stubborn epidemics.

Not all of the news is rosy, of course. Racial disparities in the United States in new incidence rates—including stagnant rates of infections among black MSM and rising infections in Latino MSM—are a reminder that we are far from dismantling the systemic racism that underlies disparate health outcomes in communities of color. The struggle to firmly establish the visibility of transgender men and women in research and data collection continues to leave gender-nonconforming individuals exceptionally vulnerable compared with other key populations.⁴ With over 200 documented new infections, largely attributed to injection drug use, since the end of 2014 in an Indiana town of only 4,200 people, we are reminded of the fragility of earlier victories in epidemics among people who inject drugs.⁵ UNAIDS has also sounded the alarm about declining international investments in HIV, which are happening at a time when HIV infections among adults have stopped declining and are rising in some regions.⁶ While the science of HIV prevention has never been more productive, unfortunately many of our triumphs continue to be overshadowed by the social, political, and economic barriers that greatly limit access for marginalized communities.

Ongoing HIV prevention research remains hopeful, however, with many possibilities for expanding and improving our current toolbox in the pipeline. A number of highly anticipated studies have launched in the past year to build upon recent exciting breakthroughs related to oral PrEP, long-acting injectable PrEP, and vaginal rings. Gilead Sciences began recruitment in the fall of 2016 to study the efficacy of Descovy, their new tenofovir alafenamide (TAF)-based version of Truvada, as PrEP. After a number of missteps that led community advocates to call for a halt to the study—including lack of transparency and community oversight—the phase III trial is now moving forward with separate community advisory groups being convened for North American and European trial sites. Despite concerns related to the long pharmacokinetics (PK) "tail" observed with long-acting injectable cabotegravir (CAB LA), a phase III trial looking at its efficacy in MSM and transgender women launched in December of last year. A primary challenge for implementation would be that individuals may need to commit to taking oral PrEP for a year or more following their final injection in order to avoid becoming infected with HIV and developing resistance as a result of the subtherapeutic levels of cabotegravir.

The International Partnership for Microbicides (IPM) is moving ahead with follow-up assessments and analyses related to their vaginal ring containing dapivirine, which last year was reported to reduce new infections in two simultaneous studies by approximately one-third overall, with greater protection occurring in both trials among women 22 years of age and older and little to no protection among women 21 years of age and younger.⁷

One new concept for prevention of bacterial sexually transmitted infections (STIs) that has gained more attention in recent years has been the use of doxycycline as a PrEP or post-exposure prophylaxis (PEP) for gonorrhea, chlamydia, and syphilis. Although the real-world possibilities for implementation remain unclear, particularly considering ongoing concerns related to drug-resistant gonorrhea, more research is being planned to assess doxycycline for prevention.

A few short years ago, passive immunization—the infusion or injection of antibodies—was the tiniest of blips on the biomedical prevention radar. Today it represents a busy and expanding area of research, due to the discovery and characterization of an ever-increasing number of broadly neutralizing antibodies (bNAbs), which are capable of potently inhibiting diverse HIV variants from multiple global clades.⁸ Several bNAbs have been manufactured for clinical testing, and the furthest along the developmental pathway, VRC01, is the subject of two large efficacy trials known as the AMP studies.⁹ The rise of passive immunization provides an important example of how a technological breakthrough can revolutionize research: the identification of the new generation of potent bNAbs was made possible by techniques that can isolate and clone the antibodies being produced by individual B cells among many millions sampled from an individual.^{10,11,12} The U.S. National Institutes of Health (NIH), whose funding is now under serious threat from the Trump administration, provided the support for much of this critical work. In an example of cross-pollination between biomedical prevention fields, bNAbs are also undergoing evaluation in microbicide formulations.¹³

The immunological process that leads to the generation of bNAbs in some HIV-positive individuals is typically long and complex, proceeding over several years,¹⁴ and reproducing this process with a vaccine—which remains the ultimate goal for researchers—presents a stern challenge. Incremental progress has continued in preclinical studies over the past year, and trials of vaccine constructs that may have the potential to guide B cells along the first steps toward bNAb production are expected to begin in 2018.¹⁵

In the meantime, vaccine candidates capable of inducing other types of immune responses that might lead to at least some level of protection—based on lessons learned from the RV144 trial in Thailand¹⁶—have advanced into an efficacy trial in South Africa, HIV Vaccine Trials Network (HVTN) 702, which began enrolling last fall.¹⁷

Table 1. PrEP and Microbicides Pipeline 2017

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
ORAL FORMULATIONS				
TAF + FTC	NtRTI/NRTI	Gilead Sciences	Oral PrEP	Phase III
TAF + FTC	NtRTI/NRTI	CONRAD	Oral PrEP	Phase I (in cisgender women)
Genvoya (EVG + COBI + FTC + TAF)	INSTI/NtRTI/NRTI	Emory University	Oral PrEP	Phase I
LONG-ACTING FORMULATIONS				
Cabotegravir	INSTI	ViiV Healthcare	IM	Phase IIb/III
Rilpivirine	NNRTI	PATH	IM	Phase II

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
MICROBICIDE RINGS, GELS, ENEMAS, FILMS, AND OTHER INSERTABLES				
Dapivirine	NNRTI	IPM (vaginal ring and rectal gel also with MTN)	Vaginal ring	Phase IIIb
			Vaginal gel	Phase II
			Rectal gel	Phase I (planned)
			Vaginal film	Phase I
Tenofovir	NtRTI	CONRAD	Vaginal ring	Phase I
			Vaginal tablet	Phase I
Tenofovir	NtRTI	Johns Hopkins University	Enema	Phase I
MIV150	NNRTI	MTN	Rectal gel	Phase I (planned)
Elvitegravir	INSTI	MTN	Rectal insert	Phase I (planned)
IQP-0528	NNRTI	ImQuest U19	Rectal gel	Phase I
Griffithsin	Cell-viral fusion—blocking agent	U19 University of Louisville	Rectal gel	Phase I
PC-1005	NNRTI, ZA, CGN	Population Council	Vaginal and rectal gel	Phase I
MVC	EI	IPM	Vaginal and rectal gel	Phase I
MVC + dapivirine	EI/NNRTI	IPM	Vaginal ring	Phase I
MK-2048 + vicriviroc	CCR5 inhibitor/ INSTI	MTN	Vaginal ring	Phase I
Dapivirine + darunavir	NNRTI/PI	CHAARM	Vaginal gel	Phase I
DS003	EI	IPM	Vaginal tablet	Phase I
Dapivirine + DS003	NNRTI/EI	IPM	Vaginal ring	Preclinical
Darunavir	PI	IPM	Vaginal ring	Preclinical
MULTIPURPOSE TECHNOLOGIES				
Tenofovir + levonorgestrel	NtRTI/HC	CONRAD	Vaginal ring	Phase I
Dapivirine + levonorgestrel	NNRTI/HC	IPM + MTN	Vaginal ring	Phase I
MB66	Anti-HIV + anti-HSV antibodies	LeafBio, Inc.	Vaginal film	Phase I

CGN, carrageenan
COBI, cobicistat
EI, entry inhibitor
EVG, elvitegravir
FTC, emtricitabine
HC, hormonal contraception
HSV, herpes simplex virus
IM, intramuscular
IPM, International Partnership for Microbicides
MVC, maraviroc

MTN, Microbicide Trials Network
INSTI, integrase strand transfer inhibitor
NNRTI, non-nucleoside analogue reverse transcriptase inhibitor
NRTI, nucleoside analogue reverse transcriptase inhibitor
NtRTI, nucleotide analogue reverse transcriptase inhibitor
PI, protease inhibitor
PrEP, pre-exposure prophylaxis
TAF, tenofovir alafenamide
ZA, zinc acetate

ORAL FORMULATIONS

With scale-up initiatives to bolster TDF/FTC awareness and utilization where it is approved as PrEP under way—along with ongoing efforts to see that the coformulation is registered and covered by national health programs in other countries—additional oral products are making their way down the biomedical prevention pipeline.

The advantages of these compounds, which include Gilead's TAF plus FTC (Descovy) and possibly its other TAF-based single-tablet regimen product that includes elvitegravir, cobicistat, and FTC (E/C/F/TAF; Genvoya)—as PrEP remain unclear.^{18,19} Possibilities include improved markers of renal and bone safety relative to TDF-inclusive regimens. Although kidney and bone problems remain uncommon and mild and are almost always reversible following drug cessation among long-term TDF/FTC PrEP users in clinical trial and demonstration project cohorts, new oral compounds may prove to be useful for those with other risk factors (e.g., underlying renal insufficiency, baseline bone mineral deficiency, concomitant use of nephrotoxic or bone-mineral-depleting medications, and advancing age).^{20,21,22,23,24,25}

Updates for PEP have also been in the works. Last year, the CDC updated its guidelines for non-occupational PEP (nPEP).²⁶ Researchers are also looking at dolutegravir (Tivicay), elvitegravir/cobicistat/FTC/TDF (Stribild), and E/C/F/TAF as alternative PEP regimens that may improve adherence to and completion of the 28-day course of prophylaxis (see Text Box, page 41). The use of doxycycline as a PrEP and/or PEP for bacterial STIs has also gained interest in recent years, with studies presented at CROI 2015 and 2017 showing an effective reduction in STIs when doxycycline was used among MSM for prevention (see Text Box, page 43).

TAF and FTC

Like TDF, TAF is a prodrug formulation of tenofovir. Unlike TDF, which is converted in the blood to the active drug tenofovir diphosphate (TFV-DP) and then taken up into cells, TAF is primarily metabolized and converted to TFV-DP inside of cells. Using a much lower dose (25 mg), TAF achieves plasma tenofovir levels that are roughly 90 percent lower but intracellular concentrations that are approximately four- to sevenfold higher.^{27,28} The reduced systemic exposure has the potential for fewer renal- and bone-related toxicities compared with TDF. TAF's low-milligram dosing also has the potential for reduced generic production costs and, ultimately, greater affordability versus TDF/FTC in low-income countries. Hence, TAF/FTC is also being eyed as an alternative to Truvada.

Enrollment for a phase III safety and efficacy trial comparing TAF/FTC to TDF/FTC for the prevention of HIV infections in HIV-negative men and transgender women who have sex with men is underway, with an estimated study completion date of September 2020.²⁹ The DISCOVER trial is being run by Gilead Sciences, the manufacturer of both Descovy and Truvada, and began recruitment in September of 2016 with an estimated 5,000 participants set to be enrolled from across the United States, Canada, and Western Europe. Participants will be randomized to two arms, one receiving active TAF/FTC and placebo TDF/FTC and the other receiving active TDF/FTC and placebo TAF/FTC. Following community pushback, Gilead modified the initial study protocol, which called for a 30-day washout period for individuals already on Truvada for PrEP.^{30,31} After at least 96 weeks of blinded treatment, and provided that TAF/FTC shows sufficient efficacy, the study will be unblinded and participants will be offered the option to continue as part of an open-label extension of DISCOVER.

With TDF set to go off patent in the United States at the end of this year and FTC going off patent in 2021, there is little mystery as to why Gilead has taken TAF off the shelf—after development was inexplicably delayed for the past decade³²—and is now following up on the FDA approval of Descovy

for HIV treatment by aggressively pursuing a phase III trial of F/TAF as PrEP before generics can come to market. If F/TAF is shown to be noninferior, its improved safety profile may give a competitive edge to Descovy over generic TDF/3TC or, eventually, TDF/FTC. Given the already excellent safety profile of TDF/FTC, health care professionals and potential PrEP users should be wary of this scheme. While F/TAF as PrEP will be the better option for some, particularly individuals with decreases in renal function, for the vast majority of PrEP users the additional financial costs of Descovy will greatly outweigh the additional benefits compared with generics.

Researchers are confident that Descovy will be noninferior to Truvada as PrEP, given positive outcomes in nonhuman primate trials. Results from CDC evaluations of TAF plus FTC in rhesus macaques that were rectally challenged with simian-human immunodeficiency virus (SHIV) were published last year and more thoroughly covered in last year's *Pipeline Report*.³³ None of the TAF-treated macaques were infected after 19 exposures—100 percent protection—whereas the previous macaque studies of TDF/FTC suggested 94 percent protection after 14 SHIV exposures.

Making heads or tails of macaque and human tissue studies has been difficult. Despite apparent protection, rectal concentrations of TFV-DP of macaques treated with TAF were lower than those of the macaques treated in previous studies with TDF. In another study presented at CROI 2016 that looked at TFV and TFV-DP concentrations in the mucosal tissues of eight HIV-negative cisgender women, the plasma levels of TFV were 19-fold lower and peripheral blood mononuclear cell levels of TFV-DP were ninefold higher than those seen following single-dose TDF 300 mg dosing in an earlier study.³⁴ Conversely, intracellular concentrations in biopsied tissues proved to be significantly lower: twofold in cervicovaginal samples and 13-fold in rectal samples. And, compared with TDF, TAF administration resulted in a higher percentage of tissue samples with undetectable drug levels: 63 percent of the rectal and 75 percent of genital tract samples had TFV and TFV-DP concentrations below the level of detection.

While DISCOVER will seek to answer lingering questions and determine efficacy for men and transgender women who have sex with men, CONRAD has launched additional investigation aimed at assessing the pharmacology of TAF in cervicovaginal tissues as a next step for understanding the potential value of TAF as PrEP for cisgender women.³⁵ The phase I trial is estimated to be completed by October of this year and will give greater insights into whether TAF/FTC is likely to show efficacy in a larger trial.

PEP Updates

A 2014 meta-analysis of randomized and nonrandomized studies reporting completion rates for PEP revealed low levels of completion of PEP in the 28 days following a possible exposure to HIV.³⁶ Researchers have been looking for alternative regimens that might have better completion outcomes.

Last year, the CDC released an update to its 2005 nPEP guidelines listing TDF/FTC and raltegravir as the preferred regimen for nPEP, with TDF/FTC, darunavir, and ritonavir as possible alternatives.³⁷ Research has shown, however, that the second daily dose of raltegravir may be challenging for people taking nPEP to remember.³⁸ Ritonavir, with its well-known gastrointestinal side effects, may also complicate nPEP completion.

A recent study with results published in March of this year found that dolutegravir with TDF/FTC was a safe and well-tolerated option for once-daily PEP in 100 gay and bisexual Australian men in need of PEP.³⁹ PEP completion was 90 percent (95% confidence interval [CI]: 84–96%). For the 10 men who did not complete dosing, nine were lost to follow-up and one discontinued due to headache. No participant was found to acquire HIV through week 12.

Another study looking at Stribild as PEP published favorable results in November, showing that among 234 participants who effectively received PEP, 215 (92%) completed 28 days of PEP, with only three switching from Stribild to another PEP because of side effects. More than 60 percent of participants reported at least one adverse event, which were mild to moderate. Fatigue and central neurological and abdominal side effects were the most frequently reported.⁴⁰ Another study is preparing to evaluate Genvoya, Gilead's TAF-based version of Stribild, as PEP.⁴¹ Researchers are hopeful that these single-tablet regimens will be capable of further improving adherence and completion.

TDF/FTC and Pregnancy

A number of studies are looking at the role of TDF/FTC in the lives of pregnant or postpartum women and for serodiscordant couples looking to conceive. Conception and pregnancy pose unique circumstances for HIV prevention; in women trying to conceive, condoms are obviously not a viable option for protection from HIV infection, and pregnant and postpartum women have been shown to be at increased risk of HIV infection largely due to reduced condom use.⁴² While treatment as prevention may itself be enough to protect the HIV-negative partner while trying to conceive,⁴³ PrEP may contribute to peace of mind and presents a simpler, potentially cheaper, and less invasive solution than methods such as sperm washing or in vitro fertilization. It may also be a safe alternative to condoms for women during and just after pregnancy.

PrEP during pregnancy has not been specifically studied as part of randomized controlled trials; however, the safety of TDF/FTC for pregnant women and fetuses has been fairly well established. For years, HIV-positive women who have become pregnant have safely taken TDF/FTC as part of treatment with no increased likelihood of birth defects or adverse pregnancy outcomes reported in the Antiretroviral Pregnancy Registry.⁴⁴ Additionally, researchers in the Partners PrEP study observed no statistically significant pregnancy-related complications among the 288 pregnancies that happened among study participants.⁴⁵ Although pregnancy led to discontinuation from the trial and the study was not meant to specifically research PrEP during pregnancy, investigators estimate that fetuses may have been exposed to either tenofovir or TDF/FTC for a maximum of six weeks each. A study presented at HIV R4P last year also found that it was safe to breastfeed while still on PrEP.⁴⁶ Still, there has previously been some indication that pregnant women taking TDF/FTC may give birth to slightly smaller babies with reduced bone density,⁴⁷ making it preferable to reduce unnecessary exposure to TDF/FTC until better information becomes available.

The Microbicide Trials Network's ongoing EMBRACE study (MTN-016), an HIV prevention agent pregnancy exposure registry that compiles information from pregnancies that occur during biomedical prevention trials, will hopefully shed further light on the effects of TDF/FTC in expectant mothers.⁴⁸ In the

meantime, some studies are attempting to develop better screening methodologies that will help limit uptake of PrEP in pregnant women with low risk of seroconversion.⁴⁹

Two ongoing observational studies are looking specifically at PrEP as an option for safer conception.^{50,51} One from the University of California, San Francisco will compare uptake, adherence, and efficacy of PrEP, sperm washing, and/or artificial vaginal insemination offered to serodiscordant couples looking to conceive. Results from the study are expected in March 2019. Another study headed up by the University of Washington will look at pregnancy rates and HIV incidence when serodiscordant couples looking to conceive are counseled on TasP, PrEP, and timed condomless sex: results will be forthcoming in summer 2018.

Doxycycline for the Prevention of Bacterial STIs

Bacterial STIs have been shown to increase the likelihood that an individual will acquire or transmit HIV.⁵² Traditional STI prevention approaches, including behavior change related to frequency/number of sexual partners and levels of condom use, appear to be largely ineffective from a public health perspective. Syphilis rates among MSM in the United States and Western Europe have also been increasing since before the turn of the century—well before iPrEx demonstrated the efficacy of Truvada as PrEP—adding to the urgency for better, evidence-based options for the prevention of bacterial STIs.⁵³

A small pilot study released in 2015 demonstrated that the antibiotic doxycycline provided as a PrEP may be effective in reducing STI incidence.⁵⁴ The study was small, with only 30 gay men and transgender women, but it showed a statistically significant 70 percent decrease in STIs when half the participants were assigned doxycycline as PrEP and half the participants were offered financial incentives to avoid infections. Absolute numbers of syphilis, gonorrhea, and chlamydia infections were all lower in the doxycycline arm; however, the study was too small to provide statistically significant reductions when infections were broken down by specific disease.

A study presented at CROI 2017 showed that doxycycline provided as a PEP in oral HIV PrEP users led to a 47 percent reduction in bacterial STIs, with a 70 percent drop in chlamydia and a 73 percent drop in syphilis, but no reduction in gonorrhea.⁵⁵ The study randomized 232 MSM from the French Ipergay PrEP study, with half of them being provided with doxycycline for STI PEP. Those in the treatment arm were told to take a 200 mg pill up to 72 hours after each episode, though nearly every participant who took a pill did so within 24 hours. Participants were followed for 8.7 months, with 212 participants—106 in each arm, completing the study. Notably, STI percentages were extremely high in each arm, though the 38 percent annual STI incidence rate in the doxycycline arm was a significant improvement compared with 70 percent in the control arm.

Two new studies looking at doxycycline for STI prevention are being conducted by the British Columbia Centre for Disease Control.^{56,57} One is a smaller pilot study that will look at the feasibility and tolerability of using daily doxycycline for syphilis PrEP in a group of 50 HIV-negative MSM who are also taking Truvada as HIV PrEP. The second study is an early phase

I study to determine whether the daily use of doxycycline is an efficacious and acceptable intervention for syphilis prevention in a group of 288 HIV-positive MSM. The study focusing on HIV-negative men currently has an estimated completion date of December 2017, whereas the study of HIV-positive men is set to run through May 2020.

Antibiotic resistance, specifically in the case of gonorrhea, will be one of the major factors in considering the future of doxycycline as STI PrEP or PEP. Although doxycycline has not been recommended as treatment for gonorrhea for years, the threat of additional resistance remains a concern given that there are so few new antibiotics in the treatment pipeline for gonorrhea.

PrEP Breakthrough Infections

TDF/FTC (Truvada) as PrEP remains the most effective, thoroughly researched, evidence-based option for preventing sexual acquisition of HIV. Out of tens of thousands of individuals taking PrEP to date, only three cases of likely breakthrough infections have been documented, validating earlier mathematical modeling indicating that Truvada was up to 99 percent effective in preventing sexual infections if taken consistently in HIV-negative individuals. However, extremely rare instances of breakthrough infections tend to gain considerable—and disproportionate—media attention when they occur.

The first and most well-documented case of a breakthrough infection was reported in Boston at CROI 2016 regarding a Toronto gay man who reported high adherence to PrEP and consistently maintained three-month checkups with his physician.⁵⁸ Dried blood spot (DBS) analysis of tenofovir levels in red blood cells showed excellent adherence leading up to the infection, as did high plasma concentrations of tenofovir at the patient's follow-up visit, though these assessments could not completely rule out the potential for a brief lapse. Despite a high likelihood of consistent adherence, the man tested positive for HIV in April 2015—two years after starting PrEP. Resistance testing indicated that the man's virus was totally resistant to FTC and carried mutations that conferred at least partial resistance to TDF. A similar second breakthrough infection coming out of New York City with convincing, though less conclusive, documentation was reported in October in Chicago at the HIV Research for Prevention (HIVR4P) conference.⁵⁹ A gay man taking PrEP with reported good adherence was diagnosed with a strain of HIV resistant to both TDF and FTC. Due to a five-month break between visits, the man's physician was unable to fully assess adherence for the entire period, though DBS testing did indicate excellent adherence over the prior three months. Both cases indicate that TDF/FTC may not be able to prevent infection from extremely rare viruses with resistance to both medications.

A third case reported at CROI 2017, involving a gay man from Amsterdam with a strain of HIV showing no resistance mutations, has raised the possibility that on extremely rare occasions even nonresistant strains might establish infection in spite of evidence of good PrEP adherence.⁶⁰ There are many mysteries and questions in this case, however. The infection occurred in the six weeks following the man's last doctor's visit, meaning that a lapse in adherence cannot be ruled out. Also, the man reported two instances of injection drug use over the period in question, though he insisted that he had used sterile equipment.

These three cases stress the importance of routine provider visits while taking PrEP and provide greater insight into the conditions that could potentially lead to breakthrough infection. The extreme rarity of breakthrough infections confirms that although PrEP is not 100 percent effective, it remains the most effective prevention option for sexual acquisition of HIV to date.

IMPLANTS AND INJECTABLE LONG-ACTING FORMULATIONS

Improving the acceptability of PrEP is one approach to strengthening adherence rates among populations at risk for HIV infection. Investment in subcutaneous implants to deliver antiretrovirals for PrEP has increased in the last year, including significant investment by the NIH and the Bill & Melinda Gates Foundation.⁶¹ Particular focus is also being placed on the development of long-acting nanosuspension formulations of antiretrovirals with PrEP potential, which may allow for doses that are separated by weeks or months. The drug furthest along the development path is CAB LA, ViiV Healthcare's integrase strand transfer inhibitor (and dolutegravir analog); however, the unexpectedly long persistence of CAB LA in a significant minority of ECLAIR trial participants, possibly tied to higher body mass index (BMI), has led to some uncertainty about how to manage the long PK tail in some individuals. A long-acting injectable version of rilpivirine (RPV LA), Janssen's non-nucleoside analogue reverse transcriptase inhibitor (NNRTI), remains on an uncertain course.

As long-acting formulations become more likely candidates for real-world use, it is imperative that researchers and key stakeholders begin actively looking at implementation challenges early. An NIH-funded review article published in 2015 looked at the importance of addressing long-acting formulation implementation issues at three levels: patient, provider, and system.⁶² Patient-level factors include targeted education and messaging, tailored supports to enhance acceptability and uptake, and effective strategies for promoting adherence/persistence and retention in care. Provider-level factors include engaging a broad mix of providers while ensuring adequate training and support for patient assessment, counseling, and follow-up. Systems-level factors include optimal delivery modalities, resource allocation, and ensuring access to populations most in need of new prevention options.

CAB LA

Encouraging preliminary results presented at CROI 2016 from the ECLAIR trial, which looked at the safety and tolerability of CAB LA as a PrEP, have led the HIV Prevention Trials Network (HPTN) to launch the first of two planned phase III studies looking at efficacy. However, significant questions remain about optimal dosing and feasibility of implementation given the unexpectedly long persistence of CAB LA in the plasma of a minority of ECLAIR participants.

Last year's Pipeline Report gave a detailed review of the outcomes of the ECLAIR trial.⁶³ The study randomized 127 HIV-negative men between 18 and 65 years of age and at low risk of acquiring HIV at screening to either CAB (N = 106) or placebo (N = 21). For the first four weeks of the trial, oral CAB (30 mg) or placebo were administered, followed by a seven-day washout period. The injection phase began at week 5 and ended at week 41, with CAB LA 800 mg or saline being administered via intramuscular (IM) injections during visits at weeks 5, 17, and 29. CAB LA was found to be well tolerated in comparison to placebo, although a minority of participants withdrew due to injection tolerability (4%) and a small proportion experienced grade 2 events such as fever, injection site itching, and injection site swelling. Two seroconversions were reported: one in the placebo group at week 23 and one in the CAB LA group at week 53, 24 weeks after the participant's final injection; however, the participant in the CAB LA group who ultimately seroconverted had no detectable CAB in blood plasma at week 53. CAB PK data throughout each 12-week dosing interval were reported. Results showed trough concentrations to be lower than the prespecified ideal at the end of the dosing intervals in approximately two-thirds of participants. On the basis of these findings, a new dosing strategy of 600 mg IM injections every eight weeks has been selected for CAB LA's continued development.

The study also included a follow-up phase with preliminary results presented at the HIVR4P conference in October 2016. There, researchers reported that in 14 out of 86 participants (17%), drug levels of CAB LA remained above the lower limit of quantification but below the protein-adjusted 90% inhibitory concentration (PA-IC90) a year after their last injection.⁶⁴ Persistence of CAB LA was associated with a higher range of BMIs, with higher BMIs leading to a longer PK tail. Additional covariate evaluation is warranted; however, these findings raise questions about CAB LA discontinuation and the possibility of drug resistance should individuals become infected with HIV while they maintain subtherapeutic yet quantifiable levels of CAB LA a year or more beyond their last injection.

To better understand the impact of CAB LA's prolonged PK, a companion phase IIa study to ECLAIR, HPTN 077, has been extended by 24 weeks.⁶⁵ The study will aim to find out how long measurable drug levels persist and if smaller and more frequent injections of 600 mg every 8 weeks may shorten the tail. HPTN 077 has enrolled approximately 200 HIV-negative volunteers in the United States, South America, and sub-Saharan Africa. The estimated primary completion date is now set for July 2017.

Despite ongoing questions related to CAB LA persistence, HPTN 083, a phase IIb/III head-to-head safety and efficacy trial of CAB LA versus oral TDF/FTC, was launched in December 2016.⁶⁶ In step 1 of the trial, lasting five weeks, participants will receive oral TDF/FTC or oral CAB 30 mg daily, depending on the randomization. In step 2, participants will receive a daily oral placebo plus active CAB LA 3 mL injections at two time points four weeks apart and every eight weeks thereafter, or active daily oral TDF/FTC plus placebo injections, for up to 180 weeks. In step 3, to cover the prolonged PK tail associated with CAB LA dosing, all participants will be required to take daily oral TDF/FTC for at least one year, starting no later than eight weeks after the last injection. The HPTN 083 trial has a planned enrollment of 4,500 transgender and MSM individuals 18 years of age and older who are at high risk for sexually acquiring HIV infection. The estimated study completion date is June 2020.

A companion study to HPTN 083, HPTN 084, is in the final stages of development, and a final protocol was posted on the HPTN website in March 2017 with plans to begin recruitment later this year.⁶⁷ Approximately 3,200 HIV-uninfected cisgender women from sub-Saharan Africa will be enrolled and randomized 1:1 to active CAB LA and placebo TDF/FTC versus active TDF/FTC and placebo CAB LA in order to measure safety and efficacy of CAB LA in women. The study duration is expected to be 4.6 years. After the study reaches the required number of incident HIV endpoints, participants will begin an open-label daily oral TDF/FTC extension for approximately 48 weeks. As part of HPTN 084, an injectable contraceptive substudy will run simultaneously for 100 evaluable participants to study the effect of CAB LA on depot medroxyprogesterone acetate and norethisterone enanthate.

RPV LA

Encouraging phase I results from the SSAT 040 study evaluating the PK of RPV LA in plasma, the genital tract in women, and the rectum in men were published in 2014.⁶⁸ Later that year, however, preliminary data from the MWRI-01 phase I study suggested that RPV LA's activity in rectal versus cervicovaginal tissues may differ considerably.⁶⁹ Although RPV levels following single 600 mg and 1,200 mg (2 × 600 mg) doses were higher in vaginal fluids versus rectal fluids, rectal tissues were found to have twice the concentration of RPV compared with vaginal tissues. In fact, rectal cell explants were fully resistant to HIV nearly two months after the 1,200 mg RPV LA injections were given, whereas vaginal and cervical cell explants appeared to be no better protected from HIV following either dose of the RPV LA.

A more recent study characterized the concentrations of RPV needed to prevent HIV infection in mucosal tissue.⁷⁰ Although rectal tissue RPV levels appeared to be sufficient to block HIV infection—concentrations were approximately fivefold higher than what would be required to suppress viral infection—2.5-fold more drug was needed in female genital tissue to demonstrate similar inhibition. These data, the authors noted, support the explant findings from MWRI-01, in which HIV infection was suppressed in rectal tissue but not in cervicovaginal tissues.

Still under way is HPTN 076, a phase II safety and acceptability evaluation of RPV LA compared with placebo. The study is set to continue through October 2017, although preliminary results were presented at CROI 2017.⁷¹ A total of 136 (100 African, 36 U.S.) women were enrolled with a median age of 31 years. Among participants, 46 percent were married, 94 percent were black, and 60 percent were unemployed. The women were randomized (2:1) to receive either oral rilpivirine 25 mg or placebo daily for four weeks. In the absence of any safety signals, the participants received either 1,200 mg RPV LA (2 mL IM injections in both gluteal muscles) or placebo every eight weeks for a total of six injections.

Acceptability, safety, and PK data were collected throughout the study. The product was paused for any participant with a grade 2 or greater related adverse event or grade 3 or greater unrelated adverse event. Ten women withdrew (eight RPV vs. two placebo) and four had product discontinued (three RPV vs. one placebo) during the oral phase (weeks 0–4). A total of 122 (80 RPV LA vs. 42 placebo) women received one or more injections; 98 (64 RPV LA vs. 34 placebo) received all six injections. During the injection phase (weeks 4–52), one woman withdrew in the placebo group and 16 product discontinuations (10 RPV LA vs. 6 placebo) occurred. Of the product discontinuations, six (8%) RPV LA and two (5%) placebo were due to adverse events, including one placebo arm participant with prolonged QTc interval. Transient grade 2 or greater liver abnormalities occurred in nine (11%) of the RPV LA participants compared with four (10%) in the placebo arm. Three RPV LA arm participants developed grade 3 or greater injection site reactions compared with none in the placebo arm. No significant difference in adverse events was observed between the two arms. Among participants who received one or more injections, the median trough concentration (C_{trough}) of RPV was 68.2 ng/mL. At week 52 (eight weeks after last injection), the C_{trough} was 91.9 ng/mL. The concentration two weeks after the first and second injections (at weeks 6 and 14) was 85.5 ng/mL and 113 ng/mL, respectively. At the last injection visit, 61 percent of women strongly agreed that they would definitely use and 73 percent that they would think about using a PrEP injectable in the future.

Overall the injections were safe, well tolerated, and acceptable. The lower-quartile RPV concentrations were consistently above the PA-IC90 at all times through eight weeks post-injection. However, based on the conflicting PK and explant infection data reported to date, compounded by the formulation's need for cold-chain storage, there is no indication of RPV LA moving into phase III trials for PrEP.

Implantable Devices

Intarcia Therapeutics, a Boston-based company developing an implantable minipump about the size of a matchstick to deliver a drug for control of blood sugar in people with type 2 diabetes, has received a \$50 million grant from the Bill & Melinda Gates Foundation to develop minipump technology to deliver antiretroviral drugs for PrEP, with an additional \$90 million available if they are successful.⁷²

Other researchers have looked at extended-release implants containing TAF. The Oak Crest Institute for Science (Monrovia, California) published encouraging animal PK data from a study of a subdermal delivery system similar to that used for removable contraceptive rods (e.g., Norplant).⁷³ Auritec, a Pasadena drug delivery company, received NIH funding to test an implant containing TAF in dogs.⁷⁴ The 40-day study found that the implant maintained drug levels 30 times higher than those needed to protect against HIV infection throughout the study period. The Sustained Long-Acting Protection from HIV (SLAP-HIV) partnership, based at Chicago's Northwestern University and supported by a \$17 million NIH grant, is working to develop an implant that can deliver either cabotegravir, rilpivirine, TAF, or the tenofovir analogue tenofovir exalidex.⁷⁵

MICROBICIDES

Intravaginal Rings

With a growing body of data suggesting that antiretroviral-based prevention modalities are effective for women who are vulnerable to HIV infection, provided that adherence levels that are consistent, there has been considerable interest in more user-friendly and longer-acting technologies. Polymeric intravaginal rings (IVRs), similar to those used to control the release of estrogens or progestogens that provide contraceptive protection, are one such technology and are currently in various stages of development. IPM's dapivirine ring, which showed limited efficacy in sub-Saharan African women in the ASPIRE and Ring studies, has generated the most excitement; CONRAD has also completed a phase I trial for a tenofovir-containing ring.⁷⁶ IPM and CONRAD are also both looking at versions of their rings that also contain the contraceptive levonorgestrel as a multipurpose prevention tool that may better meet the needs of women seeking to avoid both HIV and unwanted pregnancies.

Dapivirine

The most clinically advanced candidate is a silicone elastomer IVR containing 25 mg dapivirine (TMC120), an NNRTI licensed to IPM by Janssen Sciences Ireland UC. Data from two registrational trials, the Microbicide Trials Network's ASPIRE study (MTN-020) and the International Partnership for Microbicides' Ring Study (IPM 027), were reported at CROI 2016, with the final ASPIRE results being simultaneously published in the *New England Journal of Medicine*.^{77,78,79}

ASPIRE, a phase III trial conducted at sites in Malawi, South Africa, Uganda, and Zimbabwe, randomized 2,629 HIV-negative women between 18 and 45 years of age to receive the dapivirine IVR or a matching placebo IVR, which were self-inserted and removed once a month for a year. The Ring Study, a phase II/III evaluation at six South African sites and one Ugandan site, compared the dapivirine IVR to a placebo IVR, inserted once every month over 24 months, in 1,959 HIV-negative women between 18 and 45.

Results from both studies, presented more comprehensively in last year's Pipeline Report, suggested that the dapivirine IVR is safe and moderately effective at reducing incident HIV in African women. HIV infection rates were reduced by approximately one-third overall, with greater protection occurring in both trials among women 22 years of age and older: 56 percent in ASPIRE and 37 percent in the Ring Study, with little to no protection among women 21 years of age and younger—most likely due to lower levels of adherence.

An updated adherence analysis from ASPIRE presented at the 21st International AIDS Conference in Durban, South Africa, found that consistent users of the ring experienced 65 percent fewer infections compared to placebo.⁸⁰ Rather than looking at blood levels of dapivirine, which may be influenced by participants reinserting the ring shortly before a follow-up visit, researchers refined their analysis by looking at the level of drug left behind in rings that were returned to researchers. A ring that has been worn for a full month should have 20–21 mg of drug remaining. Any level below 22 mg was treated as indicating medium to high adherence, whereas a ring with 23.5 mg or more indicated nonadherence. Of the 2,629 women enrolled in ASPIRE, 2,359 were included in this analysis. Compared to placebo, higher adherence to the active dapivirine ring was associated with a 65 percent (95% CI 23–84, $p=0.009$) reduction in HIV-1 risk. Results were similar both for the full-study population and when excluding the two sites with lower adherence/retention (risk reduction 67%, 95% CI: 23–86), and point estimates suggested HIV-1 protection for both women >21 years (risk reduction 72%, 95% CI: 21–90) and ≤ 21 years of age (risk reduction 50%, 95% CI: -78–86). Partial/low adherence was not significantly associated with HIV-1 protection (relative risk reduction 35%, 95% CI -10–61, $P = .12$).

Qualitative interviews with 214 participants were also published last year, providing insight into important issues related to adherence.⁸¹ The rings were largely acceptable to women; however, concerns about side effects, the appearance of the rings, and the experimental nature of the rings were highlighted as barriers. At clinical visits, women were asked, "How worried are you about having a vaginal ring inside you every day for at least a year?" While 29 percent of women reported this concern at the start of the study, only four percent of participants did so at their final follow-up clinic visit. Specific concerns related to use, health, hygiene, sexual enjoyment, and social approval also decreased significantly between the start and the end of the study.

Additionally, possible detection by male partners during sex and partner opinions were of importance to the women interviewed. Although fewer than five percent of all ASPIRE study participants reported incidents of intimate-partner-related violence or other social harms, women who did report violence or social harm within a month of the interview were nearly 2.5 times more likely to have low adherence to the ring. Younger age at enrollment, having a new primary partner, and not disclosing study participation or ring use to the primary partner were significantly associated with reporting social harms. Additional new data revealed that a majority of women—64 percent—disclosed the use of the ring to their male partners at the outset of the study, but 13 percent of study participants never revealed that they were using the ring. The investigators found that neither disclosing nor concealing use of the ring affected women's adherence to the product.

IPM plans to submit the dossier of dapivirine IVR evidence required for licensure —ASPIRE and the Ring Study are only a part of an extensive research portfolio—to regulatory agencies. Two open-label evaluations of the dapivirine IVR are in the works.^{82,83} MTN-025, the HIV Open-Label Prevention Extension (HOPE) trial, is an ASPIRE follow-on study to assess continued safety and adherence, and it is currently enrolling. IPM hopes to conduct its own open-label extension follow-on study to provide former Ring Study participants with the dapivirine IVR.

Several follow-up safety studies are planned and being implemented. A trial looking at compatibility between the dapivirine ring and an antifungal clotrimazole cream commonly used to treat vaginal yeast infections is ongoing as is a trial to assess the presence of dapivirine in the breast milk of lactating women.^{84,85} A trial looking at tampon use and menses in women using the ring has been completed. Plans to investigate the potential impact of bacterial vaginosis on ring efficacy are also underway after a substudy of 41 women from the FAME-04 vaginal microbicide study, presented at CROI 2017, found a significant correlation between higher levels of non-*Lactobacillus* bacteria and lower tenofovir levels in vaginal fluid and cervical tissue.⁸⁶

Rectal Microbicide Gel and Enemas

Researchers are largely moving away from tenofovir-based rectal gels, partially due to concerns with developing an acceptable applicator. Instead, several phase I studies are set to look at other compounds for possible gel, insert, and suppository formulations.

MTN-026/IPM 038 is a phase I, randomized, double-blind, multi-site, placebo-controlled trial designed to evaluate the safety and acceptability of dapivirine gel (0.05%) when administered rectally to healthy, HIV-1–uninfected men and women.⁸⁷ Another study, MTN-33/IPM 044, is a planned phase I study looking at the PK of the dapivirine gel when administered rectally via a vaginal applicator and a coital simulation device to healthy, HIV-1–uninfected men and transgender women. Participants will be randomized to administer a single dose of study product using an applicator of up to 10 mL of gel applied as a rectal lubricant using a phallic device to simulate anal sex. Specimens will be collected at multiple time points to assess drug concentrations, ex vivo efficacy, and biomarkers of safety. MTN-037 is a phase I trial looking at a rectal gel formulation for MIV150, a new NNRTI; MTN-039 is a phase I trial set to look at the integrase inhibitor elvitegravir as a rectal gel; and ImQuest is looking at another NNRTI-IQP-0528- in its own phase I study.⁸⁸ The cell-viral fusion–blocking agent Griffithsin, which has been shown to inhibit both HIV and herpes simplex virus (HSV) infection, is also being assessed as a possible rectal gel at the University of Louisville.⁸⁹

For at least five years, scientists have been looking at a rectal douche as a possible microbicide delivery system for protection during anal sex. Enemas, already frequently used in preparation for receptive anal sex, have the added benefit of achieving more comprehensive coverage compared with rectal gels. A challenge with developing enemas is finding the right formulation with an osmolarity that is likely to lead to cellular uptake of the ARV. At HIVR4P in October, researchers presented promising results from a nonhuman primate study involving a tenofovir-containing gel that is hypo-osmolar.⁹⁰ Four formulations were tested: two were iso-osmolar and two were hypo-osmolar. Two concentrations of tenofovir were tested: 1.76 and 5.28 mg/mL. Nonhuman primates were given a single dose via rectal insertion and evacuation of the TFV liquid medium; researchers then measured concentrations of tenofovir in their blood and in rectal tissue biopsies an hour, a day, and three days after the dose. Explant challenges with simian immunodeficiency virus (SIV) were also conducted in each case. Hypo-osmolar formulations led to faster uptake of tenofovir, with the higher dose leading to drug concentrations both in blood and inside cells that were 5–11 times higher than any of the other formulations, with no indication of damage to rectal tissues with any formulation. Biopsies taken one hour after dosing with the high-dose hypo-osmolar formulation were completely protected from infection; 24 hours after dosing, two out of six samples became infected, compared with infections in biopsies from all other microbicide doses.

A study out of Johns Hopkins University is moving forward with this concept in humans. DREAM-01 is an early phase I open-label dose-escalation and variable-osmolarity study to compare the safety, PK, pharmacodynamics, and acceptability of three formulations of a TFV enema.⁹¹ Eighteen men will be enrolled, with results expected in October of this year. The goal of the study will be to identify the dose

and osmolarity of a TFV enema for HIV PrEP that achieves the desired tenofovir diphosphate target concentrations in colonic mucosal mononuclear cells that have previously been shown to confer protection from HIV acquisition in MSM.

Vaginal Microbicide Gels

The future of vaginal microbicides remains uncertain following the disappointing data from both the FACTS 001 and VOICE studies evaluating 1% tenofovir gel.^{92,93} Given these results, CONRAD is reportedly moving away from tenofovir gels, although IVRs containing tenofovir remain in the pipeline. Although adherence, rather than potency, was believed to be the primary factor associated with poor efficacy in the FACTS 001 and VOICE studies, a number of gel-based microbicides containing alternative compounds—dapivirine, maraviroc, and a broad-spectrum coformulation of MIV-150, zinc acetate, and carrageenan (see below)—are at various stages of early development. Several of these products are also being evaluated for rectal use and protection.

PC-1005

The Population Council is developing PC-1005, a combination gel containing the NNRTI MIV-150, zinc acetate, and carrageenan. PC-1005 potentially offers protection not just against HIV but also against HSV-2 and human papillomavirus. Phase I safety, PK, acceptability, and adherence data were presented at CROI 2016 and published in JAIDS in December of last year.^{94,95,96} The trial enrolled 25 HIV-negative women between 19 and 44 years of age. Following a three-day open-label evaluation of PC-1005 in five participants, 20 women were randomized to apply PC-1005 4 mL or placebo once daily for 14 days. Seventeen women completed the randomized phase of the trial (two were lost to follow-up and one withdrew before dosing). There were no severe adverse events or early discontinuations because of adverse events. MIV-150 was absorbed systemically at low levels, and there was no measurable HIV and HPV activity in cervicovaginal lavages. Acceptability was also high: 94 percent of participants reported a willingness to use the gel in the future. Additional data also indicate that PC-1005 inhibits HIV and HSV-2 infection in cervical explants in a dose-dependent manner.

PREVENTIVE VACCINES, PASSIVE IMMUNIZATION, AND ANTIBODY GENE TRANSFER

Table 2. HIV Vaccines, Passive Immunization, and Antibody Gene Transfer Pipeline 2017

Agent	Class/Type	Manufacturer/Sponsor	Status
HIV VACCINES			
ALVAC-HIV (vCP2438) + bivalent clade C gp120/MF59	Canarypox vector encoding HIV-1 clade C gp120, clade B gp41, Gag, and protease + protein boost comprising two clade C Env proteins (TV1.Cgp120 and 1086.Cgp120)	NIAID/HVTN/Bill & Melinda Gates Foundation/South African Medical Research Council/Sanofi Pasteur/GlaxoSmithKline	Phase IIb/III
pGA2/JS7 DNA + MVA/HIV62	Prime: DNA vaccine Boost: MVA vector Both encoding Gag, Pol, and Env proteins from HIV-1 clade B	GeoVax/NIAID	Phase IIa
ALVAC-HIV vCP1521	Canarypox vector encoding HIV-1 CRF01_AE Env, clade B Gag, the protease-encoding portion of the Pol protein, and a synthetic polypeptide encompassing several known CD8+ T-cell epitopes from the Nef and Pol proteins	Sanofi Pasteur/MHRP/NIAID	Phase II

Agent	Class/Type	Manufacturer/Sponsor	Status
HIV VACCINES			
AIDSVAX B/E	AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	U.S. Army Medical Research and Materiel Command	Phase II
HIVIS 03 DNA + MVA-CMDR	Prime: HIVIS DNA encoding Env (A, B, C), Gag (A, B), reverse transcriptase (B), and Rev (B) proteins Boost: MVA-CMDR encoding Env (E), Gag (A), and Pol (E) proteins	Vecura/Karolinska Institutet/SMI/MHRP	Phase II
LIPO-5	Five lipopeptides composed of CTL epitopes from Gag, Pol, and Nef proteins	INSERM-ANRS	Phase II
VICHREPOL	Chimeric recombinant protein composed of C-terminal p17, full p24, and immunoreactive fragment of gp41 with polyoxidoonium adjuvant	Moscow Institute of Immunology/Russian Federation Ministry of Education and Science	Phase II
Ad26.Mos.HIV MVA-Mosaic gp140 protein	Ad26 vectors encoding mosaic Env, Gag, and Pol MVA vectors encoding mosaic Env, Gag, and Pol gp140 protein boost	Janssen Vaccines & Prevention B.V./NIAID/MHRP/ IAVI/Beth Israel Deaconess Medical Center	Phase I/IIa
ALVAC-HIV (vCP2438) Bivalent clade C gp120/MF59 Bivalent clade C gp120/AS01B	Canarypox vector encoding HIV-1 clade C gp120, clade B gp41, Gag, and protease + protein boost comprising two clade C Env proteins (TV1.Cgp120 and 1086.Cgp120) with either MF59 or AS01B adjuvant	NIAID/GlaxoSmithKline/Sanofi Pasteur	Phase I/IIa
DNA-C + NYVAC-C	Prime: DNA vaccine encoding clade C Env, Gag, Pol, and Nef proteins Boost: NYVAC-C attenuated vaccinia vector encoding clade C Env, Gag, Pol, and Nef proteins	GENEART/Sanofi Pasteur/CAVD	Phase I/II
MYM-V101	Virosome-based vaccine designed to induce mucosal IgA antibody responses to HIV-1 Env	Mymetics	Phase I/II
DNA-HIV-PT123 + AIDSVAX B/E	DNA vectors encoding HIV-1 clade C Gag, gp140, and Pol-Nef AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	NIAID	Phase Ib
Cervicovaginal CN54gp140-Hsp70 conjugate (TL01)	HIV-1 clade C gp140 protein with Hsp70 adjuvant, delivered intravaginally	St George's, University of London/European Union	Phase I
DCVax + poly-ICLC + MVA-CMDR	Recombinant protein vaccine including a fusion protein comprising a human monoclonal antibody specific for the dendritic cell receptor DEC-205 and the HIV Gag p24 protein, plus poly-ICLC (Hiltonol) adjuvant, followed by a boost with MVA-CMDR encoding Env, Gag, and Pol proteins	Rockefeller University	Phase I
DNA-HIV-PT123, NYVAC-HIV-PT1, NYVAC-HIV-PT4, AIDSVAX B/E	DNA and NYVAC vectors encoding HIV-1 clade C Gag, gp140, and Pol-Nef AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	NIAID/IPPOX/EuroVacc/HVTN	Phase I
DNA + Tiantan vaccinia vector	Prime: DNA vector, with or without electroporation Boost: replication-competent recombinant Tiantan vaccinia strain vector Both encoding Gag, Pol, and Env proteins from HIV-1 CN54	Chinese Center for Disease Control and Prevention/ National Vaccine and Serum Institute/Peking Union Medical College	Phase I
EN41-FPA2	Gp41-based vaccine delivered intranasally and intramuscularly	PX Therapeutics/European Commission	Phase I

Agent	Class/Type	Manufacturer/Sponsor	Status
HIV VACCINES			
GEO-D03 DNA + MVA/HIV62B	Prime: DNA vaccine with GM-CSF adjuvant Boost: MVA vector Both vaccines encode Gag, Pol, and Env proteins from HIV-1 clade B and produce VLPs	GeoVax/NIAID	Phase I
GSK HIV vaccine 732461 (F4)	Gag, Pol, and Nef fusion protein in proprietary adjuvant AS01	GlaxoSmithKline	Phase I Prime-boost Phase I with Ad35-GRIN
MAG-pDNA, Ad35-GRIN/ENV	Multi-antigen DNA vaccine encoding the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVAX, IL-12 pDNA adjuvant, delivered using the electroporation-based TriGrid delivery system + two Ad35 vectors, one encoding HIV-1 clade A Gag, reverse transcriptase, integrase, and Nef, and the other encoding HIV-1 clade A Env (gp140)	IAVI/Profectus Biosciences/Ichor Medical Systems	Phase I
MAG-pDNA, rVSVIN HIV-1 Gag	Multiantigen DNA vaccine encoding the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVAX, IL-12 pDNA adjuvant, attenuated replication-competent rVSV vector encoding HIV-1 Gag	Profectus Biosciences/HVTN	Phase I
MV1-F4-CT1	Recombinant measles vaccine vector encoding HIV-1 clade B Gag, Pol, and Nef	Institut Pasteur	Phase I
MVA.HIVA	MVA vector encoding HIV-1 clade A Gag protein and 25 CD8+ T-cell epitopes	IDT/University of Oxford/Medical Research Council/University of Nairobi/Kenya AIDS Vaccine Initiative	Phase I in infants born to HIV-positive (PedVacc002) and HIV-negative (PedVacc001) mothers
MVA HIV-B	MVA vector encoding HIV-1 Bx08 gp120 and HIV-1 IIIB Gag, Pol, and Nef	Hospital Clinic of Barcelona	Phase I
PENNVAX-G DNA + MVA-CMDR	Prime: DNA vaccine encoding HIV-1 clade A, C, and D Env proteins and consensus Gag protein Boost: MVA-CMDR live attenuated MVA vector encoding HIV-1 clade CRF_AE-01 Env and Gag/Pol proteins DNA component administered intramuscularly via either Biojector 2000 or CELLECTRA electroporation device	NIAID/MHRP/Walter Reed Army Institute of Research	Phase I
PolyEnv1 EnvDNA	Vaccinia viruses encoding 23 different Env proteins and DNA vaccine encoding multiple Env protein	St. Jude Children's Research Hospital	Phase I
pSG2.HIVconsv DNA + ChAdV63. HIVconsv, or MVA.HIVconsv	Prime: DNA vaccine pSG2 Boost: chimpanzee adenovirus vector ChAdV63 or MVA vector All contain the HIVconsv immunogen, designed to induce cross-clade T-cell responses by focusing on conserved parts of HIV-1	University of Oxford	Phase I
Ad35-ENVA	Ad35 vector encoding HIV-1 clade A Env	Vaccine Research Center/NIAID	Phase I
rVSVIN HIV-1 Gag	Attenuated replication-competent rVSV vector encoding HIV-1 Gag	Profectus Biosciences/HVTN	Phase I

Agent	Class/Type	Manufacturer/Sponsor	Status
HIV VACCINES			
SAAVI DNA-C2, SAAVI MVA-C, clade C gp140/MF59	SAAVI DNA and MVA vectors encoding an HIV-1 clade C polyprotein including Gag-reverse transcriptase-Tat-Nef and an HIV-1 clade C truncated Env + Novartis protein subunit vaccine comprising a clade C oligomeric V2 loop-deleted gp140 given with MF59 adjuvant	SAAVI/HVTN/Novartis	Phase I
SeV-G(NP), Ad35-GRIN	Sendai virus vector encoding HIV-1 Gag protein delivered intramuscularly or intranasally, Ad35 vector encoding HIV-1 clade A Gag, reverse transcriptase, integrase, and Nef	IAVI/DNAVEC	Phase I
LIPO-5, MVA HIV-B, GTU-MultiHIV	Five lipopeptides comprising CTL epitopes from Gag, Pol, and Nef proteins MVA vector encoding Env, Gag, Pol, and Nef proteins from HIV clade B DNA vector encoding fusion protein comprising elements from six different HIV proteins Given in four different prime-boost combinations	INSERM-ANRS	Phase I Phase II
Ad4-mgag, Ad4-EnvC150	Live, replication-competent recombinant Ad4 vectors encoding HIV-1 clade C Env and HIV-1 mosaic Gag proteins Formulated either as enteric-coated capsules for oral administration or as an aqueous formulation for tonsillar administration	NIAID/PaxVax	Phase I
DNA Nat-B Env, NYVAC Nat-B Env DNA CON-S Env, NYVAC CON-S Env DNA mosaic Env, NYVAC mosaic Env	Prime: DNA vector encoding Nat-B, CON-S, or mosaic Env proteins Boost: NYVAC vectors encoding Nat-B, CON-S, or mosaic Env proteins	HVTN/IPPOX/CHAVI	Phase I
DNA, MVA-C, CN54rgp140 + GLA-AF	DNA vectors encoding a Gag-Pol-Nef polypeptide and gp140 Env protein, both from clade C MVA-C vector encoding Gag-Pol-Nef and gp120 Env protein from clade C HIV-1 clade C gp140 protein and GLA-AF delivered intramuscularly	Imperial College London/Medical Research Council/Wellcome Trust	Phase I
GTU-MultiHIV	DNA vector encoding fusion protein comprising elements from six different HIV proteins, administered by intramuscular, intradermal, or transcutaneous routes	Imperial College London/European Commission-CUT-HIVAC Consortium	Phase I
DNA Nat-B Env DNA CON-S Env DNA mosaic Env MVA-CMDR	Prime: DNA vector encoding Nat-B, CON-S, or mosaic Env proteins Boost: MVA vector encoding Env (E), Gag (A), and Pol (E) proteins	NIAID/CHAVI/IPPOX/MHRP/HVTN	Phase I
Trimeric gp140	Protein vaccine consisting of a trimeric gp120	Crucell/NIAID/Beth Israel Deaconess Medical Center	Phase I
MVA mosaic	MVA vectors encoding HIV-1 mosaic proteins	Crucell/MHRP/NIAID/Beth Israel Deaconess Medical Center	Phase I
DNA-HIV-PT123 AIDSVAXB/E	DNA vectors encoding HIV-1 clade C Gag, gp140, and Pol-Nef AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	EuroVacc/IAVI/Uganda Medical Research Council/UVRI Uganda Research Unit on AIDS/Centre Hospitalier Universitaire Vaudois	Phase I
Oral Ad26	Orally administered replicating Ad26 vector encoding mosaic Env protein	IAVI/University of Rochester/Beth Israel Deaconess Medical Center	Phase I

Agent	Class/Type	Manufacturer/Sponsor	Status
HIV VACCINES			
PENNAX-GP HIV-1 DNA vaccine IL-12 DNA adjuvant	DNA vector encoding Gag, Pol, and Env proteins + DNA vector encoding IL-12 adjuvant, delivered via intradermal or intramuscular electroporation	NIAID	Phase I
IHV01 (FLSC-001)	Full-length single-chain gp120-CD4 complex vaccine	University of Maryland/Bill & Melinda Gates Foundation/Profectus BioSciences, Inc.	Phase I
HIV DNA-C CN54ENV + recombinant HIV CN54gp140	DNA vector encoding HIV-1 clade C Env delivered intramuscularly and intradermally Clade C Env protein boost	Imperial College London	Phase I
Ad26.Mos.HIV + clade C gp140	Ad26 vectors encoding mosaic HIV-1 Env, Gag, and Pol + clade C HIV Env protein boost	Janssen Vaccines & Prevention B.V.	Phase I
HIV-1 Nef/Tat/Vif, Env pDNA + HIV-1 rVSV envC	DNA vector encoding HIV-1 Nef/Tat/Vif and Env Attenuated replication-competent rVSV vector encoding HIV-1 clade C Env	NIAID	Phase I
Ad4-mgag, Ad4-EnvC150 + AIDSVAX B/E	Orally administered replication-competent Ad4 HIV vaccine in combination with AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	PaxVax, Inc./NIAID	Phase I
Trivalent Ad26.Mos.HIV, tetravalent Ad26.Mos4.HIV + clade C gp140	Ad26 vectors encoding mosaic HIV-1 Env, Gag, and Pol or Ad26 vectors encoding two mosaic HIV-1 Envs, mosaic Gag, and Pol + clade C HIV Env protein boost	Janssen Vaccines & Prevention B.V.	Phase I
Tetravalent Ad26.Mos4.HIV + clade C gp140 ± mosaic gp140	Ad26 vectors encoding two mosaic HIV-1 Envs and mosaic Gag and Pol + clade C HIV Env protein boost ± mosaic HIV Env protein boost	Janssen Vaccines & Prevention B.V.	Phase I
MVA/HIV62B + AIDSVAX B/E	MVA vector encoding Gag, Pol, and Env proteins from HIV-1 clade B to produce VLPs + AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	NIAID	Phase I
DNA-HIV-PT123 Bivalent clade C gp120/MF59 Bivalent clade C gp120/AS01B	DNA vaccine encoding HIV-1 clade C Gag, gp140, and Pol-Nef + protein boost comprising two clade C Env proteins (TV1.Cgp120 and 1086.Cgp120) with either MF59 or AS01B adjuvant	NIAID	Phase I
DNA-HIV-PT123 + clade C gp120/MF59	DNA vaccine encoding HIV-1 clade C Gag, gp140, and Pol-Nef + protein boost comprising two clade C Env proteins (TV1.Cgp120 and 1086.Cgp120) in MF59 adjuvant		
PASSIVE IMMUNIZATION			
VRC01	Monoclonal bNAb administered intravenously	NIAID/HVTN/HPTN	Phase IIb
10-1074	Monoclonal bNAb administered intravenously	Rockefeller University	Phase I
3BNC117 + 10-1074	Monoclonal bNAbs administered intravenously	Rockefeller University	Phase I
P2G12	Monoclonal neutralizing antibody administered intravenously	St George's, University of London	Phase I
PGT121	Monoclonal bNAb administered intravenously	IAVI	Phase I

Agent	Class/Type	Manufacturer/Sponsor	Status
VRC01	Monoclonal bNAb administered subcutaneously or intravenously	NIAID	Phase I (adults and HIV-exposed infants)
VRC01LS	LA monoclonal bNAb administered subcutaneously or intravenously	NIAID	Phase I
VRC07-523LS	LA monoclonal bNAb administered intravenously or subcutaneously	NIAID	Phase I
ANTIBODY GENE TRANSFER			
rAAV1-PG9DP	Recombinant AAV vector encoding the PG9 broadly neutralizing antibody	IAVI/NIAID/CHOP	Phase I

AAV, adeno-associated virus

Ad4, adenovirus serotype 4

Ad26, adenovirus serotype 26

Ad35, adenovirus serotype 35

BNAb, broadly neutralizing antibody

CAVD, Collaboration for AIDS Vaccine Discovery

CHAVI, Center for HIV/AIDS Vaccine Immunology

CHOP, Children's Hospital of Philadelphia

CMDR, Chiang Mai double recombinant

CTL, cytotoxic T lymphocyte

GLA-AF, glucopyranosyl lipid adjuvant (aqueous formulation)

GM-CSF, granulocyte-macrophage colony-stimulating factor

Hsp70, heat shock protein 70

HVTN, HIV Vaccine Trials Network

IAVI, International AIDS Vaccine Initiative

IDT, Impfstoffwerk Dessau-Tornau

IL, interleukin

INSERM-ANRS, French National Institute for Health and

Medical Research-French National Agency for Research on

AIDS and Viral Hepatitis

LA, long-acting

MHRP, U.S. Military HIV Research Program

MVA, modified vaccinia Ankara strain

NIAID, U.S. National Institute of Allergy and Infectious

Diseases

Poly-ICLC, polyinosinic-polycytidylic acid with polylysine and

carboxymethylcellulose

rVSV, recombinant vesicular stomatitis virus

SAAVI, South Africa AIDS Vaccine Initiative

SMI, Swedish Institute for Infectious Disease Control

UVRI, Uganda Virus Research Institute

VLP, virus-like particle

PASSIVE IMMUNIZATION/ANTIBODY GENE TRANSFER

The Antibody-Mediated Prevention (AMP) trials represent a collaborative effort between the NIH-funded HVTN and the HPTN. The efficacy of the bNAb VRC01 will be assessed in two populations: HVTN 704/HPTN 085 aims to enroll 2,700 MSM and transgender individuals who have sex with men at sites in Brazil, Peru, and the United States, whereas HVTN 703/HPTN 081 will recruit 1,500 sexually active women at sites in Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zimbabwe. The antibody is delivered by inpatient infusion every eight weeks, which is not ideal, but a key goal of the studies is to define protective bNAb levels and thus inform the development of potentially more potent and convenient bNAb formulations. Results are anticipated by 2022.

In addition to these large efficacy trials, there are a growing number of early-phase studies of more recently discovered bNAbs that have been demonstrated to have greater breadth and potency than VRC01. These include 3BNC117⁹⁷, 10-1074⁹⁸, PGT121⁹⁹, and VRC07-523LS.¹⁰⁰

A combination of 3BNC117 and 10-1074 is also being tested, which may be an augury of the future because resistance to individual bNAbs could limit their efficacy when used alone. VRC07-523LS represents a derivative of a parent bNAb, VRC07, modified to enhance potency, breadth, and persistence in the body, thereby reducing dosing frequency—another strategy that may become more common as researchers seek ways to make passive immunization with bNAbs more user-friendly. The phase I VRC07-523LS trial is evaluating both intravenous and subcutaneous delivery.

Over the past several years, there has been considerable attention given to a potential one-shot bNAb delivery approach known as antibody gene transfer. The method draws from gene therapy research, employing adeno-associated virus (AAV) vectors modified with the genetic code for producing the bNAb of interest. Upon injection into muscle tissue, the AAV vector acts as a factory for persistent generation of the bNAb.¹⁰¹ Promising results have been reported in the SIV/monkey model,^{102,103} and the first human trial—a collaboration between the scientist Phil Johnson and the International AIDS Vaccine Initiative (IAVI)—is ongoing, involving the bNAb PG9. A recent monkey study has illuminated a potential downside, however—the approach can induce the production of antibodies against the bNAbs, significantly reducing the levels that are maintained.¹⁰⁴ Additional research will be required to better understand this problem and develop ways to address it.

Several research groups are exploring the possibility of administering bNAbs in microbicide formulations. A combination of three of the earliest generation of bNAbs to be discovered, 4E10, 2F5, and 2G12, has been evaluated in a phase I clinical trial and found to be safe.¹⁰⁵ Antibody levels capable of inhibiting HIV were detectable in cervicovaginal secretions for up to eight hours after administration, and no systemic absorption was observed. A first-in-human trial launched last year is testing the bNAb VRC01 and an antibody against HSV¹⁰⁶ delivered in a vaginal film (see table 1); the product is named MB66, and the antibodies are being produced in a new system using genetically modified tobacco plants.¹⁰⁷ The potential for delivering MB66 via vaginal ring is also under investigation.¹⁰⁸ A separate group of researchers has also used tobacco plants to produce a version of the 2G12 antibody designated P2G12; a single vaginal administration has been shown to be safe,¹⁰⁹ and an ongoing trial at St George's, University of London is now assessing intravenous delivery.

HIV VACCINES

The most significant recent news for the vaccine field has been the launching of HVTN 702, the first HIV vaccine efficacy trial to be conducted in seven years.¹¹⁰ Led by principal investigator Glenda Gray, the protocol plan is to enroll 5,400 men and women between the ages of 18 and 35 years who are at risk for HIV infection at 15 sites in South Africa. Participants will be randomized to receive placebo or ALVAC vCP2438 (a canarypox vector encoding HIV-1 clade C gp120, clade B gp41, Gag, and protease) plus a boost consisting of two clade C HIV gp120 proteins in MF59 adjuvant. The ALVAC vector is administered alone at baseline and after one month, and then in combination with the gp120 boost at months 3, 6, and 12.

The rationale for the study is derived from RV144, a large efficacy trial conducted in Thailand, which demonstrated that vaccination with similar candidates led to a small but statistically significant 31.2 percent reduction in risk of HIV acquisition.¹¹¹ Of potential importance, the final boost in RV144 was given at six months, and there is evidence that protection may have peaked at around 60 percent after one year of follow-up and then declined as vaccine-induced immune responses waned—this has led to the inclusion of an additional booster after 12 months in HVTN 702.

The vaccine regimen has been tailored for the South African setting, where HIV-1 clade C is prevalent. A preparatory trial conducted in South Africa, HVTN 100, evaluated whether the vaccines induced the types of immune responses that were associated with protection in RV144 in the majority of South African recipients, in order to decide whether the larger efficacy trial was justified. As reported at the International AIDS Conference in Durban last year, the immune response criteria—which included binding antibodies to clade C gp120 antigens, V1V2 antibodies to clade gp70 scaffold antigens, and CD4+ T-cell responses to HIV Env—were all met.¹¹²

There is one aspect of HVTN 702 that has proven slightly controversial, and that is the selection of the adjuvant for the gp120 protein boost. The purpose of adjuvants is to help stimulate the induction of immune responses against the antigens in the vaccine, and in RV144 the gp120 protein boost was delivered with the common adjuvant alum. In HVTN 702, a proprietary squalene-based adjuvant developed by Novartis Vaccines (since acquired by GlaxoSmithKline) named MF59 is being used.

The controversy derives from a macaque experiment conducted by the research group of Genoveffa Franchini at the U.S. National Cancer Institute, which aimed to recapitulate the RV144 results in animals. The researchers reported that while the RV144 vaccine regimen showed some protective efficacy against an SIV challenge, this was not seen in a group of macaques that received the gp120 protein boost with MF59 instead of alum.¹¹³ Analyses also indicated that the alum adjuvant had activated particular genes related to innate immunity and that this was linked to protection against SIV challenge. However, these were post hoc findings because the experiment was not designed or statistically powered to compare the adjuvants, and a subsequent macaque study with an alum adjuvant (albeit not precisely the same) did not duplicate the results.¹¹⁴ Other researchers, including HVTN director Lawrence Corey, have pointed out that protection against SHIV infection has been reported in some macaque studies employing MF69 as a vaccine adjuvant,¹¹⁵ countering Franchini's suggestion that it could have a negative effect.¹¹⁶ The debate has not altered the design of HVTN 702, but it is possible the issue could be revisited if no protection is observed; regular interim evaluations will be carried out by a data safety monitoring board, and the trial can be halted early if there is evidence the vaccines are failing or harmful.

An update on the status of HVTN 702 was provided on a webinar hosted by AVAC on May 8, 2017, by protocol co-chair Fatima Laher from Chris Hani Baragwanath Hospital in Soweto. The first immunizations began in October 2016 and, as of April 2017, 526 participants have been enrolled. Laher noted that the protocol has undergone a revision, with version 2 including additional details on the HIV prevention package offered to participants, including updated information related to obtaining access to PrEP. Collection of DBS samples from participants using PrEP has also been added in order to obtain data on Truvada drug levels.¹¹⁷

PrEP in Biomedical Prevention Trials

The efficacy of Truvada PrEP has raised difficult questions regarding how it should be integrated into trials of biomedical prevention interventions, whether vaccines, passive immunization, microbicides, or alternative forms of PrEP. Current UNAIDS/WHO guidelines¹¹⁸ recommend that clinical trials provide access to proven "state of the art" HIV prevention modalities for clinical trial participants, and an experimental intervention is tested to find out whether it can further reduce the risk of HIV acquisition when given in addition to these modalities. But Truvada PrEP is so efficacious that if all trial participants were to use it consistently as part of a background prevention package, evaluating whether a new experimental intervention has any significant effect on HIV risk would become extremely challenging—perhaps impossible.

PrEP is not necessarily ideal for everyone, however, and this means that there remains a need to develop other user-friendly biomedical prevention technologies and also that trial participants who choose not to use PrEP (or for whom PrEP is not recommended) can ethically be included as participants in clinical trials. The HVTN 704/HPTN 085 AMP trial offers one

example of how the issue of PrEP provision is currently being addressed: Truvada PrEP is being offered free of charge to all participants. Those participants based in the United States who choose to receive Truvada PrEP are referred to a program that integrates provision of the drug into their primary health care. Participants in Peru and Brazil, where Truvada is not yet licensed for PrEP, will be referred to demonstration projects.

In contrast, the HVTN 703/HPTN 081 AMP trial is offering information on Truvada PrEP and referrals to access programs where possible but is not providing the drug itself. The protocol explains that this approach is based on differing recommendations for PrEP use in women and the lack of local regulatory approvals, but it acknowledges HIV prevention standards are continually evolving and states “arrangements for provision of PrEP in this trial will take into account current evidence regarding PrEP efficacy in the populations to be enrolled in this trial, community consultation, guidance from international/regional/national/local and other regulatory authorities, and advice from persons/groups with bioethics and human subjects protection expertise.”

The differences between the protocols—both of which were reviewed and approved by multiple stakeholders, including community members and regulators—highlight the current gray areas regarding PrEP provision in biomedical prevention trials, which have been a topic of extensive discussion in the scientific literature.^{119,120,121} These discussions are likely to continue for the foreseeable future.

In addition to HVTN 702 and the work surrounding it, there is a second major thrust in HIV vaccine research being driven by Janssen Vaccines & Prevention B.V., part of the Janssen Pharmaceutical Companies of Johnson & Johnson. The company is sponsoring multiple studies involving combinations of two viral vectors—adenovirus serotype 26 (Ad26) and modified vaccinia Ankara strain (MVA)—and clade C gp140 Env protein boosts, with the goal of launching a first proof-of-concept efficacy trial in the near future. A key element of the program is the use of mosaic HIV antigens designed to induce immune responses capable of recognizing diverse viral variants. The research is being carried out in collaboration with Beth Israel Deaconess Medical Center/Harvard, the Bill & Melinda Gates Foundation, HVTN, IAVI, the U.S. Military HIV Research Program, the National Institute of Allergy and Infectious Diseases, and the Ragon Institute.

Several of the HIV vaccine trials that have begun over the past year are related to the Janssen program. Ad26 vectors are being administered as the priming immunizations in trivalent and tetravalent mixtures: the former includes two mosaic Gag-Pol antigens and a mosaic Env, and the latter adds a second mosaic Env. Booster immunizations comprise the same Ad26 mixtures or MVA vectors encoding two mosaic Gag-Pol-Env antigens and/or a soluble gp140 Env trimer protein (the trimeric form of Env more closely mimics the natural HIV Env protein). In some cases a second mosaic version of the gp140 Env protein¹²² is also included.

The groundwork for the effort was laid by experiments in the macaque model demonstrating significant protective efficacy against both SIVmac251 and SHIV-SF162P3 challenges.¹²³ The highest degree of protection has been observed in recipients of Ad26 prime followed by Ad26 plus gp140 protein boost; the regimen was associated with a 94% reduction in per-exposure risk of infection, and eight out of a

group of 12 macaques (66%) remained uninfected after six SHIV-SF162P3 challenges.¹²⁴ Correlates of protection included binding antibodies against the Env protein, Env-specific T-cell responses, and functional antibodies capable of inducing antibody-dependent cellular phagocytosis, a process in which antibodies promote the killing of virus-infected cells.¹²⁵

If all goes according to plan and immune response targets are met in the preparatory studies, a placebo-controlled efficacy trial (HPX2008/HVTN 705) will be launched in late 2017 or early 2018. The aim is to enroll 2,600 sexually active women aged between 18 and 35 at sites in South Africa, Zambia, Zimbabwe, Malawi, and Mozambique. The likely regimen would be the tetravalent Ad26 vector mix administered at months 0, 3, 6, and 12, with soluble gp140 Env trimer protein boosts added at months 6 and 12. The Env protein will be delivered in an alum adjuvant, so the trial may be able to contribute information to the discussion regarding the importance of alum to the protection documented in RV144.

The fate of the diverse collection of other experimental HIV vaccine candidates in the pipeline will almost certainly be significantly influenced by the outcomes of HVTN 702 and the Janssen program. No extant candidate is capable of inducing bNAbs, which remains the holy grail for the vaccine field, and so more information is required regarding the protective potential of non-neutralizing immune responses in order to rationally assess the relative promise of the current crop of contenders. That does not diminish the importance of continuing to develop vaccine candidates in order to have options for future efficacy trials as the science advances. Over the past year, updates have been offered on a variety of approaches, including intranasally administered Sendai virus vectors,¹²⁶ DNA/MVA regimens^{127,128,129} (including constructs developed by Geovax designed to encode virus-like particles¹³⁰), and a NYVAC plus Env protein combination.¹³¹ Planning is also underway to conduct a first-in-human trial of a CMV vector,¹³² which has generated considerable interest due to evidence that it led to clearance of a highly pathogenic SIV when administered prophylactically to macaques.^{133,134}

CONCLUSION

Despite encouraging signs that available prevention options may be diminishing HIV incidence in some areas, the need for increased global access and additional, more user-friendly biomedical prevention tools—particularly an effective vaccine—remains dire. The current pipeline is diverse but heavily dependent on increasingly constrained public and philanthropic funding.

The political climate in the United States, which is by far the largest financier of scientific research, is extremely concerning—the Trump administration has demonstrated a distinct antiscience bent, exemplified by its budget proposals that slash support for the NIH and CDC. The instability of the administration and the countervailing views of many congressional leaders may lessen the likelihood that these cuts will manifest, or at least reduce their severity, but vigilance is essential regarding the potential impact on biomedical HIV prevention research.

RECOMMENDATIONS

- Research sponsor and investigator adherence to Good Participatory Practice (GPP) guidelines¹³⁵ is essential in all biomedical prevention trials, particularly in the post-iPrEx era. Gilead ran into extensive pushback after developing the study protocol for the DISCOVER trial without sufficiently engaging community advocates. The trial initially required a 30-day washout period for any interested participant already taking Truvada as PrEP, which raised several ethical red flags for community advocates. Had Gilead worked with an existing trial network with more experience in working with the community, or had they initially engaged the community in a way that was in line with GPP guidelines, several complications could have been avoided.

- There is an urgent need for researchers, key stakeholders, and community advocates to establish basic ethical standards for the provision of Truvada as PrEP in HIV prevention trials. All parties involved have an obligation to determine the best way to ethically offer PrEP to participants in a way that doesn't lead to impossibly large clinical efficacy trials for new technologies.
- Additionally, ethical recruitment guidelines for clinical trials are needed for the post-PrEP era. There are a number of potential recruitment pitfalls that need to be considered; explicitly advertising the possibility of PrEP access in recruitment materials for a randomized controlled trial testing the efficacy of an unproven technology or misrepresenting the trial as a PrEP access study are just a few potentially unethical scenarios that arose with the launch of the DISCOVER trial.
- Clinical trials continue to underrepresent a number of priority populations, including youth and transgender men and women. In the United States, underrepresentation of people of color is a chronic problem in research. Researchers and funding entities should consistently require plans for recruitment of these key priority populations as part of study protocol or be required to explain why they do not find that specific recruitment is necessary or feasible. Studies should include individuals from priority populations at numbers that allow for the possibility of statistically significant outcomes. Recruiting only a handful of transgender women and then including that population in the title of the study is misleading and inadequate.
- In anticipation of long-acting injectable technologies, a recent NIH-funded review article looked at what would be necessary to fully implement these new modalities and bring them to scale. This should be standard practice for any prevention technology that seems likely to be approved for broader use; addressing implementation as an afterthought leads to significant delays in access, particularly for marginalized communities that are most in need of new options.
- As new technologies come closer to market, prices set for novel preventive technologies should be judged not only in terms of potential out-of-pocket costs for key populations, but also by the likely system-wide costs and the anticipated burden on the health care system. Pricing products solely based upon what the market will bear—as Gilead did when it set the price of its hepatitis C cure at \$96,000 for a standard course of treatment—forces private and public payers to either explicitly or implicitly ration access via arbitrary restrictions or create unnecessary hurdles. When bringing a product to market, companies should be required to provide a plan for ensuring easy, unfettered universal access, particularly when public funding has gone into any portion of the foundational research.
- Despite a moderately improved safety profile of F/TAF compared with TDF/FTC, health care providers and community members should be wary of paying higher prices for Descovy as PrEP and of discouraging uptake of potential generic PrEP options. Should Descovy prove to be noninferior as PrEP, it will be of enormous benefit for potential PrEP users with compromised renal function but will not be worth the additional cost for the majority of individuals.

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Research Toward a Cure and Immune-Based Therapies

By Richard Jefferys

INTRODUCTION

The research effort to cure HIV infection has continued to expand over the past year. The National Institute of Allergy and Infectious Diseases (NIAID) at the U.S. National Institutes of Health (NIH) announced the funding of six new Martin Delaney Collaboratorships (up from three funded previously), which are collaborative research enterprises focused on discovering an HIV cure named after the renowned activist and founder of Project Inform.¹ The grants run for five years, with each awardee tackling the challenge from slightly different angles. The recipients are:

- BEAT-HIV: Delaney Collaboratory to Cure HIV-1 Infection by Combination Immunotherapy - Wistar Institute, Philadelphia
- BELIEVE: Bench to Bed Enhanced Lymphocyte Infusions to Engineer Viral Eradication - George Washington University, Washington, D.C.
- Collaboratory of AIDS Researchers for Eradication (CARE) - University of North Carolina, Chapel Hill
- Combined Immunologic Approaches to Cure HIV-1 - Beth Israel Deaconess Medical Center, Boston
- defeatHIV: Cell and Gene Therapy for HIV Cure - Fred Hutchinson Cancer Research Center, Seattle
- Delaney AIDS Research Enterprise to Cure HIV - University of California, San Francisco (UCSF)

Details on each Collaboratory were presented by the lead investigators at the 2016 NIAID Strategies for an HIV Cure Workshop, and these presentations are available online as part of the archived meeting videocast.²

The most recent data on global financing of HIV cure research—collected by the International AIDS Society Towards an HIV Cure Initiative, AVAC, and the HIV Vaccines & Microbicides Resource Tracking Working Group—demonstrates progressive growth.³ Total support in 2015 was \$201.8 million, up from \$160.8 million in 2014. The NIH remains by far the largest contributor, accounting for more than three quarters of the total. According to a presentation by Paul Sato from the Office of AIDS Research (OAR) at an advisory council meeting last fall, research specifically identified as pertaining to an HIV cure now represents 6% of the total NIH HIV/AIDS research budget.⁴ Sato noted that this percentage does not include all of the substantial support for HIV basic science research, which generates many critical clues relevant to the pursuit of a cure. The proportion of NIH HIV/AIDS funding dedicated to cure research is certain to increase as grants expire in areas that are now considered to be low priority.⁵

Scientific progress has been significant, but incremental. There remains only one individual considered to be cured of HIV infection, Timothy Ray Brown, who in early 2017 celebrated ten years since his receipt of the stem cell transplants that led to his being cured of both a serious cancer (acute myelogenous leukemia) and HIV.⁶ Attempts to duplicate the outcome in other HIV-positive individuals requiring stem cell transplants for cancers are ongoing, but no similar successes have yet been reported.⁷ There have, however, been two additional reports of individuals experiencing a transient state of no detectable HIV activity in the absence of antiretroviral therapy (ART).

In one case presented by Nathan Cummins from the Mayo Clinic in Rochester, the HIV reservoir was greatly diminished as a result of cancer therapy, including a stem cell transplant, and there was a period of 288 days after ART was discontinued before HIV viral load reappeared and treatment was reinitiated.⁸

The second case involved an individual in whom HIV infection was detected extraordinarily early, as it occurred during a short window between screening for a pre-exposure prophylaxis (PrEP) program and starting the first dose of PrEP. The individual was switched from PrEP to ART in a matter of days (when the baseline HIV test results became available), and HIV rapidly became undetectable by multiple measures, including assessments of virus reservoirs. A careful interruption of ART was later undertaken and no HIV was subsequently detectable for 220 days, at which point a rebound in viral load occurred and ART was restarted. This latter case, initially described by Hiroyu Hatano from UCSF prior to the ART interruption,⁹ has not yet been formally presented, but was briefly cited by Jintanat Ananworanich in a cure research plenary delivered at the 2017 Conference on Retroviruses and Opportunistic Infections (CROI).¹⁰

These two individuals join the Mississippi baby¹¹ and two Boston patients¹² as examples of prolonged HIV remission. The number of cases is small, but they offer important evidence that dramatically reducing or limiting the size of the HIV reservoir can lead to a significant delay in the reemergence of the virus. A key challenge for the cure research field is to shrink the HIV reservoir to the point where viral load rebound is delayed for life in most individuals—mathematical modeling indicates this will likely require reductions of greater than 10,000-fold (>99.99%).¹³ Although the number of clinical trials of interventions that may have reservoir-reducing potential continues to increase (see Table 1), the largest declines in HIV reservoir measures that have been reported thus far are on the order of 40%,¹⁴ emphasizing the fact that the research is still at an early stage. Alternative strategies that don't necessarily rely on reservoir depletion—such as those that attempt to induce immune control of HIV and/or protect vulnerable cells with gene therapy—continue to be evaluated, with some recent hints of progress (see below for combination approaches).

Significant advances have occurred in understanding how HIV persists despite ART. Controversy has long surrounded the question of whether ART completely suppresses HIV replication in most recipients, but data has emerged over the past year that strongly favors the conclusion that it does.^{15,16} These studies found no evidence of HIV evolving during ART in adherent individuals, indicating that ongoing HIV replication is not a major mechanism of viral persistence. The results are likely to lessen interest in intensifying ART with additional antiretrovirals in cure research trials.

Focus is instead shifting to the role of proliferation of CD4 T cells containing latent HIV in maintaining viral reservoirs in the face of treatment; a growing body of evidence suggests that this phenomenon may be of central importance.¹⁷ Proliferation is part of the normal life and times of CD4 T cells, and can be driven by nonspecific signaling from immune system proteins (such as cytokines and chemokines) or by a specific response to an antigen recognized by the CD4 T cell (such as an influenza protein). Recent studies have demonstrated that CD4 T cells latently infected by HIV generate daughter cells containing a copy of the same virus when they proliferate, thereby expanding the number of cells harboring latent HIV.¹⁸ Although many HIV copies are defective,¹⁹ it is now well documented that proliferation of latently infected CD4 T cells can also increase the number of replication-competent viruses.^{20,21,22} These findings have spurred interest in studying the potential of anti-proliferative interventions to reduce or limit the HIV reservoir—an example of how basic science research can generate leads to translate into therapeutic trials.

Another potential breakthrough that has recently emerged from the realm of basic science is the identification of a cell surface marker, CD32a, which is expressed by a significant proportion of CD4 T cells that contain latent HIV.²³ This finding, if confirmed, should make it far easier to isolate latently infected CD4 T cells from individuals on ART so that they can be studied in the laboratory. In addition, the marker may offer a means of targeting the latent reservoir for elimination more specifically.

Scientists are also beginning to investigate population-specific differences in HIV persistence that may be relevant to the development of a cure. A project supported by amfAR recently debuted results showing

that the HIV reservoir may generate less viral genetic material in women than in men,²⁴ perhaps as a consequence of interactions between estrogen and estrogen receptors on CD4 T cells.²⁵ The first study comparing HIV reservoir measures in an African versus North American setting was published in May 2017;²⁶ the researchers found that the levels of replication-competent HIV were about threefold lower in a cohort of individuals on ART in the Rakai District Uganda compared with counterparts in Baltimore, USA. One possibility is that environmentally driven immune activation in the African setting²⁷ shortens the lifespan of CD4 T cells that might otherwise harbor latent HIV long-term, but further investigations are required to understand the reason for the results.

Interest in developing therapies for use in conjunction with ART has waned considerably in recent years. This is largely the result of the impressive efficacy and tolerability of modern ART regimens, which are associated with life expectancies for many HIV-positive people that are increasingly comparable to similar HIV-negative individuals.²⁸ Concerns persist, however, regarding populations whose residual risk of HIV-associated morbidity and mortality remains elevated despite ART.²⁹ These include people with a history of injection drug use and those who experience poor immune reconstitution despite HIV suppression (dubbed immunologic non-responders, INRs³⁰), a problem that is associated with late initiation of ART and older age.³¹ Inflammation and immune senescence (age-related dysfunction of immune cells) can also persist despite ART and may be linked to earlier onset of age-related morbidities such as frailty, neurocognitive impairment, and cardiovascular disease.³²

The pipeline of approaches that may address these concerns and further reduce risk of morbidity and mortality when added to ART is not completely dry, but is currently comprised of intermittent drips. Academic investigators primarily drive the research in this area, with little contribution from pharmaceutical companies (likely as a result of uncertainty about the potential market). Efforts are ongoing to pry open the spigot and promote a more robust flow of candidates for populations who might stand to benefit.

Table 1. Research Toward a Cure 2017: Current Clinical Trials and Observational Studies

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
ADOPTIVE IMMUNOTHERAPY				
Reconstitution of HIV-specific immunity against HIV	T cell therapy	NCT02563509	Guangzhou 8th People's Hospital	Phase I/II
HXTC: HIV 1 antigen expanded specific T cell therapy	HIV 1 antigen expanded specific T cell therapy	NCT02208167	University of North Carolina, Chapel Hill	Phase I
ANTIBODIES				
Vedolizumab	Anti- $\alpha_4\beta_7$ integrin antibody	NCT03147859	Ottawa Hospital Research Institute	Phase II
VR01	Broadly neutralizing monoclonal antibody	NCT02664415 (closed to enrollment)	National Institute of Allergy and Infectious Diseases (NIAID)	Phase II
3BNC117	Broadly neutralizing monoclonal antibody	NCT02446847 (closed to enrollment)	Rockefeller University	Phase I/II
3BNC117	Broadly neutralizing monoclonal antibody	NCT02588586 (closed to enrollment)	Rockefeller University	Phase I/II

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
10-1074	Broadly neutralizing monoclonal antibody	NCT02511990 (closed to enrollment)	Rockefeller University	Phase I
3BNC117 + 10-1074	Broadly neutralizing monoclonal antibodies	NCT02825797	Rockefeller University	Phase I
PGT121	Broadly neutralizing monoclonal antibody	NCT02960581 (enrolling by invitation only)	International AIDS Vaccine Initiative	Phase I
Vedolizumab	Anti- $\alpha_4\beta_7$ integrin antibody	NCT02788175	NIAID	Phase I
VRC01LS	Long-acting broadly neutralizing monoclonal antibody	NCT02840474	NIAID	Phase I
VRC01	Broadly neutralizing monoclonal antibody in acute HIV infection	NCT02591420	NIAID	Phase I
VRC01	Broadly neutralizing monoclonal antibody	NCT02471326 (closed to enrollment)	NIAID	Phase I
ANTI-FIBROTIC				
Losartan	Angiotensin receptor blocker	NCT01852942	University of Minnesota	Phase II
Telmisartan	Angiotensin receptor blocker	NCT02170246	Yale University	Phase I
ANTI-INFLAMMATORY				
Canakinumab	IL-1 β inhibitor	NCT02272946	University of California, San Francisco	Phase II
Metformin	Antidiabetic	NCT02659306	McGill University Health Center	Phase I
ANTIRETROVIRAL THERAPY				
Dolutegravir in reservoirs		NCT02924389	Emory University	Phase N/A
HIV reservoir dynamics after switching to dolutegravir in patients on a PI/r based regimen	Switching from ritonavir-boosted protease inhibitor to dolutegravir	NCT02513147	Hospital Universitari Vall d'Hebron Research Institute	Phase IV
ABX464	Inhibitor of HIV RNA export	NCT02735863	Abivax S.A.	Phase II
ABX464	Inhibitor of HIV RNA export	NCT02990325	Abivax S.A.	Phase I/II
ANTIRETROVIRAL THERAPY IN HIV CONTROLLERS				
Emtricitabine + rilpivirine + tenofovir		NCT01777997 (closed to enrollment)	AIDS Clinical Trials Group/NIAID	Phase IV
COMBINATIONS				
Maraviroc, dolutegravir, dendritic cell vaccine, auranofin, nicotinamide		NCT02961829 (closed to enrollment)	Federal University of São Paulo	Not listed
Perturbing of HIV reservoir with immune stimulation: Fluarix, Pneumovax vaccines		NCT02707692	University of California, San Diego	Not listed

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
Impact of Sirolimus and maraviroc on CCR5 expression and the HIV-1 reservoir in HIV+ kidney transplant recipients		NCT02990312	University of Maryland	Phase IV
ROADMAP: romidepsin + 3BNC117	HDAC inhibitor + broadly neutralizing antibody	NCT02850016	Rockefeller University	Phase IIa
eCLEAR: romidepsin + 3BNC117	HDAC inhibitor + broadly neutralizing antibody	NCT03041012	Aarhus University Hospital	Phase II
Panobinostat + pegylated interferon-alpha2a	HDAC inhibitor + cytokine	NCT02471430	Massachusetts General Hospital	Phase II
Research In Viral Eradication of HIV Reservoirs (RIVER): ART, ChAdV63. HIVconsv and MVA. HIVconsv vaccines, vorinostat	Therapeutic vaccines + HDAC inhibitor	NCT02336074 UK CPMS18010 (closed to enrollment)	Imperial College London	Phase II
SB-728mR-T + cyclophosphamide	Autologous CD4 T cells gene-modified via messenger RNA to inhibit CCR5 expression + transient chemotherapy	NCT02225665 (closed to enrollment)	Sangamo BioSciences	Phase I/II
SB-728-T + cyclophosphamide	Autologous CD4 T cells gene-modified via adenovirus vector to inhibit CCR5 expression + transient chemotherapy	NCT01543152 (closed to enrollment)	Sangamo BioSciences	Phase I/II
AGS-004 + vorinostat	Personalized therapeutic vaccine utilizing patient-derived dendritic cells and HIV antigens + HDAC inhibitor	NCT02707900	NIAID	Phase I
DCV3 + pegylated interferon	Dendritic-cell-based vaccine pulsed with autologous heat-inactivated HIV + cytokine	NCT02767193 (not yet open for enrollment)	Judit Pich Martínez, Fundació Clínic per la Recerca Biomèdica	Phase I
MVA.HIVconsv + romidepsin	Therapeutic vaccine + HDAC inhibitor	NCT02616874 (closed to enrollment)	IrsiCaixa	Phase I
SB-728mR-T + cyclophosphamide	Autologous CD4 T cells gene-modified via messenger RNA to inhibit CCR5 expression + transient chemotherapy	NCT02388594	University of Pennsylvania	Phase I
CD4-ZETA ± interleukin-2 (IL-2)	Gene-modified T cells + cytokine	NCT01013415 (closed to enrollment)	University of Pennsylvania	Phase I
GENE THERAPIES				
Cal-1: dual anti-HIV gene transfer construct	Lentiviral vector encoding a short hairpin RNA that inhibits expression of CCR5 and a fusion inhibitor (C46)	ACTRN12615000763549	Calimmune	Phase I/II
Cal-1: dual anti-HIV gene transfer construct	Lentiviral vector encoding a short hairpin RNA that inhibits expression of CCR5 and a fusion inhibitor (C46)	NCT01734850 (closed to enrollment) NCT02390297 (long term safety phase)	Calimmune	Phase I/II

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
VRX496	Autologous CD4 T cells modified with an antisense gene targeting the HIV envelope	NCT00295477 (closed to enrollment)	University of Pennsylvania	Phase I/II
SB-728mR-HSPC	Autologous hematopoietic stem/progenitor cells gene-modified to inhibit CCR5 expression	NCT02500849	City of Hope Medical Center	Phase I
MazF-T	Autologous CD4 T cells gene-modified with MazF endoribonuclease gene to inhibit HIV	NCT01787994 (closed to enrollment)	Takara Bio/University of Pennsylvania	Phase I
C34-CXCR4	Autologous CD4 T cells gene-modified to express HIV-inhibiting peptide C34	NCT03020524	University of Pennsylvania	Phase 0
GENE THERAPIES FOR HIV-POSITIVE PEOPLE WITH CANCERS				
Gene therapy in treating patients with human-immunodeficiency-virus-related lymphoma receiving stem cell transplant	Stem cells gene-modified with CCR5 shRNA/TRIM5alpha/TAR decoy	NCT02797470	AIDS Malignancy Consortium	Phase I/II
HIV-resistant gene-modified stem cells and chemotherapy in treating patients with lymphoma and HIV infection	Stem cells gene-modified to abrogate CCR5 expression and encode an HIV entry inhibitor C46	NCT02343666	Fred Hutchinson Cancer Research Center	Phase I
Gene-modified HIV-protected stem cell transplant in treating patients with HIV-associated lymphoma	Stem cells gene-modified to abrogate CCR5 expression and encode an HIV entry inhibitor C46	NCT02378922 (suspended)	Fred Hutchinson Cancer Research Center	Phase I
Safety of transplantation of CRISPR CCR5 modified CD34+ cells in HIV-infected subjects with hematological malignances	Stem cells gene-modified to abrogate CCR5 expression using CRISPR technology	NCT03164135	307 Hospital of PLA (Affiliated Hospital of Academy to Military Medical Sciences)	Not listed
Gene therapy and combination chemotherapy in treating patients with AIDS-related non-Hodgkin lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-shI-TAR-CCR5RZ)	NCT02337985	City of Hope Medical Center	Not listed
Busulfan and gene therapy after frontline chemotherapy in patients with AIDS-related non-Hodgkin lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-shI-TAR-CCR5RZ) + cyclophosphamide conditioning	NCT01961063	City of Hope Medical Center	Not listed

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
Gene-therapy-treated stem cells in patients undergoing stem cell transplant for intermediate-grade or high-grade AIDS-related lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-sh1-TAR-CCR5RZ)	NCT00569985 (closed to enrollment)	City of Hope Medical Center	Not listed
HORMONES				
Somatotropin	Human growth hormone	NCT03091374	McGill University Health Center	Phase II
IMAGING STUDIES				
Radiolabeled broadly neutralizing anti-HIV antibody 3BNC117 + Copper-64 radio isotope followed by MRI/PET scanning to detect HIV in vivo		NCT03063788	Bayside Health	Phase I
IMMUNE CHECKPOINT INHIBITORS				
Durvalumab in solid tumors	Anti-PD-L1 antibody	NCT03094286	Spanish Lung Cancer Group	Phase II
Pembrolizumab	Anti-PD-1 antibody in people with HIV and relapsed, refractory, or disseminated malignant neoplasms	NCT02595866	National Cancer Institute (NCI)	Phase I
Nivolumab + ipilimumab	Anti-PD-1 antibody + anti-CTLA-4 antibody in people with advanced HIV-associated solid tumors	NCT02408861	National Cancer Institute (NCI)	Phase I
IRON CHELATORS				
Deferiprone		NCT02456558 (closed to enrollment)	ApoPharma	Phase I
JANUS KINASE INHIBITORS				
Ruxolitinib		NCT02475655	NIAID	Phase II
LATENCY-REVERSING AGENTS				
Chidamide	HDAC inhibitor	NCT02513901	Tang-Du Hospital	Phase I/II
Poly-ICLC	TLR-3 agonist	NCT02071095 (closed to enrollment)	Nina Bhardwaj, MD/Campbell Foundation/Oncovir, Inc.	Phase I/II
Romidepsin	HDAC inhibitor	NCT01933594	AIDS Clinical Trials Group/NIAID/Gilead	Phase I/II
Vesatolimod in ART-treated HIV controllers	TLR-7 agonist	NCT03060447	Gilead Sciences	Phase Ib
Vesatolimod (formerly GS-9620)	TLR-7 agonist	NCT02858401	Gilead Sciences	Phase Ib
ALT-803	Recombinant human super agonist interleukin-15 complex	NCT02191098	University of Minnesota - Clinical and Translational Science Institute	Phase I
Kansui	Traditional Chinese medicine containing ingenols	NCT02531295 (suspended)	UCSF	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
OBSERVATIONAL STUDIES				
ACTG A5321	Decay of HIV-1 reservoirs in subjects on long-term antiretroviral therapy: The ACTG HIV reservoirs cohort (AHRC) study	Not listed yet, see ACTG website entry for information	AIDS Clinical Trials Group	N/A
Analytic treatment interruption (ATI) to assess HIV cure	Antiretroviral treatment interruption	NCT02437526 (enrolling by invitation only)	Mayo Clinic	N/A
Biomarkers to predict time to plasma HIV RNA rebound	Antiretroviral treatment interruption	NCT03001128	AIDS Clinical Trials Group	N/A
CLEAC	Comparison of late versus early antiretroviral therapy in HIV-infected children	NCT02674867 (not yet open for enrollment)	French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	N/A
CODEX (the "Extreme" cohort)	Long term non-progressors and HIV controllers	NCT01520844	French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	N/A
Effects of dolutegravir-based regimen on HIV-1 reservoir and immune activation	Effects of dolutegravir-based regimen on HIV-1 reservoir and immune activation	NCT02557997	University Hospital, Strasbourg, France	N/A
EPIC4	Early pediatric treatment initiation cohort study	CTN S 281	Canadian Institutes of Health Research (CIHR)/ Canadian Foundation for AIDS Research (CANFAR)/ International AIDS Society (IAS)	N/A
Establish and characterize an acute HIV infection cohort in a high-risk population	Establish and characterize an acute HIV infection cohort in a high-risk population	NCT00796146	Southeast Asia Research Collaboration with Hawaii/ Armed Forces Research Institute of Medical Sciences/ Thai Red Cross AIDS Research Centre	N/A
EURECA	Exploratory study of cellular reservoirs in blood	NCT02858414	Centre Hospitalier Universitaire de Besancon	N/A
HEATHER	HIV reservoir targeting with early antiretroviral therapy	UK CPMS17589	University of Oxford/Medical Research Council/British HIV Association	N/A
HIV-STAR	HIV sequencing after treatment interruption to identify the clinically relevant anatomical reservoir	NCT02641756 closed to enrollment	University Hospital, Ghent	N/A
Host and viral factors associated with HIV elite control		UK CPMS16146	University College London Hospitals NHS Foundation Trust	N/A
HSCT-HIV	Allogeneic hematopoietic stem cell transplantation in HIV-1-infected patients	NCT02732457	Kirby Institute	N/A
Identification and quantification of HIV CNS latency biomarkers	Identification and quantification of HIV CNS latency biomarkers	NCT02989285	St Vincent's Hospital, Sydney	N/A
ImmunoCo27	Co-adaptation between HIV and CD8 cellular immunity	NCT02886416	French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	N/A
Impact of ART adherence on HIV persistence and inflammation		NCT02797093	University of Colorado, Denver	N/A

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
ISALA	Analytical treatment interruption in HIV-positive patients	NCT02590354	Institute of Tropical Medicine, Belgium	N/A
LoViReT	Low viral reservoir treated patients	NCT02972931	IrsiCaixa	N/A
Post-analytic treatment interruption study		NCT02761200 (closed to enrollment)	South East Asia Research Collaboration with Hawaii	N/A
Predictors of time to viremia with an analytic treatment interruption	Predictors of time to viremia with an analytic treatment interruption	NCT03033017	University of Minnesota - Clinical and Translational Science Institute	N/A
Quantitative measurement and correlates of the latent HIV reservoir in virally suppressed Ugandans	Quantitative measurement and correlates of the latent HIV reservoir in virally suppressed Ugandans	NCT02154035	NIAID	N/A
TESO VIR	Tracking and exploring the source of viral rebound (ART interruption)	NCT03117985	Centre Hospitalier Régional d'Orléans	N/A
The use of leukapheresis to support HIV pathogenesis studies		NCT01161199	University of California, San Francisco	N/A
mTOR INHIBITORS				
Everolimus	Impact of everolimus on HIV persistence post kidney or liver transplant	NCT02429869	UCSF	Phase IV
Sirolimus	Safety and efficacy of sirolimus for HIV reservoir reduction in individuals on suppressive ART	NCT02440789	ACTG	Phase I/II
PROTEASOME INHIBITORS				
Ixazomib		NCT02946047	Nathan W. Cummins, M.D.	Phase I/II
STEM CELL TRANSPLANTATION				
BMT CTN 0903	Allogeneic transplant in individuals with chemotherapy-sensitive hematologic malignancies and coincident HIV infection	NCT01410344 (closed to enrollment)	National Heart, Lung, and Blood Institute (NHLBI)/ National Cancer Institute (NCI)/ Blood and Marrow Transplant Clinical Trials Network	Phase II
Maraviroc in HIV-1+ individuals requiring allogeneic hematopoietic cell transplant	Maraviroc in HIV-1+ individuals requiring allogeneic hematopoietic cell transplant	NCT03118661 (not yet open for enrollment)	Washington University School of Medicine	Phase I
HIVECT	HIV eradication through cord-blood transplantation	NCT02923076	Puerta de Hierro University Hospital	N/A
IMPAACT P1107	Cord blood transplantation using CCR5-Δ32 donor cells for the treatment of HIV and underlying disease	NCT02140944	IMPAACT/NIAID/Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)	N/A
THERAPEUTIC VACCINES				
iHIVARNA-01	TriMix & HIV antigen naked messenger RNA	NCT02888756	Rob Gruters, Erasmus Medical Center	Phase IIa

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
GTU-multiHIV + LIPO-5	DNA + lipopeptide vaccines	NCT01492985 (closed to enrollment)	French National Institute for Health and Medical Research/French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	Phase II
GTU-MultiHIV B-clade + MVA HIV-B	DNA + viral vector vaccines	NCT02972450 (not yet open for enrollment)	Inserm/ANRS	Phase II
VAC-3S	Peptide-based vaccine	NCT02041247 (closed to enrollment)	InnaVirVax	Phase II
VAC-3S	Peptide-based vaccine	NCT02390466 (closed to enrollment)	InnaVirVax	Phase I/ IIa
Tat Oyi	Tat protein vaccine	NCT01793818 (closed to enrollment)	Biosantech	Phase I/II
THV01	Lentiviral-vector-based therapeutic vaccine	NCT02054286 (closed to enrollment)	Theravectys S.A.	Phase I/II
Ad26.Mos.HIV + MVA-Mosaic	Adenovirus and modified Vaccinia Ankara strain vectors encoding mosaic HIV antigens	NCT02919306 (closed to enrollment)	Janssen Vaccines & Prevention B.V.	Phase I
Recombinant adenovirus type 5 vaccine	Viral vector vaccine	NCT02762045	Centers for Disease Control and Prevention, China	Phase I
iHIVARNA-01	TriMix and HIV antigen naked messenger RNA vaccine	NCT02413645 (closed to enrollment)	Biomedical Research Institute August Pi i Sunyer (IDIBAPS)	Phase I
MAG-pDNA + rSVIN HIV-1 Gag	DNA + viral vector vaccines	NCT01859325 (closed to enrollment)	NIAID/Profectus Biosciences, Inc.	Phase I
TRADITIONAL CHINESE MEDICINE				
Triptolide wilfordii		NCT02219672	Peking Union Medical College	Phase III
TREATMENT INTENSIFICATION/EARLY TREATMENT				
LEOPARD: Latency and Early Neonatal Provision of Antiretroviral Drugs Clinical Trial	Combination antiretroviral therapy	NCT02431975	Columbia University	Not listed
New Era Study: Treatment with multi-drug class (MDC) HAART	Combination antiretroviral therapy	NCT00908544 (closed to enrollment)	MUC Research GmbH	Not listed
Antiretroviral regime for viral eradication in newborns	Combination antiretroviral therapy	NCT02712801 (not yet open for enrollment)	National Center for Women and Children's Health, China CDC	Phase IV
DGVTRU: Immediate initiation of antiretroviral therapy during 'hyperacute' HIV infection	Combination antiretroviral therapy	NCT02656511	UCSF	Phase IV
DIORR: Dolutegravir Impact on Residual Replication	Combination antiretroviral therapy	NCT02500446	University of Melbourne	Phase IV

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
DRONE: Impact of starting a dolutegravir-based regimen on HIV-1 proviral DNA reservoir of treatment-naïve and experienced patients	Combination antiretroviral therapy	NCT02370979	University Hospital, Strasbourg, France	Phase IV
AAHIV: antiretroviral therapy for acute HIV infection	Combination antiretroviral therapy	NCT00796263	South East Asia Research Collaboration with Hawaii	Phase III
tenofovir/emtricitabine + dolutegravir or tenofovir/emtricitabine + darunavir/cobicistat	Combination antiretroviral therapy	NCT02987530 (not yet open for enrollment)	Inserm/ANRS	Phase III
VIRECURE: Impact of extremely early ART to reduce viral reservoir and induce functional cure of HIV infection	Combination antiretroviral therapy	NCT02588820	David Garcia Cinca, Hospital Clinic of Barcelona	Phase III
EIT: Early Infant HIV Treatment in Botswana	Combination antiretroviral therapy	NCT02369406	Harvard School of Public Health	Phase II/III
EARLIER: Early ART to limit infection and establishment of reservoir	Combination antiretroviral therapy	NCT02859558	AIDS Clinical Trials Group	Phase II
Peginterferon alfa-2b	Cytokine	NCT02227277	The Wistar Institute	Phase II
Peginterferon alfa-2b	Cytokine	NCT01935089 (closed to enrollment)	University of Pennsylvania/Wistar Institute	Phase II
IMPAACT P1115: Very early intensive treatment of HIV-infected infants to achieve HIV remission	David Garcia Cinca, Hospital Clinic of Barcelona	NCT02140255	IMPAACT/NIAID/NICHD	Phase I/II

Shaded entries represent additions since the 2016 Pipeline Report. For a listing including completed trials related to cure research, with links to published and presented results where available, see TAG's research toward a cure clinical trials web page at: <http://www.treatmentactiongroup.org/cure/trials>.

COMBINATION APPROACHES

An increasing number of trials are exploring the effects of combinations of agents on the HIV reservoir. At the 2017 CROI, results from a study combining therapeutic vaccination with a drug capable of reversing HIV latency—the so-called ‘kick & kill’ approach—drew considerable attention due to evidence that the interventions may have enhanced control of viral load after an ART interruption. The results were presented by Beatriz Mothe from IrsiCaixa in Barcelona.³³

Mothe and colleagues conducted a two-part trial. In the initial phase, 24 HIV-positive individuals who had started ART within three months of infection received a series of immunizations with chimpanzee adenovirus (ChAdV63) and modified Vaccinia Ankara strain (MVA) vaccine vectors, both encoding antigens designed to focus T cell responses on highly conserved parts of HIV, including elements from the Gag, Pol, Env and Vif proteins. Mothe had previously reported that receipt of these vaccines shifted HIV-specific T cell responses toward the intended conserved targets, but did not have a measurable effect on the size of the HIV reservoir.³⁴

The second phase enrolled 15 participants from the first trial and administered booster immunizations with the MVA vector before and after three infusions of the HDAC inhibitor romidepsin. Eight weeks after the final MVA dose, all participants interrupted ART, with a requirement to restart if viral load increased to more than 2,000 copies/ml.

Data were available from 13 individuals at the time of Mothe’s CROI presentation: eight quickly met the criteria to reinstate ART, but the remaining five had controlled viral load to low levels for several months, with follow up ongoing (the longest duration is a little over six months). Based on Mothe’s slide presentation, three appeared to have viral loads below the limit of detection of the assay used (20 copies/ml), whereas the other two fluctuated between the limit of detection and ~2,000 copies/ml. Mothe highlighted that the frequency of viral load containment in the cohort (~38%) was higher than had been observed in any studies involving early initiation of ART, where rates had varied from 0–15%.^{35,36} The researchers are investigating whether correlates of viral load control can be identified, with a particular focus on vaccine-induced T cell responses.

The contribution of the different interventions may be difficult to tease out, as this was an open-label, uncontrolled study in which all participants received the MVA vaccine and romidepsin. Evidence of a latency-reversing effect of romidepsin was documented, with viral load transiently increasing after each infusion. Viral load blips were also observed after MVA immunizations in 60% of participants, suggesting that the vaccine may have been stimulating production of virus from latently infected CD4 T cells specific for HIV antigens.³⁷ There was no evidence of a decrease in measures of the HIV reservoir.

Romidepsin infusions were associated with an array of side effects that are known to be caused by HDAC inhibitors—primarily grade 1 and grade 2 headaches, fatigue and nausea—and the drug also caused precipitous, but transient, declines in peripheral blood CD4 T cell counts of around 300 cells. One participant developed the serious complication of sepsis after the final romidepsin dose.

Two trials that have been initiated during the past year (ROADMAP and eCLEAR, see Table 1) are evaluating a variation of the kick & kill approach, combining romidepsin with the broadly neutralizing antibody (bNAb) 3BNC117. This bNAb was discovered by the laboratory of Michel Nussenzweig at Rockefeller University and has been shown to have potent antiretroviral activity in a Phase I trial.³⁸ The rationale for combining 3BNC117 with a latency-reversing agent in people on ART is derived from an experiment in the humanized mouse model, which found that the approach was associated with a diminution of the HIV reservoir and reduced viral load rebound after ART interruption.³⁹ A potential mechanism of action is antibody-mediated cellular cytotoxicity (ADCC): when latent HIV is stimulated to

make proteins by a latency-reversing agent, these appear on the outside of the cell, and bNAbs such as 3BNC117 can bind to the Env protein and recruit immune cells to destroy the HIV-infected target via a part of the antibody called the Fc receptor.⁴⁰

An ongoing trial in Brazil is testing a combination of interventions that includes the gold-based anti-proliferative drug auranofin. The laboratory of Andrea Savarino pioneered the study of auranofin in the SIV/macaque model, reporting that it contributed to control of SIV replication after an ART interruption.⁴¹ This research now seems prescient given the new appreciation of the role of CD4 T cell proliferation in sustaining the HIV reservoir. The regimens administered in the macaque study were complex, as is the case in the clinical trial, which involves ART intensification with maraviroc and/or dolutegravir, a dendritic-cell-based therapeutic HIV vaccine, nicotinamide (an HDAC inhibitor), and auranofin. The effects on various measures of HIV persistence will be assessed. The principal investigator is Ricardo Sobhie Diaz of the Federal University of São Paulo.

A concern that has emerged from studies of bNAbs given as single agents is that HIV can rapidly develop resistance. The first trial of a bNAb combination, 3BNC117 and 10-1074, is now underway at Rockefeller University. The activity of the bNAbs will be assessed in multiple groups of participants, including individuals that are off ART and those that are undergoing an ART interruption.

The US Military HIV Research Program (US MHRP) is collaborating with Janssen Vaccines & Prevention B.V. to study a combination of two therapeutic vaccines in individuals who initiated ART during acute HIV infection in Bangkok, Thailand. The vaccines are an adenovirus serotype 26 (Ad26) vector and an MVA vector, both of which encode mosaic HIV antigens designed to induce immune responses capable of recognizing diverse viral strains. The aim is to eventually combine these vaccines with an agonist of toll-like receptor (TLR) 7 developed by Gilead Sciences, as promising results obtained in a macaque study showed that the combination was associated with control of SIV viral load after ART interruption.⁴²

TOLL-LIKE RECEPTOR AGONISTS

TLRs are proteins that have an important role in innate immunity by recognizing certain shared features that are common to many pathogens. Stimulating TLR signaling with TLR agonists has long been of interest in cure research, as there is evidence that it may contribute to both reversing HIV latency and promoting antiviral immune responses.⁴³ In addition to the planned collaboration with US MHRP, Gilead Sciences is sponsoring two ongoing trials of their TLR7 agonist vesatolimod (formerly known as GS-9620). One involves individuals on ART and aims to assess the safety and effects on measures of HIV persistence, the second is recruiting ART-treated HIV controllers—people who initiated ART despite relatively low viral loads—and includes an analytical ART interruption to investigate whether vesatolimod influences viral load rebound.

The research group of Ole Søgaaard at Aarhus University in Denmark has been investigating a TLR9 agonist, MGN1703, after an exploratory analysis of a trial in which a similar compound was used as a vaccine adjuvant in people on ART suggested that it was associated with a slight decline in the HIV reservoir.⁴⁴ In a recently published paper, the researchers report results from a small trial that administered MGN1703 subcutaneously to 15 individuals on ART, twice weekly for four weeks.⁴⁵ They observed increased activation of natural killer cells and CD8 T cells, indicating a potential enhancement of cellular immunity. Evidence of activation of plasmacytoid dendritic cells and elevated production of alpha interferon was also documented, along with upregulation of interferon-stimulated genes. In 6 of the 15 participants, viral load became transiently detectable, consistent with MGN1703 stimulating virus production by latently infected cells, although there was no significant change in measurements of the HIV reservoir. The researchers believe the results are promising and that MGN1703 should be considered for inclusion in future studies of combination strategies targeting the reservoir.

GENE THERAPIES

A number of clinical trials of gene therapies are ongoing, but little news has emerged from this research over the past year. While not specific to HIV, Jennifer Adair from the laboratory of Hans-Peter Kiem at the Fred Hutchinson Cancer Research Center published a description of an approach that aims to address concerns about the potential accessibility of gene therapies. Dubbed “gene therapy in a box,” the method potentially allows for the creation of gene-modified stem cells at the point of care, rather than at high-tech facilities.⁴⁶

Two new gene therapy trials have recently begun. One involves the infusion of CD4 T cells that have been gene modified to express an HIV-inhibiting protein, C34, fused to part of CXCR4, a cell surface protein that can serve as a co-receptor for HIV entry. The idea is to bring the C34 protein to the sites where HIV infects vulnerable cells. The approach has shown broad and potent inhibition of diverse HIV isolates—both CXCR4-tropic and CCR5-tropic—in laboratory experiments.⁴⁷

The AIDS Malignancy Consortium has initiated a gene therapy study for HIV-positive individuals with lymphoma who require stem cell transplants. This Phase I/II trial will modify transplanted stem cells with a triple combination of anti-HIV genes developed by researchers at the University of California, Davis.⁴⁸ The primary goal is to assess the magnitude and persistence of the gene-modified cells after transplantation.

CRISPR/Cas9, a relatively new technology derived from the primitive immune system of bacteria, has generated considerable excitement because of its vaunted ability to reliably target and modify genes of interest. The research group of Kamel Khalili at Temple University has spearheaded the use of the approach as a means to excise the HIV genome from latently infected cells, reporting encouraging results in preclinical experiments.^{49,50} The media coverage of this work has at times been guilty of glossing over the challenges associated with translating the approach for use in the human body—for example, the fact that a bacterial protein is involved raises concern that the approach could induce anti-bacteria immune responses that might hamper efficacy (this has been observed in mice⁵¹). But the apparent promise of the approach for multiple diseases means that many different research groups are working to develop ways to deliver CRISPR/Cas9 as a therapy.⁵²

In the meantime, a group of Chinese researchers have become the first to use the technology in an HIV trial. CRISPR/Cas9 will be used *ex vivo* to delete the CCR5 gene from stem cells in the laboratory, with the modified cells being subsequently administered to HIV-positive individuals requiring stem transplants for hematological cancers.

IXAZOMIB

The first study of a proteasome inhibitor, ixazomib, as a potential intervention in cure research is being conducted by Nathan Cummins from the Mayo Clinic in Rochester. The drug is an FDA-approved treatment for multiple myeloma. Cummins and colleagues have a longstanding interest in manipulating cell death pathways as a means of preferentially promoting the demise of CD4 T cells that are latently infected with HIV, and proteasome inhibitors are among the candidates that they have identified.⁵³ The trial represents the first step toward translating this work into the clinic.

BROADLY NEUTRALIZING ANTIBODIES

The International AIDS Vaccine Initiative (IAVI) is sponsoring a first-in-human trial of the potent bNAb PGT121, recruiting both HIV-positive and HIV-negative individuals. Of particular interest from the perspective of cure research, PGT121 has been shown to mediate protection against a simian-human

immunodeficiency virus (SHIV) challenge in macaques by promoting clearance of infected cells from tissues.⁵⁴ The antibody also strongly suppressed SHIV replication when delivered in the therapeutic context.

Researchers in Australia plan to combine the bNAb 3BNC117 with a radiolabel to facilitate imaging studies of the locations in the body in which 3BNC117 binds to the HIV envelope protein. The first step will be to assess safety in HIV-negative individuals before moving on to HIV-positive individuals that are either off ART or on ART with suppressed viral loads.

THERAPEUTIC VACCINES

The idea of using naked DNA as a vaccine platform has been around for some time. The approach involves injecting DNA comprising the genes for the protein antigens of interest; the DNA is transcribed into RNA, which is then translated into protein. But results using this approach have, overall, been disappointing compared with what was observed in initial experiments in small animals.

In recent years, technological advances have made it possible to employ naked RNA as the delivery vehicle, and this approach has generated strong interest, particularly in the field of cancer.⁵⁶ A consortium of investigators is now exploring the potential of an RNA vaccine designed to induce immune responses to HIV. Named iHIVARNA-01, the vaccine uses messenger RNA to deliver HIV antigens combined with TriMix, an adjuvant cocktail consisting of three proteins involved in the activation of antigen-presenting cells: CD40L, CD70, and TLR4. The vaccine is delivered intranodally (into the lymph nodes). Positive preclinical results have been reported⁵⁷, and the vaccine is now the subject of a Phase IIa trial led by Rob Gruters from the Erasmus Medical Center in the Netherlands.

ABX464

ABX464 is an antiretroviral with a novel mechanism of action: it interferes with the process by which HIV RNA is spliced to assemble new virions during the viral life cycle. In studies in the humanized mouse model, administration of ABX464 was associated with a reduced HIV viral load rebound after treatment cessation compared with standard ART⁵⁸ (although it has been suggested that this may have been an artifact of the model system⁵⁹), and a preliminary trial in humans has reported that the drug was relatively well tolerated, with a hint of antiretroviral activity observed at the highest dose.⁶⁰

A Phase II placebo-controlled trial combining ABX464 with darunavir and ritonavir or darunavir and cobicistat, followed by an analytical treatment interruption, is now ongoing. A recent press release regarding this study from the manufacturer, Abivax, trumpeted: “First ever evidence of treatment-induced reduction in HIV reservoirs” and reported that 7 of 14 participants who received ABX464 showed a decline in HIV DNA levels averaging around 40%.⁶¹ Contrary to the company’s claims, a very similar HIV DNA reduction has been reported in a study that combined romidepsin with the therapeutic vaccine Vacc-4x, and it was not associated with a delay in HIV viral load rebound when ART was interrupted.⁶² The Abivax press release states that their study results will be submitted to scientific conferences and it is unfortunate that the company decided to promote them before a formal presentation has occurred. The mechanism by which ABX464 might have an effect on the latent HIV reservoir is as yet unclear.

Table 2. Immune-Based Therapy Pipeline 2017

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
Canakinumab	IL-1 β inhibitor	University of California, San Francisco	Phase II
Isotretinoin	13-cis retinoic acid	NIAID	Phase II
Lactobacillus casei shirota	Probiotic	University of Sao Paulo General Hospital	Phase II
Losartan	Angiotensin II receptor antagonist, anti-inflammatory	Minneapolis Medical Research Foundation	Phase II
Methotrexate (low dose)	Anti-inflammatory	NIAID	Phase II
Niacin	Vitamin B3	McGill University Health Center/ Canadian Institutes of Health Research (CIHR) Canadian HIV Trials Network	Phase II
Visbiome	Probiotic	University Health Network, Toronto/ CIHR Canadian HIV Trials Network	Phase II
Dipyridamole	Phosphodiesterase type 5 inhibitor, anti-inflammatory	Sharon Riddler, University of Pittsburgh/ NIAID	Phase I/II
tocilizumab	IL-6 blockade	Case Western Reserve University	Phase I/II
<i>Tripterygium wilfordii</i> Hook F	Traditional Chinese medicine, anti-inflammatory	Beijing 302 Hospital Peking Union Medical College	Phase I/II
Vorapaxar	Thrombin receptor (PAR-1) antagonist	Kirby Institute/NIAID/University of Minnesota – Clinical and Translational Science Institute/University of Melbourne/Merck	Phase I/II
Arabinoxylan rice bran supplementation (BRM4)	A product derived from rice bran treated with extracts from three mushrooms	University of Southern California	Not specified

As outlined in the introduction to this chapter, research into potential immune-based adjuncts to ART now represents a rather quiet backwater compared with the expanding sea of cure research. An antibody that inhibits the pro-inflammatory cytokine IL-1 β , canakinumab, straddles both fields to some degree—an ongoing trial is primarily studying the effects on inflammation individuals on ART, but will also measure HIV reservoirs as a secondary endpoint. The study is being conducted by Priscilla Hsue from UCSF, who presented results of a pilot evaluation of canakinumab in ten HIV-positive individuals on ART at the 2017 CROI.⁶³

The data were encouraging, with significant declines being observed in several inflammatory biomarkers, including IL-6 (levels fell by 30%) and high sensitivity C-reactive protein (41%). Imaging studies also revealed a 10% reduction in arterial inflammation. There was no evidence of an alteration in CD4 counts, so it is unclear whether canakinumab might benefit INRs. The larger trial is aiming to enroll 110 participants.

Benigno Rodriguez at Case Western Reserve University is leading a study investigating tocilizumab, an antibody against the proinflammatory cytokine IL-6, in individuals on ART. Effects on inflammatory biomarkers and the turnover of central memory CD4 T cells (measured by the cycling marker Ki67) will be assessed. The trial ended in January 2017 and results are pending.

A scattering of studies involving probiotics have been published over the past year,^{64,65} continuing to suggest benefits without providing much in the way of guidance for HIV-positive people regarding their use. The CIHR Canadian HIV Trials Network is attempting to help fill the information gap by conducting two prospective, double-blinded, randomized, placebo-controlled, multicenter pilot studies of the probiotic Visbiome.⁶⁶ One trial will enroll individuals initiating ART, whereas the other is recruiting INRs with CD4 counts below 350 cells despite ART.

A cautionary report regarding the potential dangers of probiotic use also appeared in the literature, describing a case of *Lactobacillus acidophilus* bacteraemia in an individual with AIDS that was associated with excessive consumption of probiotic-enriched yogurt.⁶⁷

Efforts to bring some clarity and coordination to the pursuit of probiotic research in HIV have received a boost with the initiation of an annual HIV Microbiome Workshop sponsored by Virology Education.⁶⁸ The third meeting is scheduled to take place from October 19–20, 2017 in Washington DC.

The only other new trial for INRs that has appeared in the clinicaltrials.gov database over the past year involves the nutritional supplement BRM4, which contains extracts from rice bran and shiitake mushrooms. The study is being conducted at the University of Southern California and is looking to enroll around 24 individuals on ART with CD4 T cell counts between 100 and 350.

A few short years ago, it appeared that the cytokine IL-7—which has shown promise for promoting immune reconstitution⁶⁹—was likely to be studied for efficacy in a large randomized trial that would have measured the effect on morbidity and mortality in INRs. But the manufacturer, Cytheris, went bankrupt, and when surveying the current state of immune-based therapy research, it appears extremely unlikely that any candidate will undergo that type of rigorous evaluation in the near future.

CONCLUSION

The cure research endeavor maintains a productive diversity, with many leads currently under investigation and constant recalibration occurring as new information emerges. The expansion in the number of Martin Delaney Collaboratories is a particularly encouraging development, particularly given that the five-year funding period offers hope that they will outlast the current US President. But at the current time, it is still not possible to predict when a broadly accessible cure might be developed. Updates on the field will be provided at the International AIDS Society HIV Cure & Cancer Forum, which takes place from July 22–23, 2017 in Paris, and the biannual HIV Persistence Meeting held on December 12–15, 2017 in Miami.

Immune-based therapy research has dwindled to a point where a pipeline barely exists, and it will require ongoing engagement of activists and other stakeholders to try and ensure that work continues in this area.

An overarching threat to all of the research described in this and other chapters is the strong anti-science bias of the Trump administration, which is proposing massive cuts to the National Institute Health, the global leader in science funding. Although there is reason to hope that the US Congress will prevent their desired decimation, ongoing vigilance will be essential to ensure that the work described in this report continues.

RECOMMENDATIONS

- Continue to increase funding for cure-related research and protect extant funding from the anti-science efforts of the Trump administration to slash the NIH budget.
- Broaden the global scope of HIV cure research to gain a better understanding of geographic and population-specific differences in HIV reservoirs.
- Work to promote and facilitate participation of diverse populations in clinical trials.
- Support social science research aiming to gain insights into how HIV cure research is perceived and understood.
- Further enhance community education on HIV cure research to both facilitate community involvement in the effort and provide accurate context for media coverage of the topic.
- Support and promote dialogue between regulators, researchers, funders, and community stakeholders on trial design issues, particularly regarding the use of analytical ART interruptions.
- Develop more user-friendly technologies for monitoring HIV rebound in individuals experiencing HIV remission to avert or lessen the risks associated with a rapid return of viral replication.
- Address the engineering challenges associated with making potentially complex interventions such as gene therapy more convenient, accessible, and affordable.
- Improve communication on concepts of HIV remission, and be clear that the maintenance of low viral load in the absence of ART may not necessarily be equivalent to suppression of HIV by ART in terms of long-term health outcomes.
- Support webcasting for all cure-related scientific conferences to facilitate greater global sharing of information.
- Remain alert for any indications that candidates studied in the cure context might have benefits as adjunctive therapies in addition to ART, for example, to enhance immune reconstitution in INRs.
- Advocate for enhanced research and development efforts to address the needs of INRs.

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The Tuberculosis Diagnostics Pipeline

By Erica Lessem

INTRODUCTION

Diagnosing tuberculosis (TB) is the first step to being able to treat it and prevent transmission. New guidelines from the World Health Organization (WHO) note that diagnosis should be “available free of charge to all persons with TB and populations at risk.”¹ Yet an estimated over four million people with TB went undiagnosed or unreported to national treatment programs in 2015; India, Indonesia, and Nigeria accounted for almost half of this gap.² Those who do receive a TB diagnosis often do so only after multiple health care visits and lengthy delays. Studies have found average delays of 28 to 30 days from when patients first contact a health care provider to diagnosis, even when patients present with overt TB symptoms.³ Drug-susceptibility testing is not widely available and is used far too infrequently, even among those diagnosed with TB and living in countries with a high burden of drug-resistant TB (DR-TB). The end result is that 40% of people with TB do not receive a diagnosis or are not reported, and DR-TB is detected in only 23% of people thought to have it.

Ending this catastrophic neglect will require two simultaneous revolutions. First, we need dramatically increased ambition in and accountability for country- and local-level uptake of all the tools—including newly WHO-endorsed ones—required to adequately diagnose TB, detect drug resistance, and swiftly link patients to treatment (see TAG’s *An Activist’s Guide to Tuberculosis Diagnostic Tools*, www.treatmentactiongroup.org/tb/diagnostic-tools). WHO’s plan to create a Model List of Essential Diagnostics, following calls from academics and activists, could help create such accountability.^{4,5,6} Second, an infusion of investment into research to move forward basic science and the diagnostics pipeline is urgently needed.

We must secure the successful development of new diagnostic tests on the horizon that offer meaningful—albeit incremental—advances, as well as true innovations that could radically simplify and improve TB diagnosis. Towards the former, notable recent progress includes the launch of a more sensitive Xpert MTB/RIF Ultra assay for diagnosing TB and detecting rifampin resistance, further evidence of the effect of urine lipoarabinomannan (LAM) testing for people with HIV, a sputum LAM assay that could revolutionize treatment monitoring, and several rapid tests inching towards launch that could bring TB and rifampin resistance testing closer to patients (GeneXpert Omni, TrueNat) or expand susceptibility testing to more drugs (Xpert XDR, RealTime MTB RIF/INH, and FluoroType MDR). These and other advances are described below.

ADVANCES IN TB DIAGNOSIS AND DRUG-SUSCEPTIBILITY TESTING

GeneXpert Ultra

Perhaps the biggest advance so far this year in TB diagnostics has been the launch of the Xpert MTB/RIF Ultra assay (Ultra).⁷ A WHO expert consultation found the Ultra cartridge non-inferior to the original MTB/RIF assay (which has still not been adequately rolled out, see textbox page 94) for diagnosing TB and detecting resistance to rifampin, based on data from a multi-center, 1,520 person study carried out by the FIND comparing the Ultra assay with MTB/RIF.⁸ This study found that Ultra’s overall sensitivity at 87.8% (95% confidence interval [CI]: 84.2 to 90.9%) was 5% higher (95% CI: +2.7 to +7.8%) than that of MTB/RIF’s at 82.9% (95% CI: 78.8 to 86.4%). The highest increases in sensitivity were found in some of the previously most difficult to diagnose patients. In people with smear-negative, culture-positive TB, Ultra’s sensitivity of 61.3% (95% CI: 52 to 70.1%) beat out MTB/RIF’s of 44.5% (95% CI: 35.4 to

Table 1. 2017 Tuberculosis Diagnostics Pipeline: Products with New Published Data or Policy Updates since the 2016 Pipeline Report

Test	Type	Manufacturer	Status
MOLECULAR/NAAT			
FluoroType MTBDR	Semi-automated direct MTB detection; PCR in a closed system; results in 3 hours	Hain Lifescience	CE marked, and launched for marketing April 2017; not yet evaluated by WHO
MTB Complex	RT-PCR	BioGx, runs on the BD Max automated platform	CE marked, and launched for marketing in Europe April 2017; not yet evaluated by WHO
TB-LAMP	Manual NAAT by loop-mediated isothermal amplification (LAMP) for MTB detection	Eiken	WHO guidance issued in August 2016 ⁹
RealTime MTB/TB MDx m2000	Automated RT-PCR for MTB detection; can be used alongside HIV RNA platform	Abbott	Average sensitivity 92.1%, (95% CI: 87.9 to 99.9%) in smear-positive and smear-negative samples ¹⁰ ; not yet evaluated by WHO
TrueNat MTB	Chip-based NAAT with RT-PCR on handheld device for MTB detection	Molbio Diagnostics, Bigtec Labs	FIND and ICMR studies underway; submission for approval in India expected end of 2017; not yet evaluated by WHO
Xpert MTB/RIF Ultra	Next-generation cartridge-based detection of MTB + rifampin resistance	Cepheid	WHO guidance issued in March 2017 ¹¹
GeneXpert Omni	Single-cartridge mobile platform for single Xpert MTB/RIF or Ultra cartridge	Cepheid	Platform under development. Launch expected third quarter 2017; not yet evaluated by WHO
Xpert XDR	NAAT cartridge for GeneXpert platforms that can detect resistance to isoniazid, fluoroquinolones, and the second-line injectable agents	Cepheid	Assay under development; not yet evaluated by WHO. Preliminary sensitivity and specificity (as compared to sequencing, and not yet peer-reviewed): ¹² <ul style="list-style-type: none"> • isoniazid 98.1%, 100%; • fluoroquinolones 95.8%, 100%; • kanamycin 92.7%, 100%; • amikacin 96.8%, 100%
ANTIBODY/ANTIGEN DETECTION			
Determine TB LAM Ag	Urine dipstick for TB LAM protein	Alere	New studies show incremental yield (additional cases detected) and correlation of LAM positivity with mortality (further supporting previous evidence that LAM can be used to accelerate treatment start and reduce mortality); ^{13,14,15} included in GLI algorithm ¹⁶

CE: Conformité Européenne (European Conformity, an indication of permission to market in Europe); GLI: Global Laboratory Initiative; ICMR: Indian Council of Medical Research; MTB: Mycobacterium tuberculosis; NAAT: nucleic-acid amplification test; RT-PCR: real-time polymerase chain reaction; WHO: World Health Organization

53.9%) by a difference of 17% (95% CI: +10 to +25%). In people with HIV, Ultra's sensitivity of 87.8% (95% CI 79.6, 93.5) was 12% better (95% CI: +4.9 to +21%) than MTB/RIF's of 75.5% (95% CI 65.8 to 83.6%). In a single small, prospective study of people with TB meningitis, Ultra detected 95% (21 of 22) of confirmed TB meningitis cases compared with only 45% (10 of 22 cases) of cases detected using MTB/RIF (P = .003). In a single study of 378 children, Ultra's sensitivity was 24% higher than that of MTB/RIF. Ultra can better differentiate clinically meaningful (i.e., rifampin-resistance conferring) mutations from 'silent' mutations than MTB/RIF (though it still doesn't detect all mutations that confer rifampin resistance, which is a growing problem, as screening with an imperfect test allows the population of bugs with mutations that are not detected to expand).

Ultra's increased sensitivity came at a tradeoff of decreased specificity, which at 94.8% (95% CI: 79.6 to 93.5%) was 3.2% lower (95% CI: -2.1 to -4.7%) than that of MTB/RIF at 98% (95% CI: 96.8 to 98.8%), especially in patients with a history of TB (difference: -5.4%, 95% CI: -9.1 to -3.1%). This is likely because Ultra detects non-viable bacilli. The WHO Report notes that "in low TB burden settings and in the testing of specimens for the diagnosis of extrapulmonary TB and paediatric TB, false positive results were not a major concern," and even a 'trace' result (a new, semi-quantitative category that corresponds to the lowest bacillary burden for detecting MTB) with Ultra is sufficient to start therapy in these populations and in people with (or thought to have) HIV. The remaining risk of overtreatment as a result of false positives in high-TB-burden settings can be mitigated by repeating the test on a fresh sample when Ultra reports 'trace' results in HIV-negative adults with signs and symptoms of TB.

The WHO supports Ultra as an alternative to the current MTB/RIF in all settings, and Cepheid, its manufacturer, will gradually phase out the current MTB/RIF assay and replace it with Ultra.

Omni

Cepheid is also slated to release another major technology improvement in the third quarter of 2017: the Omni. This portable, rugged, battery-operated, single-module (cartridge) instrument will enable the Xpert technology to reach 'level one' facilities (primary health posts and centers).¹⁷ This could help to dramatically reduce time to diagnosis for many patients and facilitate the switch from the far less sensitive smear microscopy (though smear will still be needed for treatment monitoring), and help to detect rifampin resistance much earlier. However, as it only processes one sample at a time, it is not suitable for clinics with a high attendance of people needing to be evaluated for TB, unless many are purchased. The Omni is expected to cost about \$2,700 per device.

Cepheid's original requirement of using Omni along with its connectivity software, C360, has raised important questions for the field about the ownership and parameters of use of data, whether countries allow data to be sent outside of the country (C360 hosts data on an external server based in the U.S. and U.K.), and whether third-party connectivity solutions can be used. The Global Laboratory Initiative is expected to put out a guide to connectivity solutions soon after this report goes to press.

Xpert XDR assay

Ultra enhances the GeneXpert system's ability to detect TB and rifampin resistance, and Omni aims to bring GeneXpert technology closer to where people seek care, but neither expands the drugs for which the Xpert system detects resistance beyond rifampin. That's where the XDR cartridge—sometimes referred to as the Xtend XDR—in development by Cepheid with support from the U.S. National Institutes of Health (NIH) comes in. According to data that have not yet been peer-reviewed, the test showed promising early results detecting resistance to isoniazid (sensitivity 98.1%, specificity 100%), fluoroquinolones (sensitivity 95.8%, specificity 100%), kanamycin (sensitivity 92.7%, specificity 100%), and amikacin (sensitivity 96.8%, specificity 100%) as compared with sequencing (accuracy is worse when compared

with drug-susceptibility testing by culture, the gold standard).¹⁸ Now it is just a matter of transferring this complicated test into a cartridge so it can work on either the GeneXpert or Omni system, and scaling up for manufacture. But this has been unacceptably delayed as a result of inadequate investment. Cepheid and Danaher, which acquired Cepheid, have indicated that Cepheid is working with partners to develop the XDR cartridge to prepare for its market launch.¹⁹ But the funding gap means that it will not be available until 2019 at the earliest.²⁰

The ability to rapidly and simply detect resistance to these drugs would be of tremendous value in quickly guiding the initiation of appropriate therapy. As new data show poor outcomes for treatment of isoniazid-mono-resistant TB using the standard first-line regimen, a rapid test to detect isoniazid resistance is even more important than previously thought.²¹ This could mean an even bigger market for the XDR cartridge than originally anticipated. However, using the full XDR cartridge on all TB-positive, rifampin-susceptible samples would be very expensive. It would also provide difficult to interpret and potentially undesired results about resistance to the injectables and fluoroquinolones, as running the assay in a population with a low prevalence of resistance to second-line drugs lowers its positive predictive value. Global and national guidance will have to reflect carefully on how to ensure isoniazid resistance is appropriately detected without misusing resources or misdiagnosing people. Far more optimal would be to have the isoniazid-resistance testing on the same cartridge as MTB and rifampin resistance detection, but it is not currently feasible to fit all on one assay.

At least for the meantime, line probe assay (LPA) and liquid culture will continue to play important roles in drug-susceptibility testing. Until the XDR cartridge is validated and available, second-line LPA (guidance issued by WHO in May 2016) is the only relatively quick way to determine who is eligible to receive the WHO-recommended shortened regimen for MDR-TB.

Seven years into GeneXpert rollout, and still much more to do

Recent studies from southern Africa have shown that Xpert can have a valuable effect when integrated into a complete and functional system. A pragmatic study in South Africa and Zimbabwe randomized patients in communities with high TB/HIV prevalence to intensified TB case finding with either the Xpert MTB/RIF test (and, if HIV-positive, the Determine TB LAM urine test) or sputum smear microscopy. Thirty percent more patients with TB—as later confirmed by culture—were started on treatment in the Xpert group than in the smear group at 60 days (86% versus 56%, 95% CI: 9 to 50%; $P = .0047$). Using Xpert MTB/RIF in active case finding not only increased the proportion of patients starting treatment, but also reduced the time to treatment initiation from four days to one day ($P = .0407$), and reduced the proportion of patients treated empirically or by culture (12% versus 53%; $P < .0001$).²²

A nationwide retrospective cohort study from South Africa, which has been at the forefront of the MTB/RIF rollout, revealed that the test helped reduce treatment delays (by 44 days from pre-Xpert rollout in 2011 to post-Xpert rollout in 2013, $P < .001$) and allowed for more MDR-TB to be detected and treated. However, there is still a large gap between diagnosis and treatment: in 2013, the proportion of patients with rifampin-resistant TB who had started treatment at six months was no different if they were diagnosed by Xpert or other methods (62%, 95% CI: 59 to 65% versus 64%, 95% CI: 61 to 67%; $P = .39$).²³ This points to the need to ensure that all patients diagnosed are started on treatment, and rapidly so. A recent

review article notes that “Xpert MTB/RIF will only improve patient outcomes if optimally implemented within the context of strong tuberculosis programmes and systems.”²⁴

Overall, the use of Xpert MTB/RIF still lags, despite having been WHO-recommended since 2010, and its current recommendation as the initial diagnostic test for all persons with signs and symptoms of TB.^{25,26} In 2016, the public sector procured 6.9 million cartridges under concessional pricing, up slightly from 6.2 million in 2015. But this is still far below the number that would be needed to diagnose the more than 10 million people who fall ill with TB each year. India and Indonesia have plans to scale up access to Xpert MTB/RIF, and dramatically increased procurement of modules in 2016; together they accounted for nearly half of the 8,316 modules procured in the public sector.²⁷ Whether these important tests will actually reach those in need and aid in speeding up the start of treatment remains to be seen.

Reports from users indicate that the GeneXpert devices have a short life-span and often need replacing just after the warranty ends, suggesting a need to improve service and maintenance arrangements.²⁸

GeneXpert’s use for other indications, such as early infant diagnosis (for which its qualitative test has already been prequalified by WHO) and HIV load monitoring (which is undergoing prequalification analysis now) could help to encourage rollout of the test, efficiency, and integration of care if done collaboratively. However, as procurement and as care for different conditions are largely done in silos, this opportunity has not yet been fully exploited.²⁹ The WHO Global TB Programme and HIV Department are planning to put out an information note on considerations for adoption and use of multi-disease testing devices in integrated laboratory networks, and expanding early infant HIV diagnosis (which is happening with Global Fund and Unitaid funding) will offer an opportunity for negotiating better terms, such as for service and maintenance price structure, for both HIV and TB.

Alternatives to GeneXpert

When the WHO recommended Xpert MTB/RIF, many ‘fast followers’ were expected to debut shortly thereafter. Seven years later, we see that TB diagnostic development advances slowly, not unlike the slow-growing bacteria themselves. Many tests have been dropped, while others are being used in countries such as China, India, and Korea, without multicenter evaluation in different settings with diverse epidemiology.³⁰ BD’s Max MDR-TB, Roche’s Cobas TaqMan MDR TB, Akonni’s TruArray XDR-TB, and Ustar’s EasyNat MDR-TB are all in development with timelines for market entry at least a year out.

TrueNat

Of these alternatives, Molbio’s TrueNat is the farthest along, with a large-scale, multicenter evaluation underway supported by the Indian Council of Medical Research. Early data show promise in terms of sensitivity and specificity.³¹ Review for approval in India is expected at the end of 2017.³² This battery-operated, low-throughput device would be an important competitor to Omni in India, where TrueNat’s local production would mean major savings on shipment and import duties. But the platform’s lack of full automation (it requires two precision steps) may make it less desirable elsewhere, unless cost is highly competitive.

RealTime MTB RIF/INH

Another noteworthy competitor is Abbott's RealTime platform, which is already in widespread use in central laboratories for HIV-1 load testing. The Abbott RealTime MTB (for MTB detection) and MTB RIF/INH Resistance assays are available and CE-marked (meaning the device complies with the European In-Vitro Diagnostic Devices Directive and can therefore be commercialized in the European Union)—although not yet WHO-evaluated. The latter is the first test to offer rapid isoniazid- and rifampin-resistance testing together on a high throughput system. This test is fully automated, from extraction to amplification and detection. The test's packing insert cites specificity of 97% (95% CI: 95 to 98%) among 359 culture-negative samples, and an overall sensitivity of 93% (95% CI: 89 to 96%) of 212 culture-positive samples, with 81% sensitivity (95% CI: 69 to 90%) in 63 smear-negative samples and 99% sensitivity (95% CI: 95 to 100%) in 149 smear-positive samples, as compared with culture.³³ Drug-susceptibility performance is also very good, with sensitivity of 94.8% and specificity of 100% for detecting rifampin resistance, and sensitivity of 88.3% and specificity of 94.3% for detecting isoniazid resistance. WHO evaluation of this and other high-throughput centralized platforms, such as BioGx on the BD Max automated platform, and other products by BD and Roche, is expected in the first quarter of 2018.

FluoroType MDR TB and XDR

Hain Lifescience's new FluoroType MTBDR test is a rapid molecular genetic test that—according to the company—can detect TB directly from sputum specimens.³⁴ The 'mostly' automated PCR-based process is more user friendly and faster (three hours) than Hain's existing LPA technology. The FluoroType MTBDR test putatively detects resistance to rifampin and isoniazid simultaneously in either sputum or culture samples—peer-reviewed data are not yet available, but a publication is in progress. If successful, this would address—though only at higher laboratory levels—some of the challenges of lack of ability to diagnose isoniazid resistance along with rifampin resistance discussed under the Xpert XDR section. Hain launched FluoroType MTBDR in April 2017, after it was CE-marked, and is evaluating what is needed for the test to be reviewed by the WHO in late 2017 or early 2018.³⁵ Hain notes they will have "very competitive, volume-based and market-adjusted pricing" for the product.³⁶ Development of an XDR product is expected to receive funding from an undisclosed European donor soon (we speculate the German government, given the company's location), and launch is anticipated in mid-2018.³⁷ Hain is also exploring ways to develop a pyrazinamide resistance assay—which, if developed, would be the first molecular test able to rapidly detect pyrazinamide resistance—using the FluoroType platform, but would need funding to commercialize it.

LAMP

Not to be confused with LAM (TB seems to have a branding crisis alongside its diagnostic crisis), LAMP stands for loop-mediated isothermal amplification. WHO issued guidance for the use of TB LAMP, another molecular nucleic-acid amplification test (NAAT), as a potential replacement for smear microscopy in August 2016.³⁸ Similar to Xpert, LAMP is a NAAT, and is faster (about 40 minutes) and less expensive than Xpert.³⁹ TB LAMP is more sensitive than smear microscopy, with a sensitivity of 40.3% (95% CI: 27.9 to 54.0) to 42.2% (95% CI: 27.9 to 57.9) in smear-negative samples. However, the test cannot detect drug resistance, requires several manual steps, and WHO reported that it could not make recommendation about the use of TB LAMP in the detection of TB among people with HIV due to lack of data.⁴⁰ The test may be an improvement over smear in some settings with low rates of HIV and drug resistance, but is unlikely to bring major changes to the field.

LAM testing

New data further support the urgent need to introduce Alere's urine-based Determine LAM TB test, for which WHO issued guidance in 2015 as a rule-in test for people with HIV with very low CD4 counts (<100 cells/ mm^3) or who are seriously ill. The test is particularly useful in hospital inpatient settings.

Researchers from the University of Cape Town—including Dr. Stephen Lawn, who unfortunately passed away in late 2016 after dedicating years of his life to the advancement of care for people affected by TB/HIV—conducted a study of 427 HIV-positive adults with acute medical hospital admissions, regardless of clinical presentation or symptoms. None were receiving TB care; 139 were later confirmed to have TB. In the first 24 hours of admission, sputum and urine samples were obtained from 37% and 99.5% of patients, respectively ($P < .001$). Sputum microscopy yielded just 19.4%. MTB/RIF using sputum yielded a slightly improved 26.6%. Urine LAM testing captured 38.1%, and combining MTB/RIF using sputum and urine LAM allowed for a 52.5% yield ($P < .01$). Urine LAM testing's value in improving yield was more dramatic in people with very low CD4 counts (<100 cells/ mm^3 : 18.9%, 24.3%, 55.4% and 63.5%, respectively; $P < .01$). The urine LAM test's yield was unrelated to respiratory symptoms, and specificity was 98.9% (274/277; 95% CI: 96.9 to 99.8%). A positive LAM status was strongly associated with death at 90 days (adjusted hazard ratio 4.20; 95% CI: 1.50 to 11.75). This clearly indicates that routine urine LAM testing for TB in newly admitted HIV-positive adults is feasible, provides major improvement in diagnostic yield with high specificity, is useful in identifying TB in people without respiratory symptoms and/or unable to produce sputum, and can rapidly identify patients at highest risk of death.⁴¹

A prospective observational study led by Médecins sans Frontières (MSF) in Kenya looked at the incremental diagnostic yield of urine LAM testing among hospitalized, symptomatic, and ambulatory (severely ill, CD4 < 200 cells/ mm^3 or with body mass index < 17 kg/ m^2) HIV-positive adults.⁴² Among 474 patients, 156 patients had confirmed TB—65.4% of them were LAM positive. Adding LAM increased the diagnostic yield of the algorithms from 47.4% (95% CI: 39.4 to 55.6%) to 84.0% (95% CI: 77.3 to 89.4%) when using clinical signs and X-ray; by 19.9%, from 62.2% (95% CI: 54.1 to 69.8%) to 82.1% (95% CI: 75.1 to 87.7%) when using clinical signs and microscopy; and by 13.4%, from 74.4% (95% CI: 66.8 to 81.0%) to 87.8% (95% CI: 81.6 to 92.5%) when using clinical signs and Xpert. Similar to the Cape Town study, LAM testing helped detect those at most risk of death: LAM-positive patients had an increased risk of two-month mortality (adjusted odds ratio: 2.7; 95% CI: 1.5 to 4.9).

In a third prospective TB cohort study—the first outside of Africa to our knowledge—researchers examined frozen urine samples from 109 patients with proven culture-positive TB for blinded urine LAM testing.⁴³ This is important as, unlike the sub-Saharan Africa setting that tends to have more advanced disseminated TB in the context of HIV co-infection, Thailand has more severely ill, disseminated, and pulmonary TB cases without HIV infection. The study included HIV-positive patients with TB; HIV-negative patients with disseminated TB; HIV-negative immunocompromised patients with TB; and diseases other than TB. The sensitivity of urine LAM in people with HIV was similar to that found in other studies (38.5%, 40.6%, and 45%, for CD4 T-cell/ mm^3 counts >100 , ≤ 100 , and ≤ 50 , respectively). LAM testing had an added effect in smear-negative, culture-positive people with HIV with disseminated TB with or without pulmonary involvement, increasing sensitivity to 44%. In HIV-negative patients with disseminated TB and in HIV-negative immunocompromised patients with TB, the sensitivities of the tests were 20% and 12.5%, respectively, and the specificity and positive predictive value were 100% for both groups. Positive urine LAM results were significantly associated with death.

Despite good results in such vulnerable populations, no country has yet committed to using LAM testing beyond pilot projects. The U.S. President's Emergency Plan for AIDS Relief (PEPFAR) included LAM testing in its 2017 Country Operating Plan (COP) Guidance as a commodity that can be purchased using

PEPFAR's HIV/TB budget code.⁴⁴ The Global Laboratory Initiative included LAM testing in its updated TB testing algorithms.⁴⁵ Countries with high burdens of TB/HIV must immediately roll out the Determine LAM TB test in hospital settings for all newly admitted HIV-positive patients who are seriously ill, regardless of symptoms.

LAM for treatment monitoring

A separate technology focuses on the same antigen, LAM, which underpins the Determine LAM TB test. Otsuka (developer of delamanid and OPC-167832, see Marcus Low's TB Treatment Chapter on page 129) is developing a new enzyme-linked immunosorbent assay (ELISA) that quantifies LAM concentration in sputum. In a clinical study of 308 HIV-negative participants, this assay was found to be highly specific, correctly identifying 100% (95% CI: 94.8 to 100%) of 56 people without TB and 97.8% (95% CI: 92.4 to 99.4%) of the 92 people testing negative for TB with smear, culture, and GeneXpert, but had been clinically diagnosed as TB based on symptoms and chest X-ray. LAM-ELISA's sensitivity was better than smear, detecting all 70 smear- and culture-positive samples (95% CI: 94.8 to 100%), and 50% of 58 smear-negative, but culture-positive, samples (95% CI: 37.5 to 62.5%). However, LAM-ELISA's sensitivity was still less than Xpert MTB/RIF, which detected 79.3% (95% CI: 67.2 to 87.8%) of smear-negative, culture-positive samples.⁴⁶

In a second study, LAM-ELISA was used to quantify sputum LAM concentration in 40 participants with smear-positive, pulmonary TB patients before treatment and at days 7, 14, 28, and 56 after starting standard treatment for drug-susceptible TB. LAM concentrations correlated strongly with time to detection in Mycobacterial Growth Indicator Tube (MGIT) liquid culture, and decreased during standard drug-sensitive TB treatment, indicating a potential use for treatment monitoring.⁴⁷

Otsuka, working with the Critical Path to TB Drug Regimens, is developing sputum LAM as a biomarker for measuring treatment response as an alternative to microscopy and culture. Efforts are ongoing to seek qualification from the U.S. Food and Drug Administration and the European Medicines Association to use LAM as a new drug development tool or method.⁴⁸ This LAM assay, if further developed could have role for treatment monitoring in programmatic use. However, because the ELISA platform is cumbersome, the assay is currently complex and lengthy, and thus might not be suitable for use for monitoring TB outside of clinical trials. Further investment could allow it to be improved and modified for use in routine patient care. Otsuka and outside funders should collaborate to fully develop this potentially important assay for patient care.⁴⁹

Liquid culture

Liquid culture remains the gold standard for diagnosing TB and detecting drug resistance. Automated and much faster than solid culture, it is particularly important for monitoring treatment response in people with MDR-TB, and would remain so even if Xpert XDR cartridges do successfully make it to market (since the latter cannot be used for treatment monitoring due to inability to distinguish between dead or live bacilli). Unfortunately, availability of MGIT automated liquid culture has been low, in part due to unaffordable pricing in places that were left out of a long-standing concessional pricing agreement (including some high-burden, low-income countries).⁵⁰

In an effort to improve access, the test's manufacturer Becton Dickinson (BD), FIND, the Stop TB Partnership, and the United Nations Development Programme (UNDP) announced in March 2017 an expansion of the test's concessional pricing to include 40 additional low- and middle-income countries, making a total of 85 countries eligible for reduced pricing.⁵¹ While a step forward, especially for countries like Papua New Guinea, many countries included are extremely small with low burdens of DR-TB. Many high burden countries (e.g., Ukraine and Brazil) or countries that want to use MGIT but cannot afford the high commodities cost (e.g., Tunisia) are still left out of this agreement, which perpetuates inequities through tiered pricing. BD should move towards a single low price in all low- and middle-income countries with a transparent, volume-based system for reducing price further once targets are met.

Sequencing

Liquid culture remains the gold standard for drug-susceptibility testing, as molecular tests—although extremely specific—are suboptimal in terms of sensitivity compared with phenotypic tests.⁵² But culture is time-consuming and requires high biosafety level laboratories. This leads to many patients lacking access to susceptibility testing for second-line drugs—WHO recommends the use of five effective drugs when the shortened regimen cannot be used, but many people are unable to access appropriate treatment because their TB is not fully tested for susceptibility to second-line drugs to know which would work for them. The vision of universal, comprehensive, culture-free drug susceptibility testing can only be realized with sequencing. Whole-genome sequencing is already being used for surveillance, and in developed countries such as the U.S., all newly diagnosed TB cases have samples sent for sequencing. With lower cost, easy-to-use, next-generation sequencing forthcoming, sequencing could become much more practical and affordable than it currently is. Companies such as Illumina, BioMérieux, and Genoscreen are developing sequencing for TB, and ThermoFisher's Ion Torrent-based product is on the market for research use.⁵³ Pioneering work in high-burden countries has demonstrated the potential of using sequencing to guide treatment choice: in Mumbai, good data linking outcomes with specific types of *gyrA* mutations have been used to inform treatment decisions on fluoroquinolone choice and moxifloxacin dose based on the type of mutation seen. Similarly, being able to distinguish between *inhA* and *katG* isoniazid-associated mutations could help to define those in whom higher dose isoniazid might be helpful—those with *inhA* mutations and without *katG* ones. Similarly, mutations in the *eis* promoter region are known to predict resistance to kanamycin, and certain *rrs* mutations predict resistance to all aminoglycosides.⁵⁴

Sequencing could allow for a more sophisticated, individualized approach to treatment to ensure maximal efficacy without unnecessary side effects resulting from likely ineffective drugs. This approach will require much better and more rapid linkage between diagnostic results and patient care, as well as greater willingness for individualizing treatment than is currently seen with the preferred 'one size fits most' mentality in most TB programs. Direct sequencing from clinical specimens requires extracting DNA from MTB. This would require improved collaboration to rapidly define, optimize, and validate the best methodologies for sequencing MTB from samples.⁵⁵ Finally, sequencing can only be developed to guide individual treatment when better data exist to link mutations with patient outcomes. A recent assessment of five tools—CASTB, KvarQ, Mykrobe Predictor TB, PhyResSE, and TBProfiler—found false-susceptible results from drug-susceptibility testing were mainly due to missing mutations in the resistance catalogues that the respective tools employed for data interpretation, and that cases of false resistance resulted from the misclassification of polymorphisms as resistance mutations—pointing to the need for a high-quality catalogue of resistance mutations to ensure the clinical utility of new tools.⁵⁶ The ReSeqTB database is collecting such data and has an open call for contributions.⁵⁷

Other advances in the detection of drug resistance

An important advance came in 2016 with the establishment of methodologies and minimum inhibitor concentration (MIC)⁵⁸ ranges for bedaquiline (0.015 to 0.12 µg/ml for the 7H10 and 7H11 agar dilution MICs and 0.015 to 0.06 µg/ml for the 7H9 broth microdilution MIC). However, these do not apply to MGIT, the commercial rapid liquid culture system. At the time of writing, WHO plans to publish in June 2017 an updated table of critical concentrations for second-line agents, including bedaquiline, clofazimine, and delamanid, for several culture media and MGIT. However, further research from larger data sets, such as one from Johannesburg, South Africa of approximately 1,000 patients, is needed to address concerns that the datasets informing WHO's guidance are too small.

The use of pyrazinamide—an important component of treatment of drug-susceptible and and some drug-resistant disease—also urgently needs better approaches for drug-susceptibility testing. This goal has remained elusive due to multiple resistance-conferring mutations all along the *pncA* gene, which codes for the protein that is pyrazinamide's target. Even drug-susceptibility testing on solid culture is challenging, as the acidic pH required to activate pyrazinamide impairs MTB growth. Sequencing of the *pncA* gene is likely the best way to determine resistance to pyrazinamide. As noted above, Hain is seeking funding to develop a pyrazinamide-resistance assay for the Fluorotype platform.

University of Maringá (Paraná, Brazil) researchers evaluated the resazurin microtiter assay (REMA) plate—an inexpensive, easy method that gives a colorimetric readout—at pH 5.5 for its performance in detecting susceptibility to pyrazinamide. They found that REMA was helpful for detecting pyrazinamide resistance when <50 µg/ml was considered as the cut-off, and results came in eight days. However, two known pyrazinamide-resistant isolates failed to grow at this pH level, indicating that it would be useful to evaluate this method at pH 5.6–5.9 to better understand REMA's utility in identifying pyrazinamide-resistant isolates.⁵⁹

Moving forward by stepping back—antibody testing

Blood-based TB diagnostic tests have been inaccurate and unreliable, leading to the negative WHO recommendation against their use, and indicating that more research is needed.⁶⁰ A recent study analyzed IgG antibody responses to over 100 antigens in blood samples from 755 adults with presumptive pulmonary TB and found poor sensitivity for detecting TB (35% sensitivity at 90% specificity, as compared with a minimal target of 65% sensitivity at 98% specificity established by target product profiles).⁶¹ A conventional antigen-based IgG detection test would therefore be unlikely to meet target product profile requirements, and does not merit further investment of limited TB R&D resources.

Chest X-ray

In 2016, the WHO issued a summary of its existing recommendations on chest X-ray as a screening tool for TB disease, indicating its sensitivity, its importance for diagnosing childhood TB, its additive value with GeneXpert, its use in diagnosing TB in people with HIV, and its role in ruling out active TB before treating latent TB infection.⁶² Computer-aided detection (CAD), such as the CAD4TB software, may help X-ray technicians identify TB. The WHO will review the evidence and may make a recommendation in 2017 about the use of such computer-assisted reading tools.⁶³

Improving TB detection through better sample transport

Another strategy for improving TB diagnosis in the field involves improving sample transport. The lack of a broadly accurate point-of-care test for TB leaves the field reliant on centralized testing and drug-

susceptibility testing, meaning that samples often have lengthy travels in suboptimal conditions to get from patient to lab. Over the course of storage and transit, the sample can degrade, making results less reliable. Reagents, such as cetylpyridinium, that have no need for a cold chain have been used in some settings for many years to stabilize sputum for higher quality following testing; however, its use is incompatible with culture. New commercial reagents aim to mitigate sample decay during sputum transport, improve convenience, and be compatible with culture.

OMNIgene SPUTUM is one such reagent; its sponsor says that it is compatible with culture and GeneXpert testing.⁶⁴ A recent study in Nepal of 100 samples, where transport time ranged from 2–13 days, handled samples in both the standard-of-care method and with new OMNIgene SPUTUM before submitting them for smear microscopy and GeneXpert MTB/RIF testing. The study found that overall smear results were comparable regardless of how the sputum was transported (58% in the OMNIgene group and 56% in the standard of care groups), but slightly more smear-negative samples were detected in the OMNIgene group (17% versus 13%; $P = .0655$, non-significant).⁶⁵ Another product, PrimeStore Molecular Transport Medium, by Longhorn, claims to be compatible with molecular testing (however, similar to cetylpyridinium, it cannot be used with culture as it kills the bacteria).⁶⁶ A WHO technical expert meeting in May 2017 reviewed the evidence associated with this and other sample transport innovations to advise whether these innovations are actually improvements or just more expensive; findings are expected by the end of 2017.

DETECTING LATENT TB INFECTION AND DISTINGUISHING IT FROM ACTIVE DISEASE

C-Tb

C-Tb is a new, specific skin test developed by Statens Serum Institute for two antigens, ESAT-6 and CFP10. The test aims to combine the advantages of older tuberculin skin testing, such as ease of use and inexpensiveness (and offers an alternative, as purified protein derivative used for tuberculin skin testing has been in shortage over the past few years),⁶⁷ with the specificity of interferon gamma release assays such as QuantiFERON. A double-blind, phase III randomized trial enrolled 263 individuals as negative controls, 299 occasional contacts of people with TB, 316 close contacts, and 101 people with TB disease. The study found that induration (the hard bump that develops, indicating a positive skin test) sizes were similar to traditional tuberculin skin testing, but C-Tb positivity, unlike tuberculin skin testing positivity, was not affected by BCG vaccination status. C-Tb and QuantiFERON testing agreed in 94% of participants over five years. Moreover, C-Tb test positivity trended up with increasing risk of infection, from 3% in negative controls to 16% in occasional contacts, to 43% in close contacts.⁶⁸ This test may help to better detect who is at most risk for developing active TB and in need of preventive therapy.

Quantiferon TB Gold Plus

Another approach to improving detection of TB infection is through improving the performance of interferon gamma release assays. The new-generation QuantiFERON test, QuantiFERON-TB Gold Plus, was recently evaluated in two studies. These showed that it has high concordance with its predecessor, and that the new test has a stronger association with surrogate measures of TB exposure in adults (such as average time spent with the index case).^{69,70} The independent study authors indicated that the difference in interferon gamma production in the new test's two antigen tubes (TB2–TB1) can provide an indirect estimate of specific CD8 response, which correlates with increased MTB exposure, suggesting that it might be useful for identifying people with recent TB infection.⁷¹

RECOMMENDATIONS

Promising technologies are in development that can improve testing and simplify the current convoluted pathway to diagnosis. The little that has been invested in diagnostic development thus far has yielded impressive results. However, development time, and time to widespread uptake of tests, is taking far too long. With political will and resources, great advances can be made in reducing the unconscionable diagnosis gap. Interventions are critical in the following areas:

- **TB diagnostic tool development:** important advances such as the GeneXpert Omni and Xpert XDR assay have been moving too slowly through development, and others such as Otsuka's sputum LAM for treatment monitoring are at risk of languishing, largely because of inadequate investment in TB diagnostics research and development. In 2015, only \$62.8 million was invested out of the \$364 million required.⁷² ***Increased private sector, public sector, and philanthropic investments in TB diagnostic R&D are urgently needed.***
- **Basic science research:** to move beyond sputum-based tests and all of their limitations, increased investment in basic science is crucial. Only with more investment upstream can we identify new markers of TB infection, disease, improvement, or worsening that could eventually underpin truly new, transformative diagnostic and treatment monitoring technologies. Yet basic science research in TB received just USD \$139.8 million in 2015, out of the \$455 million required.⁷³ ***Governments around the world and philanthropic institutions must increase basic science funding.***
- **Pricing:** in the current monopolistic market that diagnostic developers enjoy, pricing agreements are complex and vary widely between countries. As with drugs, a transparent, volume-based, flat pricing structure is needed for all TB diagnostics, including commodities and service and maintenance pricing. Given the distribution of resources and TB burdens, all low- and middle-income, as well as high-burden, countries should have access to a single, flat price for TB diagnostic test commodities and their related costs. Key TB product procurers, including the Global Drug Facility (GDF), UNDP, and country governments, should work together to negotiate better agreements with diagnostic developers on pricing and access. ***Companies must price products affordably and transparently, with a single low price for all low- and middle-income or high-burden countries, and transparent volume-based milestones established for further price reductions.***
- **Uptake:** though the complexity of the recommended diagnostic algorithms and pricing structures are not ideal, they do not excuse the appallingly low uptake at country level of essential tools. Access to Xpert, liquid culture, line probe assays, and, in high TB/HIV burden settings, LAM testing is vital. Yet country governments have been remiss in their introduction of these potentially life-saving tools. ***National TB programs must rapidly update guidance to ensure best diagnostic practices, and procure and implement products accordingly, including working with HIV and other programs when necessary to ensure access to testing.***

ACKNOWLEDGEMENTS

Erica Lessem thanks Wayne van Gemert, Chris Gilpin, Ruth McNerney, and Mark Harrington for their editing; Nathanael Leo for his support for references; and the contributions of many researchers, developers, and technical experts that made this chapter possible—especially Catharina Boehme, Chief Executive Officer of FIND, whose presentation at the 2017 Conference on Retroviruses and Opportunistic Infections made this chapter immeasurably easier to write.

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THE TB PREVENTION PIPELINE

By Mike Frick

INTRODUCTION

One of the tuberculosis (TB) field's most often voiced truisms has been that one-third of humanity is infected with *Mycobacterium tuberculosis* (MTB), the causative agent of TB disease. This estimate is invoked so frequently that it has become conventional wisdom and outgrown the need for a citation. A new estimate of the global burden of MTB infection, published in the past year, has brought this well-worn number into the present by accounting for changes in demography, the shifting size and distribution of the TB epidemic, and scientific advances that have improved our ability to detect and study MTB.¹ The revised figure suggests that nearly a quarter of the world's people (1.7 billion individuals) are infected with MTB. Although lower than the previous appraisal, this new estimate is far from a reassurance that the response to TB is on track. Instead, it points to the sizeable group of people in need of better options to prevent MTB infection from progressing to active, transmissible TB disease. This massive number thereby motivates the need to accelerate the development of new TB vaccines and preventive therapies and increase support for the basic science and translational research that enables progress in both areas.

The vast majority of the estimated 1.7 billion MTB-infected individuals alive today will never see their infection progress to active TB disease. But for some, events over the life course (e.g., aging, pregnancy), the presence of immune-compromising conditions (e.g., diabetes, HIV), and predisposing factors yet to be discovered increase the likelihood that what is termed latent TB infection (LTBI) will turn into symptomatic illness.² Why some people are more likely to progress from infection to disease, and how to identify these individuals within the larger group of MTB-infected people at less risk, pose two of the central questions animating research and development (R&D) for new TB vaccines and other preventive strategies, including better diagnostics and shorter, safer therapies. Answering these questions would allow public health programs to steer interventions toward those most in need and would increase the speed and efficiency of clinical trials, allowing studies to enroll fewer participants by focusing on those at greatest risk. The answers can only come from advances in basic and translational science and will likely take the form of biomarkers—the measurable biological processes, clinical phenotypes, or gene activities that signify either particular infection or disease states or the body's response to vaccination or treatment.³ The lack of biomarkers that act as prospective signatures of risk of progressing from infection to disease is one of the primary barriers slowing progress for TB prevention R&D.

Recognizing the importance of basic science to the TB prevention pipeline, this chapter opens by surveying recent advances and promising directions in understandings of host-pathogen interaction and TB pathogenesis before reviewing progress in the clinical pipelines for new TB vaccines and preventive therapies. Viewed from any of these three angles—basic science, TB vaccine development, and R&D for new chemoprophylaxis—TB prevention research is gaining momentum and entering a period energized by new thinking. Promising moves on the scientific front are being matched by increasing political attention to TB prevention. The chapter closes by discussing recent steps taken by governments to break the cycle of transmission that fuels the global TB epidemic by intervening before MTB infection becomes symptomatic, infectious illness. Garnering the political will to create, through research, and expand, through public health programs, new interventions to prevent TB rests on recognizing the estimated 1.7 billion people with MTB infection as a population with unmet health needs. Future TB cases will arise from this cohort—as well as from those yet to be infected—so governments should see investments in TB prevention R&D as part of a commitment to ensuring the health of present and future constituents.

PROGRESS IN TB PREVENTION SCIENCE

In January 2017, scientists gathered in Vancouver, Canada, at a Keystone Symposium to discuss new developments in basic understandings of TB. Samuel Behar, one of the scientific chairs of the conference, opened the meeting by recounting the example of Nobel Prize–winning physicist Isidor Rabi, who worked on the Manhattan Project during World War II and later became an advocate against nuclear proliferation. Behar set the tone for the meeting by quoting Rabi’s mother, who at the end of each school day asked her son not “what did you learn today?” but instead “did you ask a good question today?” Judging by presentations at the Vancouver Keystone Symposium, that emphasis on asking good questions has permeated the TB basic science field, which feels more open to and better connected with other research areas, and more inclusive of a variety of disciplines, than it has in recent years.

The period following the disappointing results from the phase IIb trial of TB vaccine candidate MVA85A in 2013 sent many in the TB field back to the basics to rethink the hypotheses—some would say dogmas—that have guided the field for at least the last 15 years.^{4,5} Scientists rethought the role of the pro-inflammatory cytokine interferon gamma (IFN γ) in protection against TB disease; questioned the utility of the animal models used to test vaccine candidates before launching clinical trials; and applied new technologies (e.g., positron emission tomography/computed tomography [PET/CT] imaging) to shed light on the complex dynamics of MTB interacting with its human host at sites of infection in the lung.⁶ From this work, a more complicated story has emerged in which MTB infection and TB disease are now understood to lie along a continuum of host-pathogen activity rather than exist as separate, mutually exclusive conditions.⁷ This more nuanced framework has created the space to embrace the complexity behind once monolithic concepts (e.g., what is ‘latent’ about latent TB infection?) and to approach longstanding challenges—for example, the ability of MTB to evade, withstand, and sometimes turn the body’s immune response to its advantage—with the insights of allied disciplines at hand.

Cross-disciplinary insights into MTB

If discussions during the “back to basics” years sometimes felt like circling the same ground repeatedly, the revised story has come with a habit of asking good questions that are taking the field in new directions. This habit is borne by the encouragement of what Valerie Mizrahi, the co-chair of the Vancouver Keystone Symposium, called “orthogonal thinking.” Two lines are orthogonal if they intersect at right angles, and TB basic science is now rife with examples of research projects that combine the tools and approaches of different, intersecting disciplines to make headway on longstanding challenges. One promising example is the combination of structural chemistry and molecular biology to visualize and understand the unique properties of MTB’s cell wall.⁸ The mycolic acids (essentially long chains of carbon atoms) that compose the outer membrane of the MTB cell wall give it its famous “waxy” character, which protects the organism from the body’s immune response as well as from many antibiotics. Better understanding the features of this mycolic acid–rich membrane could clear a path for developing new diagnostics and therapeutic agents. Progress here has benefitted from the development of more sophisticated methods for imaging specific cell wall components.⁹

Staining techniques—such as the Ziehl–Neelsen stain, developed in the 1880s—take advantage of the unusual properties of the mycobacterial cell wall to color-label MTB cells in sputum when viewed under a microscope. This technique forms the basis of sputum smear microscopy, which remains the most widespread TB diagnostic method but comes with major limitations: it is nonspecific to MTB and cannot distinguish dead MTB cells from live ones. One study sought to tackle this problem by developing small-molecule fluorescent probes attached to a kind of sugar called trehalose that is metabolized by MTB and incorporated into the cell wall. MTB cells that take up this trehalose probe fluoresce green, but so do other non-MTB components of sputum, making it difficult to separate MTB from other organisms.¹⁰ A related study overcame this limitation by modifying the trehalose dye so that it only fluoresces after

incorporation into the MTB cell wall.¹¹ Because its uptake requires MTB to metabolize it, the resulting fluorescent dye—called DMN-tre—can distinguish live MTB cells from dead ones.

If validated in field settings, this imaging technique could represent a major advancement over traditional staining by offering an improved method for sputum smear microscopy based on the same ubiquitous microscope platform. More immediately, it could provide a powerful tool for monitoring the progress of clinical trials by allowing researchers to measure reductions in pulmonary bacterial burden in TB treatment trial participants. For basic scientists, the DMN-tre dye might provide a way to investigate the changing dynamics of the MTB cell wall at different points in the adaptive immune response with a high degree of spatial resolution.¹² Work on DMN-tre is continuing, and the dye is currently being studied for its ability to selectively label MTB cells that are live and replicating and distinguish these from live but non-replicating organisms.¹³ This application would be a major boon to TB treatment and prevention science, as the field has lacked satisfactory ways to study the behavior of the live, non-replicating cells thought to exist during various stages of infection and disease.

Advances in translational science

The multiple potential applications of the DMN-tre dye, spanning from the lab to the clinic, offer a good example of the translational science that now occupies a more central place in TB prevention research. Translational science refers to the iterative process of turning observations in the lab, clinic, or community into interventions that improve public health.¹⁴ Observations from all three arenas—lab, clinic, and community—are driving translational TB prevention research projects through collaborations that include once odd pairings: basic scientists are teaming up with public health practitioners; vaccine developers are building basic science into clinical trials; and animal modelers are partnering with each other to improve existing model systems and share insights gleaned from experimental work across different species. In short, there is an encouraging trend toward reciprocally informed preclinical and clinical research and studies using various animal systems in synergy.

The merits of the several animal models used in TB R&D have inspired considerable debate, and conversations on the subject tend to pick up in intensity after major clinical trials return disappointing findings (as after the MVA85A phase IIb trial).^{15,16,17,18} When wading through the thick details of these discussions, it is helpful to recognize the bigger context in which animal modeling occurs. Animal models are tools that, like analogies, enable scientists to make comparisons between two things based on partial similarities.¹⁹ No single animal model system recapitulates MTB infection and TB disease in humans perfectly, but for these comparisons to be useful, animal models need to represent human TB in significant and meaningful respects. In the spirit of the Vancouver Keystone Symposium, what is at stake is less about selecting the right animal model and more about asking good questions given the models at hand, keeping limitations in mind when interpreting results, and working to improve model systems to pursue questions that cannot be answered with available frameworks.

An example of the latter approach is the use of Collaborative Cross (CC) mice to achieve greater genetic diversity in the mouse model. CC mice overcome the limited genetic repertoire and non-ideal population structure of the mouse models commonly used in medical research by offering a large panel of well-characterized, multiparental, recombinant inbred lines with greater genetic diversity.²⁰ One recent study used CC mice to investigate the relationship between bacillus Calmette-Guérin (BCG) efficacy, host genotype, and TB susceptibility.²¹ The investigators found that, on an aggregate level, mice from different lines displayed variable susceptibility to TB, different immunological responses to infection, and no durable protection from BCG vaccination—all to be expected from observations in humans. However, at the level of individual mouse genotypes, the story was more complicated: TB pathogenesis and immune responses differed across CC mouse strains; BCG efficacy varied by host genotype; and these qualities—MTB susceptibility and BCG efficacy—were separable, heritable genetic traits.²² The lack of BCG efficacy

overall was driven by a few mouse lines in which vaccination offered no protective effect as measured by reduction in bacterial load in the lungs and spleen. In the words of the investigators: "Based on these findings, it is not clear that optimizing a vaccine to protect a single standard laboratory strain of mouse will produce an intervention that is broadly efficacious in an outbred population, or even that a single vaccine is capable of protecting genetically diverse individuals."²³

An extension of this project is using CC mice to model the complex interaction between environment, host genotype (susceptibility), bacterial genotype (virulence), and phenotype (outcome of MTB exposure or infection).²⁴ Essentially, the investigators are asking: What happens when one takes a panel of diverse mice, combines that with a panel of diverse MTB clinical isolates, and starts getting closer to the host-pathogen dynamics found in the real world? The study seeks to identify host-pathogen quantitative trait loci (QTLs), or sections of DNA (the loci) that correlate with variations in a given phenotype (the quantitative trait). Many QTL mapping studies focus on either the host or the pathogen genome, but the approach being pursued here takes into account the complex interaction between QTLs underlying host phenotypes (e.g., bacterial burden in the lungs or how well an animal controls infection) and bacterial fitness.²⁵ The incorporation of host and pathogen diversity into animal model systems may clear a path for experimentally pursuing a number of questions of importance to TB vaccine developers. For instance, what does protective immunity look like within and across genetically diverse human populations encountering genetically diverse strains of MTB? How can researchers account for the complex interplay between MTB, its human host, and the broader social and natural environment when designing vaccines? Can a single vaccine protect all people from all strains of MTB?

CC mice are one example of broader efforts to better represent the complexity of human TB within animal model systems. Other research projects are working with several different animal models to provide new insights into one of the thorniest questions in TB prevention science: What role do T cells play in protective immunity, and how do they play it? A growing body of detailed immunology work in mice and nonhuman primates suggests that some CD4+ T-cell responses can be protective while others may be pathogenic, and understanding the difference will be critically important for designing effective vaccines. Most TB vaccine candidates to date have sought to generate protection through immunity mediated by CD4+ T cells that release type 1 helper (Th1) cytokines such as IFN γ and tumor necrosis factor alpha (TNF α).²⁶ The emphasis on Th1 immunity reflects a wealth of data showing that humans and other species deficient in CD4+ T cells are extremely susceptible to MTB infection and progressive disease. And yet a study measuring BCG-specific CD4+ and CD8+ T-cell responses in nearly 6,000 infants found no correlation between the magnitude of expression of Th1 cytokines and protection against developing TB over two years of follow-up.²⁷ Genetic analyses suggest that the MTB genes coding for the epitopes most frequently recognized by human T cells appear little changed over time, raising the possibility that detection by Th1 T cells may somehow aid MTB.²⁸ That could be the case if overproduction of pro-inflammatory cytokines such as IFN γ by T cells reflects a loss of immune control or ongoing damage to lung tissue, which could create opportunities for the onward transmission of MTB.

In this vein, one recent study of MTB infection in mice suggests that overproduction of IFN γ can lead to worse outcomes, but that the role of IFN γ may change at different sites of infection (e.g., lung versus spleen).²⁹ In the lung, IFN γ accounted for only 30 percent of CD4+ T cell-dependent bacterial control (measured by reduced bacterial load six weeks post-exposure) but was responsible for over 80 percent in the spleen.³⁰ While increasing IFN γ production by CD4 T cells aided bacterial control in the spleen, it worsened pathology in the lung and led to earlier death. Importantly, the PD-1 receptor (a type of off switch that keeps T cells from attacking other immune cells) prevented excess IFN γ production.³¹ These findings hold a number of implications. First, it may be just as important for TB vaccines to promote regulation of IFN γ as it is expansion of IFN γ -producing T cells. Second, even if some amount of IFN γ production is necessary for protection, it may not be the most interesting thing T cells do when responding to MTB infection in the lungs (although it may have more importance when fighting disseminated TB).

Third, timing as well as location matter when measuring pathogenic versus protective qualities of CD4+ T-cell responses. Studying the lungs and spleen of mice after necropsy is relatively straightforward, and PET/CT imaging has allowed researchers to produce composite pictures of inflammation-based activity in the lungs of larger mammals like nonhuman primates. However, most immunology work in humans still depends on assaying samples of peripheral blood. The extent to which measurements taken from blood reflect disease processes in the lung is unknown, and studies in nonhuman primates have found that T cells in circulating blood (the systemic immune response) do not closely reflect T-cell responses observed in lung lesions (the local immune response).^{32,33} By relying on peripheral blood, there is a risk that researchers will miss observing the complexities of host-pathogen interaction directly and instead only view the traces of this activity that end up in blood.³⁴ A similar qualification applies to the endpoints used in animal model versus human studies. Most studies in animals gauge “control” by assessing bacterial load in the lungs—the one thing usually not measured in clinical trials. This difference in endpoints offers an important reminder that animal model systems are by definition approximations, not mirrors, of human TB.

Related work in mice has shown that the differentiation of CD4+ T cells is another important factor in their ability to effectively respond to MTB.^{35,36} (Differentiation is the process by which T cells assume specialized phenotypes—e.g., becoming either memory or effector cells—when presented with antigen by other immune cells that have encountered a pathogen.) In one study, the outcomes of differentiation shaped how well CD4+ T-cell subsets migrated into the lung from the lymph node and circulating blood. Less differentiated cells appeared better at migrating, whereas those with more terminal differentiation tended to remain in the lung vasculature.³⁷ The ability of T cells to enter the lung may prove more important for protection against MTB than their ability to produce large amounts of IFN γ . A follow-on study identified characteristics of Th1 immunity that influence the differentiation of T cells into more and less protective types.³⁸ Considered together, these findings suggest that vaccine developers will need to look beyond whether candidate vaccines can expand IFN γ -producing CD4+ T cells to consider other factors such as a vaccine’s effect on cell differentiation.

Much of this work has taken place in mice, but supporting observations have also been made in nonhuman primates. A presentation of these results at the Vancouver Keystone Symposium ended with a vibrant, fluorescent image of a granuloma from a macaque lung.³⁹ The image revealed a pileup of T cells clustered around the edge of the granuloma with just a few at the site of infection in the central core. The photograph was beautiful and offered a striking example of the power of imaging to open new windows into seeing human cells in physical relation to MTB. When one zooms out from the particular details of individual studies, many of the recent advances in TB basic and translational science coalesce into the insight that relationships matter. It matters how we relate observations of host-pathogen interactions made in animal models to the more complicated humans they stand in for before TB prevention concepts and constructs enter clinical testing.

Movements in experimental medicine

Progress in translational science for TB prevention ultimately hinges on opportunities to work in humans. To this end, vaccine developers have made concerted efforts to design vaccine trials in ways that promote collaboration between basic scientists and product developers. One strategy involves nesting small experimental medicine studies into larger clinical trials. Such studies take advantage of the opportunity to work in humans to conduct detailed immunology or to develop tools for pursuing such work.⁴⁰ For example, last year’s *Pipeline Report* reviewed a phase I study of TB vaccine candidates H4:IC31, H56:IC31, and BCG revaccination in South African adolescents. Sponsored by Aeras and the U.S. National Institutes of Health (NIH) HIV Vaccine Trials Network, the study aims to collect a wide array of immunological data to inform the development of novel immune assays that may help to identify correlates of risk or protection.⁴¹ Another experimental medicine study sponsored by Aeras will open

soon at St. Louis University. Fifteen adult volunteers will undergo leukapheresis (a process in which white blood cells are separated from other parts of the blood) at two time points: pre-BCG vaccination and post-BCG vaccination.⁴² White blood cells (leukocytes) are central actors in the immune system, and this study will collect the large quantity of these cells needed for assay development and a range of other scientific applications (e.g., exploring the function of particular immune cell subsets).

PROGRESS IN TB VACCINE DEVELOPMENT

On the clinical side, TB vaccine developers are preparing to release results from several large trials for the first time since the 2013 publication of initial findings from the phase IIb trial of MVA85A. TB vaccine candidates M72/AS01E and H4:IC31 are expected to complete phase IIb and phase IIa trials, respectively, within the next year. In some respects, these two studies represent the before and after of a major shift in strategy that took place in the TB vaccine field after 2013. Up until that point, most clinical development programs focused on testing the ability of candidate vaccines to prevent TB disease (POD). In recent years, developers have started designing studies around two alternative primary outcomes: prevention of infection (POI) and prevention of recurrence (POR). POI studies assess whether vaccines can prevent MTB infection, whereas POR trials evaluate the ability of vaccines to prevent relapse or reinfection in the estimated four to six percent of people who develop disease after successfully completing treatment.

Both POI and POR trials “are intended to show the biologic activity of vaccine candidates using more focused populations specifically selected to reduce sample size.”⁴³ In other words, POI and POR studies are tactics on the road to licensing a new vaccine that prevents TB disease. The hope is that POI and POR trials will shorten this road by quickening the pace and decreasing the cost of clinical trials while yielding glimpses of efficacy at earlier time points to inform the selection of candidates to take forward into larger efficacy trials. The success of these tactics will depend on the extent to which the underlying mechanisms of prevention of infection or recurrence correlate to prevention of disease. Because this correlation is unknown, prevention of disease will likely remain the primary outcome measure of late-stage efficacy trials, as regulatory authorities may be reluctant to approve a new TB vaccine based on surrogate markers related to POI or POR. This qualification is compounded by the fact that there is no direct test for MTB infection. Available methods for diagnosing MTB infection—the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs)—only measure immune reactivity to MTB. Furthermore, these tests cannot reliably predict an MTB-infected individual’s likelihood of disease progression.

While the strategy has changed, the composition of the TB vaccine pipeline bears marked similarity to previous years. The 2017 pipeline contains 14 candidates under active clinical development, representing three main constructs (**Table 1**). Four subunit vaccines pair different combinations of MTB antigens with immune-modifying adjuvants; five viral-vectored vaccines employ weakened viruses to deliver antigen; and five whole-cell vaccines are based on genetically attenuated MTB or closely related mycobacterial species. These vaccines have been studied in a range of populations—from BCG-vaccinated infants to HIV-infected adults—with current efforts now focused on POI or POR trials among HIV-negative, MTB-uninfected adolescents and adults.

Prevention of disease trials

GlaxoSmithKline’s (GSK’s) **M72/AS01E** TB vaccine candidate is nearing the conclusion of a phase IIb efficacy trial in 3,573 MTB-infected, HIV-negative adults in South Africa, Kenya, and Zambia. M72/AS01E is a subunit vaccine that pairs two MTB antigens (32A and 29A) with the AS01E adjuvant. Participants received either two intramuscular doses of M72/AS01E or placebo administered 30 days apart. The primary endpoint is incident cases of pulmonary TB disease (unassociated with HIV), and the primary outcome analysis is case driven, meaning that the trial must accrue a sufficient number of TB cases in order to trigger the analysis.⁴⁴ GSK reported that it was close to nearing the required number in

April 2017, and GSK and Aeras expect to release the first efficacy results in early 2018.⁴⁵ As this is the first efficacy study of a TB vaccine since the MVA85A phase IIb trial, these results will generate substantial interest.

Table 1. TB Vaccines in Development

Agent	Class/Type	Sponsor(s)	Status
<i>M. vaccae</i>	Whole-cell <i>M. vaccae</i>	Anhui Zhifei Longcom	Phase III
M72/AS01E	Protein/adjuvant subunit vaccine	GSK, Aeras	Phase IIb
DAR-901	Whole-cell <i>M. obuense</i>	Dartmouth University, Global Health Innovative Technology Fund	Phase IIb
VPM1002	Live rBCG	Serum Institute of India, Vakzine Projekt Management, Max Planck Institute for Infection Biology, TBVI	Phase IIb
H4:IC31	Protein/adjuvant subunit vaccine	Aeras, SSI, Sanofi Pasteur, Valneva	Phase IIa
H56:IC31	Protein/adjuvant	SSI, Aeras, Valneva	Phase IIa
MTBVAC	Live genetically attenuated MTB	University of Zaragoza, Biofabri, TBVI, Aeras	Phase IIa
ID93/GLA-SE	Protein/adjuvant	Infectious Disease Research Institute	Phase IIa
RUTI	Fragmented MTB	Archivel Farma	Phase IIa
Ad5Ag85A (aerosol)	Viral vector	McMaster University, CanSino	Phase I
ChAdOx1.85A + MVA85A	Viral vector	Oxford University	Phase I
MVA85A (aerosol)	Viral vector	Oxford University, TBVI	Phase I
MVA85A-IMX313	Viral vector	Oxford University, Imaxio	Phase I
TB/FLU-04L	Viral vector	Research Institute for Biological Safety Problems, Kazakhstan	Phase I
rCMV	Viral vector	Oregon Health and Science University, VirBio, Aeras	Finishing preclinical development
ChAd3 + MVA (aerosol)	Viral vector	GSK, Transgene, Aeras	Finishing preclinical development

ChAd: chimpanzee adenovirus vector

GSK: GlaxoSmithKline

MTB: *Mycobacterium tuberculosis*

MVA: modified vaccinia virus Ankara

rBCG: recombinant bacillus Calmette-Guérin

rCMV: recombinant cytomegalovirus

SSI: Statens Serum Institut

TB: tuberculosis

TBVI: TuBerculosis Vaccine Initiative

Prevention of infection trials

TB vaccine candidate **H4:IC31** is nearing the end of a phase IIa trial in 990 South African adolescents. H4:IC31 is a subunit vaccine that combines MTB antigens Ag85B and TB10.4 with IC31, an adjuvant owned by the French company Valneva. The vaccine was developed by the Statens Serum Institut (SSI) of Denmark and licensed by Sanofi Pasteur. The phase IIa trial contains three arms: one-third of participants received two doses of H4:IC31, one-third received placebo, and one-third were revaccinated with a

single dose of BCG. The first two arms are double-blinded; the BCG revaccination arm is open label. The trial is powered to compare H4:IC31 versus placebo and BCG revaccination versus placebo, but not to compare H4:IC31 to BCG. Primary outcome measures include safety and prevention of MTB infection as measured by rates of IGRA (in this case, Qiagen's QFT-Gold test) conversion from negative to positive. The trial needs to accrue 64 cases of MTB infection for the primary outcome analysis. Aeras reports that the trial reached this milestone in the summer of 2016, when the data safety and monitoring committee, after reviewing the available data, recommended that the study complete the protocol and continue to accrue additional cases during follow-up.⁴⁶ Aeras expects to release results in the first quarter of 2018.

As the first phase IIa study of a TB vaccine candidate under the POI paradigm, the phase IIa trial of H4:IC31 had to stake out a position on one of the thorniest issues for POI trials: selecting the right primary endpoint. It remains unclear what effect H4:IC31 or BCG would have on QFT conversion if efficacious. If a protective effect appeared soon after vaccination, would it prevent QFT conversion from happening at all? Or would vaccination primarily help the recipient clear infection by controlling bacterial replication rather than blocking infection entirely? In this event, trial participants could QFT-convert from negative to positive upon infection post-vaccination and then revert to negative at a later time point. To unpack this question, the phase IIa trial contains many secondary outcomes, including assessing prevention of MTB infection by comparing rates of *sustained* IGRA conversion (defined as conversion to positivity with no reversion during the follow-up period).⁴⁷ To inform the secondary analyses, participants who QFT convert are undergoing repeat testing according to a carefully determined schedule to assess whether conversions remain stable over time.⁴⁸ The complexity involved here is a product of the limitations of available diagnostic technologies, as the meaning of IGRA conversion is unclear. Rather than detect the presence of infection directly, IGRAs measure the release of IFN γ by circulating white blood cells in response to MTB antigens. We know that QFT converts to positive when infection occurs, but we cannot assume the opposite: that QFT will revert to negative when infection is cleared.

The H4:IC31 phase IIa study is the first prospective, randomized, placebo-controlled clinical trial to evaluate whether BCG revaccination can prevent MTB infection. If the study finds that adolescents revaccinated with BCG have lower rates of QFT conversion than those receiving placebo, it could generate substantial public health interest, as BCG is safe, inexpensive, licensed, and widely used. Under this scenario, Aeras has considered conducting a follow-on phase IV trial in the same adolescent population to see if BCG revaccination could prevent TB disease—similar, perhaps, to the BCG-REVAC cluster-randomized community study done in Brazil in the early 2000s.^{49,50} Such a study would require a very large sample size but could be simpler to conduct in comparison to a phase III trial of an investigational product. A phase IV study would provide the opportunity to collect biological samples, which could be analyzed for correlates of protection to inform future research. In contrast, a compelling result for H4:IC31 might lead to a phase IIb/III POD trial in a broader population under a global licensure strategy.⁵¹

The **MTBVAC** vaccine candidate is a live, genetically attenuated form of MTB made less virulent by the deletion of two genes (*phoP* and *fadD26*). Discovered at the University of Zaragoza, MTBVAC is being developed in collaboration with Biofabri, a Spanish biotechnology company, with support from the Tuberculosis Vaccine Initiative. MTBVAC completed a first-in-human phase I safety study in Switzerland in 2015 and is currently completing a phase Ib safety, dose-escalation, and immunogenicity study comparing three doses of MTBVAC to BCG in South African infants.^{52,53} This trial includes an initial safety arm in adults; with safety demonstrated in this group, the study proceeded to the infant cohort in February 2016. A phase IIa study in South African newborns is planned for 2018.⁵⁴ In addition, MTBVAC is preparing for a phase IIa trial in QFT-negative and QFT-positive South African adults.⁵⁵ Participants will receive either one dose of MTBVAC (at one of four dose levels) or placebo administered intradermally. Primary outcome measures will assess safety, whereas secondary outcomes will investigate POI measured

by QFT conversion in adults without MTB infection at study start.⁵⁶ MTBVAC provides an interesting example of a vaccine candidate following two lines of development: the infant studies are assessing whether MTBVAC can replace BCG, while the work in adults is designed to test whether MTBVAC can boost BCG.⁵⁷

Another whole-cell mycobacterial vaccine candidate—**DAR-901**—is continuing a phase IIb POI trial among BCG-vaccinated, MTB-uninfected adolescents in Tanzania.⁵⁸ DAR-901 is a form of inactivated *Mycobacterium obuense* developed at Dartmouth University and manufactured from the master cell bank of SRL 172, an earlier vaccine candidate studied in the phase III DarDar trial.⁵⁹ The primary difference between DAR-901 and SRL 172 is that DAR-901 is grown in broth rather than agar, a more scalable production method. The phase IIb POI trial is fully enrolled with 650 adolescents aged 13–15.⁶⁰ Participants received either three 1 mg doses of DAR-901 or placebo administered intradermally and will undergo repeat IGRA testing using Oxford Immunotec's T-Spot at 12 and 24 months after immunization.⁶¹ The 1 mg dose was selected based on a three-dose phase I study among BCG-vaccinated adults in the United States conducted by Dartmouth University and Aeras. Results showed that a 1 mg dose was safe and well tolerated and induced cellular and humoral immune responses to MTB antigens comparable to those observed with a five-dose series of SRL 172 in the DarDar trial.⁶² Investigators expect to complete the phase IIb adolescent study by the end of 2018 and are planning for a possible phase III prevention of disease trial to start in 2019.⁶³

H56:IC31 is a subunit vaccine developed by SSI that contains three MTB antigens (Ag85B, ESAT-6, and Rv2660c) in combination with the IC31 adjuvant. This vaccine will soon begin a phase IIa POI trial at two sites in Tanzania and South Africa. It took considerable effort to prepare H56:IC31 for POI work. First, SSI had to develop an IGRA without ESAT-6 since this antigen is present in both commercially available IGRA tests such as QFT-Gold and in the H56:IC31 vaccine itself.⁶⁴ Using QFT-Gold to measure MTB infection in H56:IC31-vaccinated participants could result in false positives if the ESAT-6 in the vaccine were to prime the same antigen-specific T cells that the test looks for as an indication of MTB infection. The ESAT-6-free IGRA contains four antigens (CFP10, Rv3865, Rv3615c, and Rv2348), and studies in Denmark, Egypt, Tanzania, and South Africa suggest it performs comparably to QFT-Gold.⁶⁵ Second, in order to design the phase IIa study with sufficient statistical power, Aeras and SSI had to conduct a pilot study to determine the background rate of QFT conversion in the target population at the site in Tanzania, which is participating in a TB vaccine trial for the first time.⁶⁶

With the ESAT-6-free IGRA in hand and the pilot project completed, Aeras and SSI expect the phase IIa study to open for enrollment in September 2017.⁶⁷ The study will enroll 1,400 adolescents in two arms: participants in the first will receive two doses of H56:IC31 and those in the second will receive two doses of placebo. The 5 µg dose of H56:IC31 was selected in part based on the immune profile associated with this dose level in a phase I study. In this study, vaccination with 5 µg of H56:IC31 stimulated robust T-cell activity while avoiding the terminal differentiation and T-cell exhaustion seen at higher doses.⁶⁸ As summarized above, related work in mice suggests that T cells with less differentiated phenotypes are better at migrating to sites of infection in the lung. The primary outcome will compare the rate of conversion between those vaccinated with H56:IC31 and placebo, and secondary endpoints will assess sustained conversion based on repeat testing.

Prevention of recurrence trials

Prevention of recurrence work remains more nascent than the POI trials, but several POR studies are underway or planned. SSI and Aeras have applied for funding for a POR trial of H56:IC31.⁶⁹ Data in mice and nonhuman primates indicate that vaccination with H56:IC31 could reduce the risk of reactivation and help control MTB infection as measured by microbiological, immunologic, and radiographic assessments.^{70,71} One key difference between the animal model work and the pending

trial is that the mice and nonhuman primates in the preclinical studies were vaccinated before infection, whereas the phase IIa study will give H56:IC31 to people who already have active TB disease. As designed, participants will enter the trial upon diagnosis of active TB, at which point MTB will be isolated from their sputum. After six months of standard TB treatment, participants will be vaccinated with either H56:IC31 or placebo and followed for two years for recurrent disease, defined as either reinfection or relapse.⁷² Secondary endpoints will try to distinguish between these two possible causes. Individuals with recurrent disease will submit a sputum sample at re-diagnosis to see if the strain of MTB is identical to the one taken from the first sample (likely relapse) or a new strain (likely reinfection).⁷³

The subunit vaccine **ID93/GLA-SE** is completing a phase IIa dose-ranging study in 60 South African adults who have completed treatment for TB disease in preparation for future POR work. Developed by the Infectious Disease Research Institute, ID93/GLA-SE combines MTB antigens Rv2608, Rv3619, and Rv3620 with the GLA-SE adjuvant. The phase IIa trial is evaluating the safety and immunogenicity of two doses of ID93/GLA-SE administered intramuscularly at three dose levels.⁷⁴ In January 2017, the trial reached the final date of data collection for its primary outcome measure; results will inform a future phase IIb POR trial.

According to news reports, **VPM1002**—a live, recombinant form of BCG—is being readied for POR work among adult TB patients in India.⁷⁵ First developed by the Max Planck Institute for Infection Biology, VPM1002 was licensed to the biotech company Vakzine Projekt Management, which subsequently out-licensed development and marketing rights to the Serum Institute of India in 2013.⁷⁶ In addition to the planned POR trial in India, VPM1002 has entered a phase IIa safety, tolerability, and immunogenicity study in BCG-naïve, HIV-exposed and HIV-unexposed South African newborns.⁷⁷ This study reflects VPM1002's original development pathway as a potential BCG-replacement vaccine.

Preclinical watch: innovative concepts approaching clinical development

Sizing up the pipeline for new TB prevention tools requires considering its roots in preclinical research. A comprehensive review of vaccines and preventive therapies in preclinical development is beyond the scope of this chapter, but a few promising activities are worth highlighting.

Scientists at Oregon Health & Science University (OHSU) are developing a viral-vectored TB vaccine based on recombinant cytomegalovirus (rCMV) with backing from Vir Biotechnology, a new company that has funding from the Bill & Melinda Gates Foundation and venture capital firms.^{78,79} This work is closely related to longstanding efforts by the same team at OHSU to develop CMV as a potential HIV vaccine. In 2013, investigators published results showing that a rhesus CMV vector led to impressive clearance of simian immunodeficiency virus (SIV) in macaques.⁸⁰ CMV is believed to be a potent inducer of the effector memory T-cell responses seen as critical in the control and clearance of infections.⁸¹ Publication of nonhuman primate data on the use of CMV as a TB vaccine vector is forthcoming.

In addition to rCMV, other promising viral-vectored candidates are preparing to enter the clinical pipeline. For example, GSK and the French biotechnology company Transgene are wrapping up preclinical activities on an aerosolized TB vaccine construct that combines a chimpanzee adenovirus vector (ChAd3) with modified vaccinia virus Ankara (MVA), the same vector used for vaccine candidate MVA85A.⁸²

One of the most exciting nascent developments in TB preventive therapy is the TB LEAP project, which is exploring the potential for long-acting treatments for MTB infection.⁸³ The project is growing up in the shadow of the more firmly rooted Long-Acting/Extended Release Antiretroviral Resource Program (LEAP). Not all drugs are suitable for long-acting formulations, but those that are carry several potential advantages, including less frequent dosing, improved bioavailability, and easier patient adherence. As a starting point, TB LEAP has developed target product profiles for ideal long-acting formulations of TB preventive therapy to guide developers working in this area.⁸⁴

PROGRESS IN TB PREVENTIVE THERAPY DEVELOPMENT

The bulk of work to develop new TB preventive therapies continues to focus on the drug rifapentine; six planned or ongoing trials include rifapentine either alone or in combination with isoniazid (**Table 2**). Much of the current interest in rifapentine builds on the successful phase III trial conducted by the Tuberculosis Trials Consortium (TBTC) at the U.S. Centers for Disease Control and Prevention (CDC) and the NIH's AIDS Clinical Trials Group (ACTG) that established the safety and non-inferiority of once-weekly rifapentine given with isoniazid for 12 weeks (the 3HP regimen) compared with nine months of daily isoniazid (9H).⁸⁵ Several research groups are building on this success by studying the combination of rifapentine and isoniazid under different durations and dosing schedules. The year 2017 also saw forward movement in clinical trials investigating preventive therapy for individuals exposed to drug-resistant TB (DR-TB). Until now, no randomized controlled chemoprophylaxis trials have examined how to treat probable infection with DR-TB. As a result, clinical practice has varied widely, and the WHO *Guidelines on the Management of Latent Tuberculosis Infection* identify “adequately powered randomized controlled trials . . . to define the benefits and harms of treatment of MDR-TB contacts” as an urgent research priority.⁸⁶

Table 2. Clinical Trials of Tuberculosis Preventive Therapy

Study/Regimen	Status	Population	Sponsor(s)
A5279 Self-administered daily rifapentine and isoniazid for 1 month (HP) (vs. daily isoniazid for 9 months [9H]) NCT01404312*	Fully enrolled	People with HIV either living in high-TB incidence settings or with a positive TST or IGRA	ACTG
4R versus 9H 4 months of self-administered daily rifampin (4R) (vs. 9H) NCT00931736*	Fully enrolled	TST/IGRA+ adults, including people with HIV who are not on ARVs whose efficacy is reduced by rifampin	McGill University, Canadian Institutes of Health Research
WHIP3TB 6 months of daily isoniazid (6H) versus 3HP (given once) versus p3HP (given once a year for two years) NCT02980016*	Enrolling	People with HIV (>2 years of age) without active TB in high-TB-incidence settings	KNCV, USAID

Study/Regimen	Status	Population	Sponsor(s)
V-QUIN 6 months daily levofloxacin (vs. placebo) ACTRN12616000215426**	Enrolling	Household contacts (adults, adolescents, and children) of individuals with MDR-TB	NHMRC, VNTP
P2001 12 weeks of supervised 3HP NCT02651259*	Enrolling	HIV-positive and HIV-negative pregnant and postpartum women with MTB infection	IMPAACT
CORTIS 3HP versus no intervention and active surveillance for TB NCT02735590*	Enrolling	HIV-negative adults with MTB infection deemed high risk for disease progression as identified by a gene-based signature of risk	University of Cape Town
A5300B/12003/PHOENIX 26 weeks daily delamanid (vs. isoniazid)	Beginning enrollment Q2 2018	High-risk (HIV+, TST/IGRA+, or <5 years old) household contacts (adults, adolescents, and children 0–5 years old) of individuals with MDR-TB	ACTG, IMPAACT
TBTC Study 37/ASTERoid 6 weeks of daily rifapentine (6P) (vs. rifamycin-based standard-of-care regimens [3HP, 4R, 3HR])	Beginning enrollment Q1 2018	Household contacts, people with HIV, individuals with recent TST or IGRA conversion, and other persons at high risk of disease progression	TBTC, TBESC, UK MRC, University College London
A5365 1 month self-administered daily rifapentine given once per year for three years (vs. one round of 3HP)	Protocol development	HIV-positive adolescents and adults in settings with low to medium TB incidence	ACTG

* Clinicaltrials.gov identifier; for more details, see <http://www.clinicaltrials.gov>

** Australian New Zealand Clinical Trials Registry identifier; for more details, see <http://www.anzctr.org.au>

ACTG: AIDS Clinical Trials Group, NIAID

ARVs: antiretrovirals

IGRA: interferon gamma release assay (QuantiferON-TB Gold In-Tube [QFT] or T-SPOT TB test)

IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Group, NIAID

MDR-TB: multidrug-resistant tuberculosis

NHMRC: National Health and Medical Research Council (Australia)

NIAID: U.S. National Institute of Allergy and Infectious Diseases

TB: tuberculosis

TBESC: Tuberculosis Epidemiologic Studies Consortium, U.S. Centers for Disease Control and Prevention

TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention

TST: tuberculosis skin test

UK MRC: Medical Research Council, United Kingdom

USAID: U.S. Agency for International Development

VNTP: Vietnam National Treatment Program

For a list of TB preventive therapy trials focused on children, please see “The Pediatric Tuberculosis Diagnostics and Treatment Pipeline for Children” chapter of this year’s Pipeline Report.

Clinical trials of rifapentine-based preventive therapy

WHIP3TB is a phase III study sponsored by the KNCV Tuberculosis Foundation with financial support from the U.S. Agency for International Development (USAID) studying the safety and effectiveness of 3HP among 4,000 individuals with HIV two years of age and older in Ethiopia, South Africa, and Mozambique, settings of high TB transmission and TB/HIV coinfection.⁸⁷ The study is proceeding in two stages. The first stage is comparing 3HP to six months of daily isoniazid (6H). The primary objective is to compare treatment completion between the two regimens; secondary objectives will compare 3HP to 6H with respect to TB incidence, all-cause mortality, and discontinuation of therapy due to adverse events. Stage 2 of WHIP3TB is enrolling concurrently with stage 1 and contains three arms. Participants

will receive either one course of 6H, one round of 3HP, or two rounds of 3HP with one given each year for two years (referred to as pulsed 3HP, or p3HP). After two years of follow-up, the primary outcome analysis will compare the effectiveness of a single round of 3HP versus p3HP in preventing TB disease in people with HIV.

Each stage of WHIP3TB seeks to answer a question of high public health relevance. If 3HP performs favorably in stage 1, the results would support the regimen's use as an alternative to isoniazid preventive therapy (IPT), the uptake of which has remained poor in most TB/HIV high-burden countries. The p3HP strategy being tested in the second stage is intended to assess the durability of protection offered by 3HP in areas where recurrent disease is common. Understanding durability is important given evidence that the protective effect of IPT wanes soon after a person stops taking it—at least in settings with a high force of infection, such as the gold mines of South Africa.⁸⁸

The combination of rifapentine and isoniazid (HP) for TB prevention in people with HIV in high-transmission settings is being studied in the NIH's ACTG study A5279. This trial is comparing the effectiveness of self-administered daily HP taken for one month versus 9H. The primary outcome will assess the time from randomization to first diagnosis of active TB disease.⁸⁹ The trial hit its targeted enrollment of 3,000 participants at the end of 2014 and will complete participant follow-up in November 2017; results could be released as early as the first quarter of 2018. A pharmacokinetics (PK) study nested into the trial has already reported results showing that four weeks of daily HP can be safely administered to people with HIV on efavirenz-based therapy without clinically meaningful reductions in efavirenz concentrations that might jeopardize viral suppression.⁹⁰

In addition, the ACTG is developing a protocol for a study (A5365) to compare the efficacy of three annual cycles of daily HP given for one month to a single course of 3HP in people with HIV age 13 and older. The trial is intended to complement the aforementioned A5279 and WHIP3TB studies by applying the pulsed approach of WHIP3TB to the daily HP regimen studied in A5279. If approved by the ACTG, A5365 will take place in medium-to-high TB-endemic settings (places with an annual TB incidence between 40 and 300 per 100,000 population) and exclude countries with the highest TB incidence rates, such as South Africa. The study remains in protocol development.

The TBTC is taking another approach by asking whether rifapentine can prevent TB when given alone, without isoniazid, in low-incidence settings. The phase III ASTERoiD trial (TBTC Study 37) will assess the safety, tolerability, and effectiveness of rifapentine given daily for six weeks (6P) in preventing TB among persons with high risk of disease progression in settings of low to medium TB incidence.⁹¹ The study is a joint effort between TBTC, the CDC's Tuberculosis Epidemiological Studies Consortium, and the U.K. Medical Research Council. Patient groups eligible for the trial include people with HIV, close contacts of people with TB, persons with a documented negative-to-positive TST or IGRA conversion within two years, or those who have recently emigrated to the U.S. or U.K. from a high-TB-burden country, among others. Data from the first 1,120 participants will inform an early safety analysis; in total, the trial will enroll 3,400 people. The investigators hope to open enrollment by January 2018.⁹²

The ASTERoiD trial will compare 6P to a composite control arm composed of three rifamycin-based standard-of-care regimens (3HP, four months of daily rifampicin [4R], or three months of daily rifampicin plus isoniazid [3HR]). 6P offers a number of theoretical advantages over 3HP. Rifapentine is thought to have less liver toxicity than isoniazid, so removing isoniazid from the regimen could improve safety. With fewer safety concerns and daily administration, 6P could be self-administered, eliminating the expense associated with direct observation of therapy. The shorter six-week duration and daily dosing schedule might also improve adherence over the longer 12-week, once-weekly dosing of 3HP. In addition, daily dosing may lessen the risk of rifapentine-associated flu-like hypersensitivity reactions seen in a minority of patients receiving HP once weekly; this syndrome appears more frequently when rifapentine is dosed

intermittently (for more on this point, see below). The trial will study rifapentine at a lower dose (600 mg) than that associated with hypersensitivity reactions in previous studies (900 mg).

Continuing the TBTC's history of including vulnerable populations in research—a commitment to equity that ensures that persons most at risk of TB can enjoy the benefits of scientific progress—ASTERoID investigators have voiced their willingness to open the trial to pregnant women in the second or third trimester pending favorable results from the early safety analysis.⁹³ Pregnant women with MTB infection face an increased risk of developing active TB yet have been systematically excluded from TB prevention trials.⁹⁴ Existing TB prevention regimens have undergone evaluation in more than 40 clinical trials, including eight phase III trials and 13 that focused on HIV-positive adults, all of which excluded pregnant women.⁹⁵ Recently, three community advisory boards issued a joint call for researchers to find ways to safely include pregnant women in TB trials in order to rectify this historic exclusion and provide evidence-based guidance to clinicians.⁹⁶ The willingness of ASTERoID investigators to consider opening the trial to pregnant women pending an interim review of safety data marks a positive step forward and follows on the heels of two studies run by the NIH International Maternal Pediatric and Adolescent Clinical Trials Network (IMPAACT) that are studying IPT and 3HP in pregnant women. P1078 is evaluating IPT given antepartum versus postpartum in pregnant women with HIV, and P2001 is studying the PK and safety of 3HP given to pregnant women with or without HIV (for more information on these trials, see “The Tuberculosis Diagnostics and Treatment Pipeline for Children” on p. 143).^{97,98}

Perhaps the biggest news in the pursuit of optimized rifapentine-based TB preventive therapy in the past year came from one of the smallest studies. At the 2017 Conference on Retroviruses and Opportunistic Infections (CROI), investigators from the NIH Clinical Center presented results from a phase I drug-drug interaction study in healthy volunteers that sought to characterize the effects of 3HP on the steady-state PK of dolutegravir, an antiretroviral drug.⁹⁹ The study stopped early when two out of four enrolled participants developed hypersensitivity reactions marked by nausea, vomiting, and fever. The biological explanation for these adverse events is unclear. Plasma samples from each participant showed higher than expected levels of isoniazid, and cytokine assays revealed increased levels of inflammatory markers such as IFN γ and TNF α following the second rifapentine dose. The investigators are planning to analyze blood samples for evidence of anti-isoniazid and anti-rifapentine antibodies that might help to explain the hypersensitivity response.¹⁰⁰

In the poster presented at CROI, the investigators conclude that “these data suggest that co-administration of dolutegravir and 3HP should be avoided.”¹⁰¹ It is too soon to foreclose on the co-administration of 3HP and dolutegravir based on a single phase I study in four healthy volunteers, but this concerning finding deserves further investigation—and sooner rather than later. Dolutegravir is already part of preferred first-line regimens for treating HIV in many high-income countries, and its use is expected to increase quickly in low- and middle-income countries thanks to sublicenses brokered by the Medicines Patent Pool between ViiV Healthcare, the originator company, and several generic manufacturers.¹⁰² The expanding reach of dolutegravir dovetails with the expected scale-up of 3HP under a project led by the Aurum Institute with support from Unitaid that will catalyze the market for 3HP by supporting its use in 12 high-TB burden countries. Very soon, clinicians will confront the question of whether people with HIV receiving dolutegravir can safely take 3HP to prevent TB. Providing fact-informed guidance on this point will require answering a number of questions, including:

- Can dolutegravir safely be given with 3HP to people with HIV? The phase I study presented at CROI was conducted in HIV-negative, MTB-uninfected volunteers. For HIV-positive people, it will be important to investigate whether the risk of hypersensitivity is associated with CD4+ T-cell levels. Rifapentine hypersensitivity reactions have been observed more frequently in persons otherwise healthy.¹⁰³ If this is the case, individuals with more CD4+ T cells might face a greater risk than those with more serious immunosuppression.

- Relatedly, can rifapentine be co-administered with dolutegravir in people with HIV without prior IGRA or TST testing for MTB infection?
- Is there a lower risk of hypersensitivity when HP is given daily rather than weekly? Some evidence suggests that intermittent administration of rifapentine increases the risk of hypersensitivity.¹⁰⁴
- Are reduced dolutegravir exposures in the presence of HP clinically meaningful? If dolutegravir needs to be dose-adjusted with HP, is it sufficient to dose-adjust just once a week (i.e., on the day 3HP is given)?

To begin answering these questions, investigators from Johns Hopkins University and the Aurum Institute are planning to conduct a safety and PK study of dolutegravir and weekly HP. Unitaid will support this study as part of the 3HP market-shaping project led by the Aurum Institute, and the investigators hope to report results by spring 2018.

Clinical trials of preventive therapy for contacts of people with drug-resistant TB

The ACTG and IMPAACT networks are partnering on the PHOENIX study (A5300B, I2003B), a cluster-randomized phase III trial that will compare the safety and efficacy of 26 weeks of delamanid versus isoniazid for preventing TB over two years of follow-up among household contacts of patients with multidrug-resistant TB (MDR-TB). The study will enroll over 3,450 household contacts from an estimated 1,725 households. Eligible household contacts include adults and children over five years of age who are HIV positive, at high risk of disease progression (e.g., on TNF treatment), or have a positive TST or IGRA; children ages 0–5 are eligible regardless of TST or IGRA status. Since this is one of the first large-scale MDR-TB household studies in history, the ACTG and IMPAACT first conducted an observational feasibility study to prepare sites for the larger trial. With the feasibility study completed, the two networks plan to open PHOENIX for enrollment in the first half of 2018 after delamanid dosing results are available for infants zero to two years old.¹⁰⁵

The V-QUIN study, sponsored by the University of Sydney with funding from the Australian National Health and Medical Research Council, is a cluster-randomized trial evaluating the safety and efficacy of six months of daily levofloxacin versus placebo for preventing TB among household contacts of MDR-TB patients in Vietnam.¹⁰⁶ The study will enroll adults and children living in the same household as MDR-TB patients within the past three months. Children under age 15 will only be randomized to receive the intervention following a favorable review of safety data in the older adolescent and adult cohort. In total, the trial aims to enroll over 2,700 household contacts from nearly 1,350 households. The TB CHAMP study in South Africa is similar to V-QUIN in comparing levofloxacin to placebo but will focus on child contacts age 5 and under (see “The Pediatric Tuberculosis Treatment Pipeline” beginning on page 143 for a detailed discussion of pediatric TB drug research).

PROGRESS IN POLITICAL WILL FOR TB PREVENTION

The spate of activity in TB prevention research is a signal of scientific opportunity, but is this signal reaching governments? In many respects, the politics of TB prevention are where the science was a few years ago—shaking off old paradigms to take the first cautious steps that mark any new direction. As the historian Christian McMillen documents in *Discovering Tuberculosis*, a global history of TB in the twentieth century, prevention took a back seat to treatment under the DOTS strategy that defined TB control in the 1990s and early 2000s.¹⁰⁷ Now, with the advent of the WHO End TB Strategy, TB prevention is finally coming to the fore. The End TB Strategy envisions a world without TB and aims to reduce TB mortality by 95 percent and TB incidence by 90 percent by 2035 compared with 2015.¹⁰⁸ Multiple mathematical models indicate that reducing TB incidence by this magnitude will require reducing the reservoir of

people infected with MTB, which will itself require research to develop better diagnostics, vaccines, and preventive therapies.^{109,110}

Governments have a pivotal role to play in supporting the development of the required new tools. Several events on the global and national levels in recent years suggest that more political attention is turning toward TB prevention, but there have also been some missed opportunities and unnecessary oversights along the way. Some of the more encouraging actions include:

- *Global guidance:* Three years after issuing its first-ever *Guidelines on the Management of Latent Tuberculosis Infection*, the WHO is updating the guidance to offer a more consolidated approach to treating MTB infection across high- and low-income countries. The original guidelines contained two sets of recommendations: one for high- and upper-middle-income countries with TB incidence less than 100 per 100,000 in the population and a second for “resource-limited countries and other middle-income countries.”¹¹¹ The new guidance will issue recommendations on several closely watched topics, namely a possible endorsement of 3HP as an alternative to IPT in high-incidence settings and a potential recommendation to give preventive therapy to all household contacts at risk of TB rather than just children under five years of age.
- *Market shaping:* The inclusion of TB prevention as an “area of intervention” in Unitaids’ TB portfolio gives governments an unprecedented opportunity to strengthen the implementation of TB preventive services.¹¹² As a first foray into this area, Unitaids’ support of the Aurum Institute–led consortium to scale up 3HP among people with HIV and children in a dozen countries will help to consolidate the market for rifapentine by driving up purchase volumes, lowering the price of the drug, and facilitating its registration in low- and middle-income countries. Key to success will be Sanofi’s willingness to expeditiously register rifapentine in TB-endemic countries and set a fair, affordable price for the drug on the international market.
- *National initiatives:* For decades, most national TB programs have thought of TB prevention as limited to IPT for narrowly defined high-risk groups or BCG vaccination for infants (although BCG is typically administered as part of the expanded program on childhood immunization outside of TB centers). Most efforts to broaden the field of action on TB prevention have proceeded slowly, but a few countries are introducing bold initiatives. For example, South Korea has announced that all Koreans will be tested for MTB infection at two points in their lives—once at age 15 and again at age 40—as part of a national push to reduce TB incidence from 86 per 100,000 to 12 per 100,000.¹¹³ In addition, the U.S. CDC has drawn up plans for a major initiative targeting the reservoir of MTB infection, which it calls “the final frontier of TB elimination in the USA.”¹¹⁴

These developments justify a cautious optimism. The decades-long saga to study and implement IPT reminds us that the history of TB prevention is a history of contestation. In *Discovering Tuberculosis*, McMillen details how IPT rose and fell in favor over the years—and not always in sync with the TB epidemic or the potential of the science. As late as 1982, on the edge of a world about to confront AIDS and the epidemics of TB/HIV and MDR-TB that would follow, a joint report by the WHO and the International Union Against TB and Lung Disease argued that “in practice, [IPT] has virtually no place in developing countries.” Interest in IPT picked up again a decade later as a way to respond to TB/HIV. In 1989, Jonathan Mann, then-director of the WHO Global Programme on AIDS, wrote that “delaying or preventing TB may be the single most important thing that can be done in developing countries for prolonging the survival of HIV-infected persons.” Following this, WHO called for and helped launch several trials of IPT in Africa, yet this renewed scientific interest was not enough to keep prevention anywhere near the center of the TB response. As McMillen notes, “during the height of research [in the early 1990s], political and administrative support for IPT was, publicly, lukewarm at best.”

To ensure the next chapter of TB prevention enjoys more consistent support, the following recommendations must be fulfilled:

- **Governments, pharmaceutical companies, and foundations must increase funding for TB prevention research.** To capitalize on the recent turn toward translational science, funding mechanisms must be flexible and durable enough to support the cross-disciplinary, multi-year, iterative work between lab, clinic, and community required to move the field forward.
- **Vaccine and drug developers should continue to design clinical trials that maximize opportunities for scientific learning.** For vaccine developers, this could entail conducting more experimental medicine studies. Similarly, drug developers should identify opportunities to support investigator-initiated science by nesting small, focused studies (e.g., of the kind funded by the NIH RO1 mechanism) in larger clinical trials. By making the most of opportunities to conduct research in humans, these studies provide a way to advance translational science alongside product development. Such studies often investigate critical questions to inform the use of novel interventions in populations most at risk of TB (e.g., children, pregnant women, people with HIV).
- **All governments must mainstream prevention into national TB strategies and begin planning for the eventual introduction of new tools—even if they remain years away.** To ensure timely access to new TB prevention products, implementation must anticipate scientific progress—as the tragically slow scale-up of new drugs and diagnostics to respond to DR-TB has demonstrated.¹¹⁵ This is especially true for TB prevention, given the longstanding neglect of the topic under previous global strategies. Many countries still consider themselves to be high incidence and therefore exempted from efforts to scale up preventive therapy. Under the End TB Strategy, this mindset must change—all countries at all epidemic levels can take steps to prevent TB by interrupting the cycle of transmission.
- **Activists and civil society must mobilize to support TB prevention research and hold governments accountable for translating scientific advances into practice.** Last year, Treatment Action Group urged activists to “take up TB prevention as a unified cause and break with the habit of advocating for vaccines, preventive therapy, and infection control as separate and unrelated technological fixes.” That advice is more important than ever. Over 60 percent of public funding for TB research comes from the United States government, and with an anti-science administration in power, defending biomedical research will require a united effort.^{116,117} Scientists, too, must become advocates and defend the instrumental and intrinsic value of their work.

Thanks to concerted research efforts, the TB field is preparing to enter an era in which prevention will mean more than BCG or IPT. But we cannot assume that the science underway will capture sufficient political will to see this research through to its end. To garner political commitment, TB prevention science will need to be translational in several respects. The same iterative approach to working between lab, clinic, and community that underlies many of the most promising scientific developments of recent years should be applied to the interface between TB prevention research and the global political agenda taking shape around TB. Politics and science may seem perpendicular to each other, but—to borrow Valerie Mizrahi’s expression—it will take orthogonal thinking to make sustained progress on a challenge as complex as preventing TB disease among the estimated 1.7 billion people with MTB infection alive today.

ACKNOWLEDGEMENTS

Mike Frick thanks Christine Sizemore and Katrin Eichelberg for thoughtful reviews of an early draft and the many researchers and developers who provided study updates. Audrey Kaem offered the cloistered space above Brooklyn’s Atlantic Avenue where this chapter was written.

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The Tuberculosis Treatment Pipeline: A Breakthrough Year for the Treatment of XDR-TB

by Marcus Low

INTRODUCTION

Arguably, the most critical questions in TB treatment today are “What is the optimal regimen for the treatment of multi-drug resistant TB (MDR-TB)?” and “What is the optimal regimen for the treatment of extensively drug-resistant (XDR) and pre-XDR-TB?” To both of these questions we have at best interim answers. The World Health Organization (WHO)-recommended shortened nine-month “modified Bangladesh” regimen for the treatment of MDR-TB (kanamycin, moxifloxacin, prothionamide, clofazimine, isoniazid, pyrazinamide, and ethambutol) has only observational data to support it and involves a large number of difficult-to-tolerate drugs.¹ In addition, a number of experimental regimens that are currently in randomized controlled trials (RCTs) that utilize new drugs such as bedaquiline and delamanid seem set to surpass it by significantly reducing both the number of drugs and the duration of treatment. At present, there is no standard of care for pre-XDR and XDR-TB, although one experimental regimen is performing remarkably well in an ongoing clinical trial.

The Nix-TB trial is a single-arm trial that is still ongoing (see the bedaquiline section below for more details), but its success in appearing to treat XDR and pre-XDR-TB with far fewer drugs in far less time than ever before nevertheless represents a medical breakthrough with multiple positive implications for the outcomes of all forms of DR-TB, for the real-world use of the first new TB drug from a new class approved in 40 years (bedaquiline), and for raising the hopes of people with TB and their providers—along with a host of regulatory and access issues. Treatment outcomes for people with XDR and pre-XDR-TB are typically extremely poor, with five-year mortality rates as high as 73%.² Thus, even though the evidence for the Nix-TB regimen is still very limited and does not come from an RCT, it has set a high bar for other treatment regimens for advanced, previously poorly treatable disease. Although calling the Nix-TB regimen the “standard of care” for XDR and pre-XDR-TB may be premature, a strong case can be made that any XDR and pre-XDR treatment trials in the foreseeable future should include the Nix-TB regimen as the control arm, especially given the questionable ethics of using the existing so-called standard of care, which, in addition to being difficult to tolerate and having poor outcomes, has no randomized clinical trial data to support it.

Although the Nix-TB regimen has put a flag in the sand as far XDR and pre-XDR-TB is concerned, the situation is much more complicated when it comes to MDR-TB. Multiple combinations of new, old, and repurposed drugs are currently being studied in multiple ongoing trials across the world (see table 2 for a summary of these trials). With some notable exceptions, such as the NEXT-TB trial, most critical trials will only report results in 2021, and even then we will not be guaranteed clear answers. Even so, as is the case with the recent recommendation of the shorter MDR-TB regimen, the WHO may again change their guidance prior to the scientific question being settled. Incidentally, results from STREAM stage I, the RCT that is comparing the now WHO-recommended shorter MDR regimen to the previous WHO standard of care, is only expected in 2018.

In an important initiative aimed at focusing and directing TB drug development, the WHO has developed a set of target regimen profiles (TRPs) that lay out profiles for rifampin-susceptible TB, rifampin-resistant TB, and for a pan-TB treatment regimen. Although a highly effective, very short course pan-TB regimen would be a major step forward in the fight against TB, there is no universal agreement as to what extent a pan-TB regimen should be prioritized in drug development, nor is there agreement as to what exactly it means (the WHO TRP definition describes it as being applicable where drug-susceptibility testing [DST]

is not available, whereas most advocates would want a pan-TB regimen to be of use in all forms of TB, as they would want DST to be universally available and accessible). It is notable, however, that a pan-TB TRP has been included in these TRPs and that the 3P Project—an innovative drug development initiative and funding framework—explicitly aims to support the development of a pan-TB regimen.³

Even with the WHO's TRPs in place and with much debate over TB drug development in recent years, there are still many unanswered questions as to the optimal pathways for the development of various specific drugs and regimens. Some researchers are attempting to use experimental data, experiments in mice, and various mathematical techniques to predict which combinations of drugs at which dosages are likely to be most effective. One study in a mouse model, for example, identified a regimen of clofazimine, bedaquiline, ethambutol, and pyrazinamide as having significant potential.⁴ Given that there are thousands of possible drug and dose combinations, such studies may be important for ensuring that research dollars are optimally spent, although it should be acknowledged that these models are often based on very limited data that may or may not be relevant to the treatment of humans.

Questions continue to be raised as to whether enough data are gathered before proceeding to phase III trials in TB, which, if true, would reduce the odds of success in phase III. A proposed solution is to expand the scope of phase II trials by carrying out more phase IIc trials, in which experimental regimens are studied for longer periods than in current phase IIa and IIb trials.⁵ Consistent with this thinking, a recent meta-analysis concluded that, "The existing evidence base supporting Phase II methodology in tuberculosis is highly incomplete. In future, a broader range of drugs and combinations should be more consistently studied across a greater range of Phase II endpoints."⁶

In addition to these various strategies aimed at optimizing the progress of new candidates in the TB drug development pipeline, economic factors have a significant role in how and in which combinations drugs are developed. Although we can now report some progress (see below), the development of sutezolid has been delayed by many years for reasons relating to its ownership. Otsuka recently announced its intention to develop its new drug candidate, OPC-167832, in combination with delamanid (Otsuka's other TB drug). The entry of a new compound into the pipeline is welcome, but it is unclear whether, and at what stage, this new compound will be made available for testing with compounds not owned by Otsuka.

As has been the case in recent years, drug regulators will play a critical role in shaping the research that does or does not get done. Important decisions will again have to be made regarding the amount of evidence required for drug registration (see clofazimine below) and the potentially valuable role that phase IIc trials may have in optimizing TB drug development. In relation to TB, regulators also have the particularly difficult task of ensuring that enough data are gathered both on the safety and efficacy of individual drugs and on the safety and efficacy of combinations of drugs. With the likely lowering of regulatory standards through the 21st Century Cures Act in the U.S. and so-called Adaptive Pathways in Europe, there is a risk that critical data on new and repurposed drugs may not be gathered and that the evidence base for these drugs may remain insufficient, perpetuating the unacceptable situation that has been the case with virtually all MDR-TB drugs for decades.

Finally, the developments reported in this chapter must be considered against a background of a TB R&D landscape that remains largely defined by the fact that it is woefully underfunded. According to the latest TAG *Report on Tuberculosis Research Funding Trends*, investment in TB research dropped by \$US53.4 million, from \$674 million in 2014 to \$620.6 million in 2015.⁷ This is less than one-third of what the *Global Plan to Stop TB* estimates is required. Although there is now some momentum behind a planned UN High-Level Meeting on TB in 2018 (it will be preceded by a Ministerial Meeting in November 2017), the true test of governments' commitment in the fight against TB will ultimately not be the declarations that will come from these meetings, but the concrete financial investments that governments make in the fight against TB, particularly in TB R&D.

UPDATES ON NEW COMPOUNDS IN DEVELOPMENT

Table 1. Drugs in development for tuberculosis

Drug	Class	Sponsor(s)	Phase
bedaquiline	diarylquinoline	Janssen, TB Alliance, NIAID, SAMRC, the Union, Unitaid, USAID	III
delamanid	nitroimidazole	Otsuka, NIAID, Unitaid	III
pretomanid	nitroimidazole	TB Alliance	III
sutezolid	oxazolidinone	Sequella, NIAID, TB Alliance	Ila (developers will have to repeat early stage studies, see text)
Q203	imidazopyridine	Qurient, Infectex, PanACEA	II
SQ109	1,2-ethylene diamine	Infectex, Sequella, PanACEA	II (phase III controversially claimed in Russia, see text)
PBTZ169	DprE1 inhibitor	Nearmedic, iM4TB, BMGF	II
OPC-167832	carbostyryl	Otsuka, BMGF	I
LCB01-0371	oxazolidinone	LegoChem Biosciences	II

BMGF: Bill and Melinda Gates Foundation; NIAID: National Institute of Allergy and Infectious Diseases (U.S.); PanACEA: Pan African Consortium for the Evaluation of Antituberculosis Antibiotics; SAMRC: South African Medical Research Council; The Union: International Union Against Tuberculosis and Lung Disease; USAID: The U.S. Agency for International Development

Bedaquiline

Bedaquiline is the most widely used of the new drugs for the treatment of TB. By April 2017, an estimated 8,828 patients had received the drug—5,387 of whom were in South Africa.⁸ Concerns about the safety of bedaquiline were based on the ten deaths in the interventional arm of the registrational phase IIb C208 study, and the risk of QT prolongation (a potentially dangerous disturbance in the heart's electrical activity). The accumulating evidence for the drug from the thousands of patients who have gotten it under routine programmatic use, however, suggests that the drug is in fact quite safe and that the risk of QT prolongation is manageable in the vast majority of cases. A guidelines development group convened in June and September 2016 to review the WHO's 2013 interim guidance on bedaquiline and made some important updates to the language—including on the use of the drug in people with HIV and in adolescents—and recommended the use of bedaquiline in anyone with MDR-TB who were not eligible for the shortened regimen, but did not change the overall conditional recommendation on the use of the drug, and, disappointingly, WHO only issued a meeting report rather than updated guidelines.⁹

In arguably the most important TB-related study findings reported in the last year, the bedaquiline-containing Nix-TB regimen has proven to be highly effective in the treatment of XDR-TB, pre-XDR-TB, and treatment-intolerant or treatment-non-responsive MDR-TB. The Nix-TB trial is a single-arm, open-label trial of bedaquiline, pretomanid (formerly Pa-824), and linezolid given for six months, with an extra three months added if participants are sputum culture positive at four months.¹⁰ Interim findings were presented at the Conference on Retroviruses and Opportunistic Infections (CROI) in February 2017. Of the 72 patients enrolled in the study, 40 had finished treatment and 31 had finished six months of follow-up. Four patients died—all in the first eight weeks. Of the 31 who finished six months of follow-up, only two had relapsed or been re-infected. It should be stressed that further follow-up is ongoing and more relapses may yet occur (in phase III trials, patients are normally followed up for at least one year to ensure relapse-free cure). Remarkably, all of the surviving patients were culture negative at four months—74% were

already negative at eight weeks. The expected linezolid toxicities of peripheral neuropathy (painful nerve damage) and myelosuppression (a decrease in bone marrow activity leading to fewer red and white blood cells and platelets) were said to be “common but manageable.” Seventy-one percent of patients had at least one linezolid dose interruption. It is expected that more up-to-date findings will be presented at other meetings, including the 2017 Union World Conference on Lung Health.

The TB Alliance, which sponsors the Nix-TB trial, is planning a further trial of 180 people using the Nix-TB regimen, but with the key difference that the four study arms will be randomized to different linezolid doses and durations (details in the linezolid section below), in the hope of reducing this toxicity without sacrificing efficacy. Given that this trial (known both as NC-007 and ZeNix) is designated as a phase III trial, it is intended to allow for the registration of this regimen for the treatment of XDR-TB, pre-XDR-TB, and treatment-intolerant and treatment-non-responsive MDR-TB.¹¹ It is not known whether the TB Alliance will seek conditional registration prior to the completion of this study, nor is it known what steps will be taken to ensure wider pre-approval access to the regimen. Enrollment in ZeNix is anticipated to start in October 2017—results are not anticipated until January 2022.

A retrospective, observational study of 428 DR-TB patients given bedaquiline-containing regimens in 15 countries recently showed encouraging safety and efficacy. Sputum smear and culture conversion rates in MDR-TB cases were 88.7% and 91.2%, respectively, at the end of treatment. Bedaquiline was interrupted as a result of adverse events in 5.8% of cases. A single patient died after having had electrocardiographic abnormalities that, according to the study authors, were “probably non-bedaquiline related.”¹²

Meanwhile, bedaquiline continues to be used in a number of other ongoing randomized controlled trials that will, in coming years, provide important additional information on its safety and its use in combination with various other drugs. The bedaquiline phase III study, STREAM stage II, is ongoing and results are expected in December 2021.¹³ Other important trials including bedaquiline are NEXT-TB (now due to be completed late in 2019 as a result of contractual delays),¹⁴ study TB-PRACTECAL AKA 1541 (estimated study completion in March 2021),¹⁵ and endTB (estimated study completion in April 2021) (see table 2 for more details on these studies).

Initial findings from the ongoing NC-005 phase II trial presented at the 2017 CROI suggest that a combination of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (BPamZ) has both good bactericidal activity and safety.^{16,17} The TB Alliance is planning to test this regimen in a larger phase III trial, NC-008.

Another important phase II trial to watch is trial A5343, which in its three arms adds bedaquiline, delamanid, and a combination of the two to the WHO-recommended shortened MDR-TB regimen (with clofazimine removed in each case as a result of the increased risk of QT prolongation when used with bedaquiline). The study should provide critical information about the safety and pharmacokinetics of using these two new drugs together. HIV-positive study participants will be given the integrase inhibitor dolutegravir, which will provide useful information on the use of dolutegravir with the new TB drugs. Recruitment has been slower than anticipated, however, and ClinicalTrials.gov lists January 2019 as the anticipated primary completion date and January 2021 as the final study completion date.¹⁸

Delamanid

The delamanid phase III trial is listed as “completed” on ClinicalTrials.gov and top-line findings are expected to be presented at the Union World Conference on Lung Health in October 2017.¹⁹ Although the trial will provide critically important data on delamanid specifically—and a sub-trial will provide data on the use of delamanid with antiretrovirals (ARVs)—it is unlikely to herald the introduction of a new

MDR-TB treatment regimen, as the intervention arm in the study simply adds delamanid to an existing background regimen, the old, pre-“Bangladesh,” 24-month regimen.

Delamanid is also being tested in a number of interesting new regimens, most notably in the endTB trial (see table 2). The MDR-END trial, which is evaluating a regimen containing delamanid, linezolid, levofloxacin, and pyrazinamide for 9 or 12 months, is also potentially important (completion expected at the end of 2019).²⁰ The same regimen as the MDR-END trial, with arms for various shorter durations, will be studied in the H-35265 trial (recruitment to start August 2017 and study completion expected in August 2021).²¹ As noted earlier, the A5343 trial should provide useful data on the use of delamanid in combination with bedaquiline.

On World TB Day 2017, South Africa’s Minister of Health announced that the country would launch an expanded access program to provide delamanid to 400 patients in that country. The drugs are being donated by Otsuka. As with the bedaquiline expanded access program in South Africa, the delamanid program should provide useful real-world data on the safety of the drug.

Despite the progress in South Africa, the delamanid compassionate use program has been extremely slow to get off the ground. Only 563 patients worldwide have received delamanid as of April 2017—most of whom are in MSF projects.²² As of April 2017, delamanid has only been registered with four regulatory authorities (with dossiers submitted in four additional countries).

The struggle in recent years to get compassionate access to the new TB drugs has highlighted the complexities created by differing legal mechanisms for early access in different countries and different levels of willingness from drug developers to engage in such programs. In response to this, Treatment Action Group and the Global TB Community Advisory Board have proposed a unified compassionate access entity that would help facilitate compassionate access to new drugs.

Pretomanid

It has been a mixed year for the development of pretomanid. On the positive side, it is one of the three drugs in the remarkably effective Nix-TB regimen (see the bedaquiline section above). It will also be included for further study in people with XDR and pre-XDR-TB and people with non-responsive or treatment-intolerant MDR-TB in the ZeNix trial, and as part of the bedaquiline-pretomanid-moxifloxacin-pyrazinamide regimen in the NC-008 trial.

Less encouragingly, in December 2016, the TB Alliance took the decision not to re-open enrollment in the controversial phase III STAND trial. Enrollment in the trial was placed on hold following three deaths in the intervention arm; at the time there were fears that the deaths may have been pretomanid related. The trial, which tests the combination of pretomanid, moxifloxacin, and pyrazinamide for the treatment of both DS and DR-TB, was cleared to resume enrollment, but will continue only with participants that were already enrolled, leaving the trial underpowered. The decision not to resume enrollment, presumably out of increased interest in other regimens, raises ethical questions regarding the expectations study participants have that the studies they take part in will produce meaningful (and sufficiently powered) findings. Even prior to the hold, the STAND trial was controversial given differing views as to whether sufficient phase II data existed to warrant proceeding to phase III, and whether the study design would allow for meaningful interpretation of a range of possible results.

Instead of STAND, the TB Alliance is now focusing on NC-008, a phase III trial that tests the STAND regimen plus bedaquiline. The use of this BPamZ regimen is supported by promising results from the NC-005 trial (see above).

Pretomanid is also being studied in multiple arms of the phase II/III TB-PRACTECAL study (see table 2).

Sutezolid

Although development of the oxazolidinone sutezolid began alongside that of linezolid in the mid-1990s, it has taken much longer to yield results. Linezolid was approved by the U.S. Food and Drug Administration (FDA) in 2000, whereas sutezolid is paralyzed in phase IIa, with no clinical progress since 2012.²³ Even with significant toxicities, linezolid is proving to be an important drug for the treatment of highly resistant forms of TB (see discussion of the Nix-TB trial in the bedaquiline section). If, as some hope, sutezolid turns out to be as effective as linezolid, but safer, then it could turn out to be a critically important drug for the future of TB treatment, potentially replacing linezolid in emerging XDR-TB regimens such as that in the Nix trial.

After being in limbo for some years at Pfizer, the pharmaceutical company Sequella acquired the license to sutezolid in 2011.²⁴ Over the following six years, Sequella did virtually nothing to further develop the drug. Some of the drug's intellectual property is, however, held by Johns Hopkins University. In January 2017, after extensive negotiations, Johns Hopkins licensed sutezolid to the Unitaid-funded Medicines Patent Pool (MPP). This move essentially opens up the further development of sutezolid to any interested party willing to agree to the license terms offered by the MPP.

One obstacle to the development of sutezolid is that, even though patent barriers were removed by the MPP license, pre-clinical and early clinical data already conducted by Pfizer and Sequella have not been shared either publicly or directly with other developers. This means that interested developers, such as the TB Alliance, will have to repeat some of this early research, which will further delay the development of sutezolid. Had Sequella shown more competence and urgency regarding the development of sutezolid, its reluctance to share this data would have made sense as part of a strategy to be first to market. As it stands, there is little evidence that the company has the means to further develop this potentially important drug.

A proposed development pathway has been presented at meetings by the Aurum Institute in which sutezolid would be tested as part of a regimen together with bedaquiline and delamanid in a single-arm trial in patients with XDR-TB.²⁵ Should that trial succeed (although definitions of success are unclear, as there is no proposed control arm for comparison), the trial would be expanded to patients with MDR-TB with the eventual goal of verifying a pan-TB regimen that could be used in cases in which DST is not available, but there is evidence indicating that patients' isolates may not be fully susceptible. Whether regulators and ethics boards will accept the lack of a control arm in these trials is unclear. Some advocates argue that the rationale for an uncontrolled study is no longer acceptable, as the Nix-TB trial has provided a feasible potential comparator regimen, and that any trial of a new regimen for the treatment of XDR-TB should include the regimen used in the Nix-TB trial as a control.

SQ109

Preliminary results of a putative phase IIb/III trial of the drug SQ109 were presented at a meeting in Moscow in November 2016. This trial, however, had only 140 participants—a low number for a phase III MDR-TB trial—and it appears that no post-treatment follow-up was reported. According to the website of Infectex, the company with the rights from Sequella to develop SQ109 in Russia, the results “demonstrate satisfactory profile of safety and tolerability of SQ109 as well as the increase in effectiveness of the standard regimen of chemotherapy in combination with SQ109 in patients with multidrug-resistant tuberculosis.”²⁶ We have not been able to find these results reported in a peer-reviewed medical journal.

Meanwhile, the two SQ109-containing arms in a PanACEA trial testing high-dose rifampin were stopped early because pre-specified efficacy thresholds were not met.²⁷ SQ109 may nevertheless still have a future in combination with other drugs provided that any anti-TB activity of the agent in humans can be convincingly demonstrated.

Q203

Q203 is an experimental TB drug that is being developed by the pharmaceutical company Qurient. Similar to bedaquiline, it functions by inhibiting energy metabolism, although it is thought that the two drugs could work synergistically. A phase I dose-escalation study is under way and an EBA study is expected to start before the end of 2017.²⁸

PBTZ169 and BTZ043

PBTZ169 is an experimental DprE1 inhibitor that is active on the mycobacterial cell wall and is being developed by iM4TB (a non-profit supported by the Bill and Melinda Gates Foundation). According to ClinicalTrials.gov, a phase I safety and dose-finding study has been completed, but the results have not yet been published.²⁹

In the same class as PBTZ169 is BTZ043, which is being developed by the PANACEA consortium. The compound has shown promising safety and efficacy in a mouse model; phase I trials in humans are expected to start soon.

OPC-167832

At the 2016 Union World Conference on Lung Health, the pharmaceutical company Otsuka announced its development of a new drug in the carbostyryl class called OPC-167832, indicating that it will be co-developed with delamanid (Otsuka's other TB drug). Human trials are reportedly underway (although we failed to find any trials listed on ClinicalTrials.gov, the EU Clinical Trials Register, or the WHO International Clinical Trials Registry Platform) and the FDA has granted fast-track status.³⁰ It is as yet unclear whether Otsuka will allow OPC-167832 to be tested as part of other novel regimens with drugs owned by other companies.

LCB01-0371

LCB01-0371 is an experimental oxazolidinone that is being developed by LegoChem BioSciences. A phase II safety and early bactericidal activity study of the drug is expected to be completed in late 2017.³¹

OPTIMIZING THE USE OF APPROVED AND REPURPOSED DRUGS

One of the persistent problems in TB is the relative weakness of the evidence base. It is unclear whether certain long-used drugs are used at optimal dosages and in optimal combinations. In recent years, however, there has been a resurgence in studies reappraising and repurposing drugs that have been on the market for some time, for decades in some cases.

Isoniazid

Isoniazid is a long-standing component of the standard DS-TB treatment regimen and is also used in high doses in the shortened MDR-TB regimen. The ongoing ACTG5312 trial is testing whether increasing the

dosage of isoniazid can help to overcome existing low-level resistance to the drug. The study is expected to report in 2018.³² High-dose isoniazid is also being used in the NEXT-TB trial.

The need to determine optimal treatment in the face of isoniazid resistance is underlined by a recent meta-analysis that showed substantially worse outcomes in patients with isoniazid mono-resistance receiving standard DS-TB treatment compared with patients who have fully drug-susceptible TB.³³ It is anticipated that these findings may lead to updated guidelines for the treatment of TB in people with isoniazid mono-resistance, but the implementation of such guidelines would be complicated by the fact there are currently no quick and affordable tests for isoniazid resistance (see TB diagnostics chapter, page 91).

Rifamycins

A recently published study concluded that increasing the dosage of rifampin to 35 mg/kg (the current standard is 10 mg/kg) was safe, reduced the time to culture conversion in liquid media, and could be a promising component of future, shorter regimens for DS-TB. The study tested four experimental arms with rifampin dosages of 35 mg/kg, 20 mg/kg, and 10 mg/kg in various regimens against the standard of care for DS-TB. The only arm to show significantly faster culture conversion in liquid media was the DS-TB standard of care with the rifampin dose increased to 35 mg/kg. Arms containing SQ109 and moxifloxacin failed to show superiority to the standard of care.³⁴

Rifampin's sister drug, rifapentine, is being tested in study TBTC 31/ACTG A5349 as part of two four-month regimens for the treatment of DS-TB. The first experimental regimen in this trial simply replaces rifampin with rifapentine and reduces the continuation phase to two months. The second experimental regimen is the same as the first, but replaces ethambutol with moxifloxacin and continues moxifloxacin for the continuation phase. This study is ongoing and is only expected to be completed in late 2019.³⁵

The much-anticipated TRUNCATE-TB trial will test whether DS-TB treatment can be shortened to two months for some patients using combinations of new and repurposed drugs, including the rifamycins. After being a possibility for years, this trial is now expected to start recruitment in August 2017.

Fluoroquinolones

As with a number of TB drugs, the optimal dose for the fluoroquinolone levofloxacin is not known. The phase II Opti-Q study, which is designed to answer this question in patients with MDR-TB, has finished recruiting and is expected to be completed in late 2017. The study will evaluate levofloxacin doses of 11 mg/kg, 14 mg/kg, 17 mg/kg, and 20 mg/kg, all taken with an optimized background regimen.³⁶

Levofloxacin is also being used in the H-35265 trial, the NEXT trial, the STREAM trial, and in a Chinese study in which it is added to the current DS-TB standard of care regimen given for four and a half months instead of the normal six months.³⁷ Moxifloxacin is similarly being used in a number of ongoing trials (see table 2).

Clofazimine

Clofazimine, a riminophenazine that has long been used for the treatment of leprosy, is recognized as a "core second-line agent" in the latest WHO guidelines even though there is only limited evidence from trials on its use for the treatment of TB. Last year we reported that Novartis's planned phase IIC/III clofazimine study CLAM320B2202 was set to start in April 2017. The study would have provided valuable data on the safety and efficacy of clofazimine by comparing a background regimen plus

clofazimine to a background regimen plus placebo. Given the inclusion of clofazimine in the new WHO guidelines, the planned study design was, however, no longer viable, as clofazimine is now part of the standard of care. In response, Novartis opted to cancel the study and the company is now seeking a TB indication without a phase III study. Given the drug's large body of safety data to support its use and indications of its efficacy from routine use, the broader access that a TB indication would provide may be warranted. However, there are many important gaps in our knowledge about the drug, including its individual contribution to the efficacy of a TB treatment regimen, optimal dosing and duration of treatment, and interactions with other drugs. It is not known whether regulators will make registration conditional on conducting additional trials, as was the case with bedaquiline in the U.S. and delamanid in the EU. One concern is that the recently passed 21st Century Cures Act will allow for such early approvals without the necessary checks and balances to ensure that enough is ever learned about the drugs in question. The half-century legacy of poorly studied drugs for MDR-TB should warn us against jumping once again down a slippery regulatory slope towards access without answers.

Some limited data on clofazimine should, however, be forthcoming from the END-TB, TP-Practecal, STREAM stage I and STREAM stage II trials, although these trials are not designed for, or powered to, measure clofazimine-specific effects. Some retrospective, individual patient data on the use of clofazimine currently being compiled by Dick Menzies at McGill University should also shed some light on the drug. In addition, a phase IIc trial called A5362 (also called Clo-Fast) is being planned in which clofazimine will be added to the standard of care for DS TB with the treatment duration being reduced from six months to four months.³⁸

Linezolid

Linezolid is an oxazolidinone with potent activity against TB. There is compelling evidence that it improves culture conversion and cure rates when added to treatment regimens for drug-resistant tuberculosis. However, linezolid has a narrow therapeutic window, and the optimal dosing strategy remains unknown.³⁹

Linezolid is also one of the three drugs that make up the regimen used in the Nix-TB trial (see bedaquiline section above). Although significant linezolid-related toxicity was reported in the Nix-TB trial, it appears to have been manageable in all of the cases reported thus far. Optimizing the dosing and duration of linezolid in this regimen is the key focus of the planned ZeNix follow-up trial. In ZeNix, four arms will receive either linezolid 1200 mg once daily for six months, linezolid 600 mg once daily for six months, linezolid 1200 mg once daily for 2 months, or linezolid 600 mg once daily for 2 months.

Linezolid is also part of experimental regimens being studied in the H-35265, NEXT-TB, END-TB, and MDR-END DR-TB trials.

Although linezolid is mainly being studied and used for drug-resistant forms of TB, it is also being used in at least two trials for drug-susceptible TB. In one ongoing trial, it is hypothesized that replacing ethambutol with linezolid will increase the sputum culture conversion rate by 15% after two months.^{40,41} Another ongoing study will evaluate the two-week mycobactericidal activity, safety, tolerability, and pharmacokinetics of six different dosing schedules of linezolid in people with DS-TB.⁴²

Nitazoxanide

Nitazoxanide is a broad-spectrum antiparasitic and antiviral drug that was first developed in the 1980s and, in recent years, has been explored as a potential treatment for TB. A phase II, 14-day, early bactericidal activity study of nitazoxanide in treatment-naïve patients with drug-susceptible, uncomplicated pulmonary TB is scheduled to complete by the end of 2017.⁴³

Carbapenems

Carbapenems represent a potentially unique anti-tuberculosis option. Emerging evidence demonstrates that they target the *Mycobacterium tuberculosis* cell wall and β -lactamase. A recent review concluded that they appear to kill TB, at least in the active phase, with possible greater potency when given along with a β -lactamase inhibitor.⁴⁴ Imipenem and meropenem are increasingly being used as companion drugs in delamanid- or bedaquiline-containing regimens in the treatment of extensively resistant strains, but must be delivered intravenously multiple times daily. The evidence for carbapenems for the treatment of TB is, however, still highly limited.

Faropenem is an oral penem of a class closely related to the carbapenems. A study scheduled to complete in March 2018 will evaluate the early bactericidal activity of faropenem with amoxicillin/ clavulanic acid in patients with pulmonary TB.⁴⁵

Table 2. Regimens in advanced-stage clinical trials

Study Name	Experimental Arms	For Treatment of	Number of Participants	Phase	Estimated Study Completion Date
NEXT-TB	BDQ, LZD, LEVO, PZA, ETH/INH/TRZ	MDR	300	III	Late 2019
END-TB	BDQ, LZD, MOXI, PZA, BDQ, LZD, LEVO, PZA, CFZ, BDQ, LZD, LEVO, PZA, DLM, DLM, LZD, LEVO, PZA, CFZ, DLM, MOXI, CFZ, PZA	MDR	750	III	April 2021
MDR-END	DLM, LZD, LEVO, PZA	MDR	238	II	Late 2019
TB-PRACTECAL	BDQ, PRE, LZD, MOXI BDQ, PRE, LZD, CFZ BDQ, PRE, LZD	MDR	630	II/III	March 2021
Nix-TB	BDQ, PRE, LZD	XDR, pre-XDR	200	III	October 2021 (results published on ongoing basis)
ZeNix	BDQ, PRE, LZD	XDR, pre-XDR	180	III	January 2022
H-35265	DLM, LVX, LZD, PZA	MDR	300	III	August 2021
STREAM stage II	BDQ, CFZ, LEVO, EMB, PZA, INH, PRO, BDQ, CFZ, LEVO, PZA, INH, KAN	MDR	1155 (with stage I)	III	December 2021
STREAM stage I	MOXI, CFZ, EMB, PZA, INH, PRO, KAN	MDR	1155 (with stage I)	III	2018
Delamanid phase III	DLM + background	MDR	511	III	Completed (top-line findings late 2017)

BDQ: bedaquiline; CFZ: clofazimine; DLM: delamanid; ETH: ethionamide; EMB: ethambutol; INH: isoniazid; LEVO: levofloxacin; KAN: lanamycin; MOXI: moxifloxacin; PRE: pretomanid; PRO: prothionamide; PZA: pyrazinamide

RECOMMENDATIONS

- Governments, and especially the governments of countries with high TB burdens, should dramatically increase their investment in TB R&D. It is imperative that total global investment increases from the current \$600 million/year to the estimated \$2 billion/year that is needed. Whether or not governments manage to meet this need will provide a concrete test of the actual political will behind the various political commitments that will be made at the 2018 UN High Level Meeting on TB.
- The TB Alliance must urgently initiate an expanded access program for pretomanid so that more patients with XDR, pre-XDR-TB, or non-responsive or treatment-intolerant MDR-TB can have the option of trying the NiX regimen. Given that the TB Alliance is a non-profit organization, donors should provide financial support for this expanded access program.
- Medicines regulators should continue to ensure that sufficient data on the safety and efficacy of new drugs are gathered before drugs are approved. Efforts at deregulation through the 21st Century Cures Act in the U.S. and via Adaptive Pathways in the EU should be resisted. At the same time, regulatory delays in high-TB-burden countries must be addressed as a matter of urgency.
- Drug developers should include more phase IIc/III trials in their development plans to reduce the risk of failure in phase III.
- Governments and donors should support the establishment of and fund the operations of an international pre-approval access mechanism as proposed by Treatment Action Group and the Global TB Community Advisory Board.
- Governments must ensure that all people, irrespective of the form of TB that they have, have access to optimal TB treatment regimens as indicated by the available scientific evidence, and to DST to guide the choice of that optimal regimen.

Thank you to Erica Lessem and Mark Harrington from Treatment Action Group for help and guidance with this chapter. Thank you to Professor Richard Chaisson, Professor Gary Maartens, Professor Nicholas Paton, and Professor Keertan Dheda for sharing information relating to their work. I take sole responsibility for all errors in the text.

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The Tuberculosis Diagnostics and Treatment Pipeline for Children

By Lindsay McKenna

INTRODUCTION

An unacceptable disparity exists between the estimated burden of tuberculosis (TB) in children and the number actually diagnosed and put on TB treatment each year. In 2015, just 384,300 of an estimated one million children (38 percent) with TB were reported to national authorities.¹ To reach the remaining 62 percent of children with TB, efforts to identify children at risk for TB are urgently needed. Strategies should include household contact investigation programs, improved referral systems, and decentralized capacity to diagnose and treat childhood TB within maternal child health and primary care programs where sick children often first present for care. Research and development (R&D) will be critical to preventing, detecting, and curing TB in more children.

Enrollment in and planning of TB prevention, treatment shortening, and pharmacokinetic (PK) and safety studies in children continue to progress, in some cases producing interim results and bringing new pediatric formulations closer to market. Yet without intensified efforts to identify and screen children at risk of TB, the impact of these long-awaited advances will be severely limited. The inadequacy of existing diagnostic tests for children contributes to the challenge of finding and diagnosing children with TB.

This chapter discusses recent progress in R&D for pediatric TB diagnosis and treatment, highlights areas in need of further study, and makes recommendations to help expedite research necessary to further improve the diagnosis, prevention, and treatment of drug-susceptible (DS-) and drug-resistant (DR-) forms of TB in children.

DIAGNOSTICS

The World Health Organization (WHO) recommends several TB tests for use in children.^{2,3,4} Existing tests and those under development that are designed to detect TB bacteria (see “The Tuberculosis Diagnostics Pipeline” beginning on page 91) are suboptimal for children, who often have fewer TB bacteria in their bodies than adults (paucibacillary disease). The usefulness of sputum-based tests is limited in young children, who often experience difficulty producing sputum and have high rates of extrapulmonary TB.⁵ Even using the gold standard of culture, microbiological confirmation of TB is obtained in only 15–20 percent of children with clinically diagnosed TB.⁶ Thus, most childhood TB is diagnosed empirically, based on presumption rather than confirmation of disease, using a combination of clinical and epidemiologic information. Given the limits of existing TB tests, empirical diagnoses are essential for children to access TB treatment. However, an empirical diagnosis offers no information about drug resistance—unless there is a close contact/index case with a defined resistance profile—and makes monitoring of treatment response difficult.

Efforts to optimize the performance of existing tests in children and to identify and validate gene signatures and biomarkers for use in the development of new tests for TB diagnosis and treatment monitoring are discussed below.

Optimizing Xpert for Children

The WHO’s recommendations for the use of Xpert MTB/RIF (Cepheid, Sunnyvale, CA) in children apply to pulmonary and extrapulmonary specimens, including cerebrospinal fluid (CSF), lymph nodes, and other tissues.⁷ A meta-analysis found that, while better than smear microscopy at detecting TB in samples from children, Xpert MTB/RIF is less sensitive than culture, which itself has imperfect sensitivity in children.

The sensitivity of Xpert MTB/RIF on induced or expectorated sputum from culture-negative children clinically diagnosed with TB was just two percent.⁸ Research is ongoing to determine the sensitivity of Xpert MTB/RIF on alternative specimen types and to optimize specimen sample collection and processing to improve diagnostic yields in children.⁹ Cepheid's second-generation Xpert cartridge, Xpert MTB/RIF Ultra (Ultra) appears to offer limited additional sensitivity.¹⁰

A prospective cohort study enrolling 272 HIV-positive children younger than 13 years old from eight hospitals in Burkina Faso, Cambodia, Cameroon, and Vietnam found that Xpert used on a combination of alternative samples (nasopharyngeal aspirate, stool sample, and string test) performed similarly to Xpert used on standard samples (gastric aspirate or expectorated sputum) in children with culture-confirmed TB (sensitivity: 75.9 vs. 72.4 percent).¹¹ Still, Xpert detected only 23 of 29 children (79.3 percent) with culture-confirmed TB and just 3 of 116 children (2.6 percent) with probable TB (classified using the Intrathoracic Tuberculosis Definitions for Diagnostic Research in Children¹²), maintaining the test's shortcomings and the diagnostic dilemma for children with culture-negative TB.¹³

A hospital-based study in 379 South African children younger than 13 years old found that the sensitivity and specificity of Xpert on stool were 31.9 percent and 99.7 percent, respectively, compared with bacteriologic confirmation by culture or Xpert on respiratory samples, including gastric or nasopharyngeal aspirates and induced or expectorated sputum. Just 45.1 percent of children with culture-confirmed TB and severe disease were stool Xpert positive. These findings suggest that the use of Xpert on stool may be limited to confirming TB in children who present with severe pulmonary TB disease. Compared with sputum or other samples, stool is less invasive and is relatively easy to collect from children, so Xpert on stool should be considered as a rule-in test with the potential to get sicker children started on TB treatment more quickly.¹⁴

Refinements made to increase the sensitivity of Xpert MTB/RIF by decreasing the clinical limit of detection 10-fold, from 130 to 10 colony-forming units per milliliter (CFU/mL), have resulted in the development of a second-generation cartridge, Ultra. In a multicenter study, Ultra demonstrated noninferiority to MTB/RIF. Ultra was 17 percent more sensitive than MTB/RIF among participants with smear-negative, culture-positive TB (see "The Tuberculosis Diagnostics Pipeline," page 91). In pediatric studies, Ultra demonstrated sensitivity of 95 percent compared with 45 percent for MTB/RIF for the detection of TB meningitis (TBM) in CSF and 71 percent sensitivity versus 47 percent for MTB/RIF on pediatric respiratory samples.¹⁵ Ultra's higher sensitivity over MTB/RIF on pediatric pulmonary and extrapulmonary TB samples is an important advance but, again, may not confer much benefit to children with culture-negative TB.

The Unitaid-funded TB SPEED (**S**trengthening **P**ediatric TB Services for **E**nhanced **E**arly **D**etection) project is one of two grants awarded under Unitaid's 2016 call for proposals to scale up better TB treatment for children.¹⁶ The project, to be implemented by the University of Bordeaux in Sierra Leone, Côte D'Ivoire, Cameroon, Uganda, Mozambique, and Uganda, includes operational research to test an innovative decentralized diagnostic strategy and to optimize the collection and processing of alternative pediatric samples, including stool and nasopharyngeal aspirates. The project also includes a randomized clinical trial to improve TB detection among children with severe pneumonia ($N = 3,000$ children <5 years old). Market impact and forecasting analyses will build an evidence base for future scale-up of effective interventions identified by the TB SPEED project.¹⁷

Optimizing the performance of existing tests in populations known to produce smear- and culture-negative samples (e.g., children, people living with HIV) remains important. Several efforts are under way, but to radically improve rates of confirmed TB diagnosis in children with TB, a next-generation, rapid diagnostic test that is not sputum or pathogen based, and instead dependent on the host's immune response, may be required.

Developing New Tests for Children

Numerous reports have emerged on candidate gene signatures and biomarkers capable of differentiating between TB disease states in pediatric and adult cohorts. Yet few have been independently validated and translated into diagnostic tests relevant to clinical practice.¹⁸ A systematic review of biomarker studies found that of 399 candidate biomarkers of TB disease, just 12 have been confirmed in prospective studies, and only one—lipoarabinomannan (LAM)—has been translated into a clinical assay and endorsed by the WHO (Alere Determine LAM).¹⁹ Several factors limit the advancement of gene signatures and biomarkers from discovery to further stages of development, chief among them the size and cost of independent validation studies given the limited funding for TB R&D, in particular TB diagnostics research.²⁰

The following sections provide updates on promising gene signatures and biomarker-based assays in development for the diagnosis of children with TB, as well as recommendations to further advance research and development in this area.

Gene Signatures

A gene signature is a group of genes differentially expressed under certain biological or other conditions, for example, in the presence of TB infection or disease. In 2014, Anderson et al. from the ILULU Consortium published the performance of a 51-transcript signature for distinguishing TB disease from other diseases and from TB infection in children.²¹ Since these findings were published, to facilitate translation into a point-of-care diagnostic, the ILULU Consortium has narrowed its signature down from 51 to three genes. For distinguishing TB from other diseases, the three-gene signature demonstrated 93.3 percent sensitivity and 80 percent specificity in pediatric test data sets from South Africa and Malawi and 95.5 percent sensitivity and 73.1 percent specificity in a pediatric validation data set from Kenya. Work to refine the selected thresholds to further improve the specificity of the three-gene signature is ongoing.²²

Sweeney et al. from the Stanford Institute for Immunity, Transplantation and Infection identified a different but overlapping three-gene signature, which they validated in 11 independent data sets including both children and adults from 10 countries. Their three-gene signature demonstrated 86 percent sensitivity and specificity for TB infection versus culture-positive TB in children, but TB scores in children with culture-negative TB were significantly lower than those in children with culture-positive TB, suggesting lower sensitivity in children with culture-negative TB.²³ Since these findings were published in 2016, the Stanford Institute for Immunity, Transplantation and Infection has conducted a prospective validation study of its three-gene signature in a cohort from Brazil. Further information regarding study design was not available at the time of writing, but published results are expected soon.²⁴

Biomarker-Based Assays

C-Tb for TB infection

The Statens Serum Institute's C-Tb test is a skin test based on ESAT-6 and CFP10, antigens specific to TB that are also the foundation of interferon gamma release assays (IGRAs). Like the tuberculin skin test (TST), the C-Tb test does not require a laboratory. It has improved specificity that, in contrast to the TST, is not affected by BCG vaccination. A phase III trial, including 86 participants 5–17 years old and 35 younger than 5 years old from Spain, found the C-Tb test safe and highly concordant with IGRAs in individuals aged 5 years and older. Positive results increased with the risk of TB infection.²⁵ These findings should be interpreted with caution, as the trial was not powered to test C-Tb's performance in the pediatric subgroup. A separate phase III trial conducted in South Africa, including 600 children, found

that C-Tb, TST, and IGRAs performed equally well, but low CD4+ T cell counts (<100 cells/mm³) reduced test performance.^{26,27} More complete published results are expected soon.²⁸

TAM-TB for TB disease

The TAM-TB test is a rapid, blood-based T-cell activation marker assay that has so far been evaluated in adults and a small cohort of HIV-positive and HIV-negative Tanzanian children six months to 16 years old ($N = 113$). In this prospective proof-of-concept study, the TAM-TB assay demonstrated 83.3 percent sensitivity among children with culture-confirmed TB and 96.8 percent specificity among children classified as not having TB. Sensitivity was highest in culture-positive cases and decreased with decreasing clinical diagnostic certainty (38 percent in children with highly probable TB; 17 percent in children with probable TB).²⁹ Further assessments of TAM-TB's performance, especially in young, malnourished, and HIV-positive children, are needed. After a long period without funding, this assay is now being developed into a kit version. A small study to evaluate the kit version of the TAM-TB assay, funded by the German Center for Infection Research (DZIF), is expected to open to enrollment in Munich in 2017. Further funding to evaluate the TAM-TB test in adults and children from high TB burden settings is currently being sought.³⁰

Recommendations

Despite continued incremental progress in improving the sensitivity of existing TB tests and diagnostic strategies in children, a point-of-care test that can accurately detect TB in children, especially those with culture-negative disease, remains elusive. Radically improving rates of diagnosis in children with TB will require a gene signature or biomarker-based test that is not sputum based.

Studies to discover new candidate gene signatures and biomarkers are numerous, but those to test and validate them against clinical endpoints in heterogeneous populations are rare. Efforts are needed to reduce gaps between discovery, validation, and translation into diagnostic tests that will benefit children with TB. Toward this end, increased investments in research to discover and validate gene signatures and biomarkers, and innovation to translate these into simple and affordable tests for TB, are necessary. In 2015, just \$4.4 million and \$2.2 million was spent globally on research and development for pediatric TB diagnostics and basic science, respectively.³¹

Evaluating promising biomarkers and gene signatures identified in adult cohorts in children is important, but pediatric-specific discovery and validation efforts remain necessary, especially considering age-dependent differences in the immune response to TB and the broad spectrum of TB disease observed in children.³² Basic scientists and clinical investigators should seek out and foster collaborations in order to maximize knowledge gained by promoting the implementation of substudies within ongoing or planned pediatric studies, including treatment trials, to help identify or validate gene signatures or biomarkers of TB that are reliable independent of age, nutritional status, and coinfection with other pathogens common in children with TB (HIV, pneumonia, etc.) and sensitive enough to detect culture-negative or paucibacillary TB.

Harmonized and collaborative biorepositories are critical to biomarker discovery and development. The Foundation for Innovative New Diagnostics is developing a curated TB biomarker database linked to its biobank, allowing for streamlined validation of biomarkers using well-characterized specimens from diverse patient populations across a variety of ages and geographic regions.³³ Researchers should consider contributing their data sets to this and other publically accessible databases such as the U.S. National Institutes of Health Gene Expression Omnibus.

In the meantime, there is an urgent need to scale up and decentralize screening and diagnosis of pediatric TB infection and disease using a combination of existing tools and empirical diagnoses. Globally, despite significant scientific advances, death rates for childhood TB have not changed between the pretreatment era (before 1946) and 2016 (21.9 vs. 22 percent).^{34,35} This dismal finding highlights the large proportion of children with TB who are not detected and, as a result, die untreated each year. This seems particularly egregious given the extent of pediatric TB treatment R&D efforts discussed in the next section.

TREATMENT

TB prevention, treatment shortening, and PK and safety studies in children continue to progress, in some cases producing interim results and bringing new pediatric formulations closer to market. Table 1 provides an overview of ongoing and planned pediatric TB prevention and treatment studies. The subsequent section offers updates on studies that have advanced or produced results within the last year.

Table 1. Ongoing and Planned TB Prevention and Treatment Studies in Children

Study/Regimen	Status	Population(s)	Sponsor(s)
PREVENTION			
P4v9 4 months of self-administered daily rifampin for prevention of TB NCT00170209*	Enrollment complete; results expected 2017	HIV-positive and HIV-negative infants, children, and adolescents 0–17 years old with LTBI	CIHR, McGill University
Titi 3 months of isoniazid and rifampin or 6 months of isoniazid for prevention of TB (implementation study)	Enrolling; final results expected 2018	HIV-positive and HIV-negative infant and child contacts <5 years old	Expertise-France/the Union
TBTC 35 PK and safety of rifapentine/isoniazid FDC for prevention of TB	Planned; opening 2017	HIV-positive and HIV-negative infants, children, and adolescents 0–12 years old with LTBI	TBTC, Sanofi
TB-CHAMP 6 months of levofloxacin vs. placebo for prevention of MDR-TB (substudy planned using delamanid for child contacts of FQ-R TB patients)	Planned; opening 2017	HIV-positive or HIV-negative infant and child household contacts 0–5 years old; children will get new pediatric formulation	BMRC, Wellcome Trust, DFID, SA MRC
ACTG A5300/ IMPAACT P2003 (PHOENIX) 6 months of delamanid vs. isoniazid for prevention of MDR-TB	Planned; opening 2018	High-risk (HIV+, TST+, or <5 years old) infant, child, adolescent, and adult household contacts of index patient with MDR-TB	NIAID, NICHD
V-QUIN 6 months of levofloxacin vs. placebo for prevention of MDR-TB	Enrolling; final results expected 2020	HIV-positive or HIV-negative adult household contacts; inclusion of adolescents and children <15 years old expected in 2017	NHMRC
TREATMENT - DRUG-SENSITIVE TB			
Treat Infant TB PK and safety of FLDs using 2010 WHO dosing guidelines for treatment of TB	Enrollment complete; results published 2016	HIV-positive or HIV-negative infants <12 months old with TB	Unitaid/TB Alliance (STEP-TB Project)

Study/Regimen	Status	Population(s)	Sponsor(s)
PK-PTBHIV01 PK of FLDs using 2010 WHO dosing guidelines for treatment of TB NCT01687504*	Enrollment complete; results presented 2016	HIV-positive or HIV-negative children 3 months to 14 years old with TB	NICHD
OptiRif Kids PK, safety, and dose optimization of rifampin for treatment of TB	Enrolling; results expected 2019	HIV-negative infants and children 0–12 years old with TB	TB Alliance
SHINE 4 vs. 6 months using 2010 WHO dosing guideline—adjusted FLD FDCs for treatment of nonsevere TB	Enrolling; results expected 2020	HIV-positive or HIV-negative infants, children, and adolescents 0–16 years old with nonsevere TB	BMRC, DFID, Wellcome Trust
TBM-KIDS Safety and efficacy of high-dose rifampin ± levofloxacin for treatment of TBM	Enrolling; results expected 2019	HIV-positive or HIV-negative infants and children with TBM	NICHD
COTREATMENT WITH ARVs			
DATiC PK of FLDs using 2010 WHO dosing guidelines for treatment of TB and interactions with lopinavir/ritonavir and nevirapine NCT01637558*	Enrolling; results expected 2017	HIV-positive or HIV-negative infants, children, and adolescents 0–12 years old with TB	NICHD
IMPAACT P1106 PK of rifampin and isoniazid with nevirapine or lopinavir/ritonavir NCT02383849*	Enrolling; results expected 2018	HIV-positive or HIV-negative low-birth-weight/premature infants	NIAID, NICHD
PK-TBHIV02 PK and safety of nevirapine with rifampin-containing TB treatment NCT01699633*	Enrolling; results expected 2017	HIV-positive children 3 months to 3 years old with TB	NICHD
IMPAACT P1070 PK and safety of efavirenz with rifampin-containing TB treatment NCT00802802*	Enrollment complete; results presented 2016	HIV-positive children 3 months to <3 years old with TB	NIAID, NICHD
PK-PTBHIV03 PK and safety of efavirenz with rifampin-containing TB treatment NCT01704144*	Enrolling; results expected 2017	HIV-positive children and adolescents 3–14 years old with TB	NICHD
HIVPED001 PK and safety of superboosted lopinavir/ritonavir (1:1) with rifampin-containing TB treatment NCT02348177*	Enrolling; results presented 2016	HIV-positive infants and children with TB weighing 3–15 kg; DNDi developing standalone ritonavir booster formulation	DNDi, AFD, UBS Optimus Foundation, MSF
IMPAACT P1101 PK and safety of raltegravir with rifampin-containing TB treatment NCT01751568*	Enrolling; results expected 2018	ARV-naive, HIV-positive children and adolescents 2–12 years old with TB	NIAID, NICHD

Study/Regimen	Status	Population(s)	Sponsor(s)
ODYSSEY PK and safety of dolutegravir with rifampin-containing TB treatment NCT02259127*	Enrolling; results expected 2019	HIV-positive children and adolescents 6–12 years old with TB	PENTA Foundation
IMPAACT P2006 Dolutegravir vs. lopinavir/ritonavir and interactions with rifampin-containing TB treatment	Planned	HIV-positive infants and children 1 month to 3 years old with TB	NIAID, NICHD
TREATMENT – DRUG-RESISTANT TB			
MDR-PK 1 PK and safety of SLDs for treatment of MDR-TB	Enrollment complete; interim results presented; final results expected 2017	HIV-positive or HIV-negative infants, children, and adolescents with MDR-TB or LTBI	NICHD
MDR-PK 2 PK, safety, and dose optimization of SLDs for treatment of MDR-TB	Enrolling; interim results presented; final results expected 2020	HIV-positive or HIV-negative infants, children, and adolescents with MDR-TB	NICHD, SA MRC
232 PK and safety of delamanid; OBR for treatment of MDR-TB NCT01856634*	Enrolling; final results expected 2018	HIV-negative infants, children, and adolescents 0–17 years old with MDR-TB; children ≤5 years old will get pediatric formulation	Otsuka
233 6 months of delamanid; OBR for treatment of MDR-TB NCT01859923*	Enrolling; final results expected 2020	HIV-negative infants, children, and adolescents 0–17 years old with MDR-TB; children ≤5 years old will get pediatric formulation	Otsuka
IMPAACT P2005 PK and safety of delamanid; all-oral OBR for treatment of MDR-TB	Planned; opening 2018	HIV-positive or HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB	NIAID, NICHD
JANSSEN C211 PK and safety of bedaquiline; OBR for treatment of MDR-TB NCT02354014*	Enrolling; final results expected 2025	HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB; children ≤12 years old will get pediatric formulation	Janssen
IMPAACT P1108 PK and safety of bedaquiline; OBR for treatment of MDR-TB	Planned; opening 2017	HIV-positive or HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB	NIAID, NICHD
*U.S. National Institutes of Health clinical trial identifiers; for more information, go to ClinicalTrials.gov .			

AFD: French Development Agency
 ART: antiretroviral therapy
 ARV: antiretroviral
 BMRC: British Medical Research Council
 CIHR: Canadian Institutes of Health Research
 DFID: Department for International Development (United Kingdom)
 DNDi: Drugs for Neglected Diseases Initiative
 FDC: fixed-dose combination
 FLD: first-line drug
 FQ-R: fluoroquinolone-resistant

IMPAACT: International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group, U.S. National Institutes of Health
 LTBI: latent tuberculosis infection
 MDR-TB: multidrug-resistant tuberculosis
 MSF: Médecins Sans Frontières
 NHMRC: National Health and Medical Research Council (Australia)
 NIAID: National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health
 NICHD: National Institute of Child Health and Human Development, U.S. National Institutes of Health
 OBR: optimized background regimen

PENTA: Pediatric European Network for Treatment of AIDS
 PK: pharmacokinetics
 SA MRC: South African Medical Research Council
 SLD: second-line drug
 TB: tuberculosis
 TBM: tuberculous meningitis
 TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention
 TST: tuberculin skin test
 UBS: Union Bank of Switzerland
 WHO: World Health Organization

Research Updates

TB Prevention Studies

The Union's **Titi** study of three months of daily isoniazid and rifampin (3HR) or six months of daily isoniazid (6H) to prevent TB disease in children under five years old opened to enrollment in 2016. This study will evaluate the feasibility of implementing these two regimens in infant and child contacts of people with DS-TB. Children treated with 3HR will receive the new pediatric fixed-dose combination (FDC) of isoniazid and rifampin developed for use during the continuation phase of active TB treatment. Results are expected at the end of 2018.³⁶

Tuberculosis Trials Consortium study 35 (**TBTC S35**) is poised to open for enrollment in 2017. This study follows Sanofi's completion of a bioavailability and safety study of the components of its fixed-dose dispersible of rifapentine and isoniazid (HP) and a rifapentine (P) stand-alone dispersible to be used to facilitate dose adjustments in young children.³⁷ These formulations will be used in TBTC S35 to evaluate the PK and safety of three months of once-weekly rifapentine and isoniazid (3HP) to prevent TB disease in children. Discussions regarding the investigational new drug status of the study and initial challenges in formulation development have contributed to a series of delays in the study's progress.

TB CHAMP, which will evaluate whether six months of levofloxacin can prevent multidrug-resistant (MDR-TB) disease in household contacts under five years old, is poised to open for enrollment this year. Macleods completed a small bioavailability study of its dispersible formulation in adults. A lead-in PK substudy to test levofloxacin exposures achieved in children with the new dispersible formulation is underway. The trial is expected to open at three sites in South Africa in the second half of 2017.³⁸

V-QUIN, designed to evaluate whether six months of levofloxacin can prevent MDR-TB disease in adult household contacts, is currently enrolling children for periodic screening for disease, without randomization. The investigators expect to commence randomization of adolescents and children <15 years old in the second half of 2017, pending an upcoming resubmission to the National Ministry of Health Ethics Committee in Viet Nam.³⁹

The AIDS Clinical Trials Group (ACTG) and International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) networks successfully completed a feasibility study in advance of the **PHOENIX** trial, which will compare six months of delamanid to isoniazid to prevent MDR-TB disease in household contacts of people with confirmed MDR-TB and is expected to open in early 2018.⁴⁰

TB Treatment Studies

DS-TB

A study of first-line treatment in infants and children in Ghana (**PK-PTBHIV01**; N = 113; 47.8 percent of children less than five years old), using WHO-recommended doses, found that children with HIV and TB had significantly lower exposures to rifampin, pyrazinamide, and ethambutol than children with TB alone.⁴¹ This is one of several studies that have found that the higher doses recommended for children by the WHO starting in 2010 still produce lower drug exposures measured by C_{max} (peak drug exposure) and area under the curve (AUC, or total drug exposure) in children compared with adults.⁴²

Given the previously demonstrated association between low drug exposures and poor treatment outcomes in children,⁴³ there is an urgent need to determine whether exposures with recommended doses for children result in good outcomes, even if they do not match the levels achieved in adults.

The **SHINE** study, which opened to enrollment in the third quarter of 2016, will evaluate whether it is possible to shorten treatment from six to four months for less-severe smear-negative forms of TB in children. The SHINE study uses the new pediatric FDCs aligned with WHO-recommended doses and includes nested PK studies in both HIV-positive and HIV-negative participants. Since SHINE is powered to look at efficacy, it may be able to provide some insights as to whether currently recommended doses for first-line TB drugs in children and the exposures they achieve are adequate (achieve good outcomes). These insights may be limited in their applicability to children with more severe forms of TB (i.e., miliary TB, TBM, and other extrapulmonary manifestations) that likely require higher levels of drug exposure in order for drugs to reach each of the infected sites and to exert their effects.

OptiRif Kids, which opened in the first quarter of 2017, will further explore low rifampin exposures observed in other studies in young children⁴⁴ and evaluate rifampin doses necessary to achieve exposures in children that match higher doses evaluated in adults (up to 35–40 mg/kg) and found to be safe, well tolerated, and able to kill more mycobacteria (see “The Tuberculosis Treatment Pipeline,” beginning on page 129). Starting with the currently WHO-recommended dose, modeling techniques will be used to determine escalating doses to be evaluated in the study cohorts.

Modeling has also informed the higher dose of rifampin (recommended range: 10–20 mg/kg) that will be administered to some of the children with TBM enrolled in **TBM-KIDS**.⁴⁵ Children will be randomized to receive the standard of care (isoniazid, rifampin, pyrazinamide, and ethambutol); isoniazid, pyrazinamide, ethambutol, and high-dose rifampin (30 mg/kg); or isoniazid, pyrazinamide, high-dose rifampin (30 mg/kg), and levofloxacin dosed at 20 mg/kg for children older than two years and 15 mg/kg for children two years old or younger (recommended range: 10–15 mg/kg once daily for children older than five years of age and 15–20 mg/kg split into two doses for children five years of age or younger). The investigators expect the 30 mg/kg dose of rifampin to achieve exposures in children that approximate those from recent studies to optimize the treatment of TBM in adults. Neurologic and neurocognitive outcomes will also be assessed and PK/PD relationships explored.⁴⁶

Cotreatment With Antiretrovirals

HIVPED001, a study evaluating superboosted lopinavir/ritonavir administered in a ratio of 1:1 (standard lopinavir/ritonavir is administered in a ratio of 4:1) with rifampin-containing TB treatment to infants and young children, produced final results in 2016. The study determined that exposures following superboosted doses of lopinavir/ritonavir (1:1) with rifampin are noninferior to exposures following standard doses of lopinavir/ritonavir (4:1) without rifampin.⁴⁷ Virological efficacy and safety were also comparable. These results led to strengthened WHO recommendations to use superboosting in TB/HIV co-infected children on lopinavir/ritonavir.⁴⁸ Acceptability of existing standalone liquid formulations of ritonavir is poor on account of their taste. The Drugs for Neglected Diseases Initiative and Cipla developed and tested several taste-masked granule and pellet formulations of ritonavir, but they were unable to cover the bitter taste without compromising bioavailability. The Drugs for Neglected Diseases Initiative plans to test the acceptability of a powder formulation developed by AbbVie that is bioequivalent to the existing liquid formulation but not taste masked.⁴⁹

Studies to characterize drug-drug interactions (DDIs) between rifampin and anti-HIV compounds, including integrase inhibitors (**P1101**; **ODYSSEY**; **P2006**), in children are ongoing. The availability of alternative HIV regimens for children with TB has gained attention as rates of resistance to non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, nevirapine) have increased among children.⁵⁰ DDIs between rifampin and protease inhibitors (e.g., lopinavir and ritonavir), though possible to overcome as discussed above, make dosing difficult.

DR-TB

Estimates of the burden of MDR-TB among children range from 25,000 to 32,000 cases per year.^{51,52} Yet few children globally are treated for MDR-TB. An individual patient systematic review and meta-analysis of children treated at any time in the past for MDR-TB identified only 1,000 such children.⁵³ Severe gaps in diagnosis and difficulties obtaining bacteriologic confirmation in children might explain this vast discrepancy, but the historical lack of experience with, knowledge about, and child-friendly formulations of the second-line TB drugs used to treat MDR-TB likely contribute, as well.

Encouragingly, there has been increased activity in this area in recent years. Studies designed to fill PK and safety data gaps to inform the safe and optimal use of existing and new second-line drugs in children have produced interim results, and studies to shorten and improve treatment regimens have included limited numbers of adolescents and children or are in advanced stages of planning for these populations.

PK and Safety Data

Ongoing analyses of data collected in **MDR-PK 1**, which completed enrollment in 2015, and **MDR-PK 2**, still open, continue to produce pediatric PK and safety information for existing second-line drugs, including levofloxacin, moxifloxacin, linezolid, ethionamide, para-aminosalicylic acid, terizidone, and other drugs. Pediatric studies of the newer second-line drugs delamanid, bedaquiline, and pretomanid continue to progress, but at very different paces.

Population PK models, combining PK data from multiple individuals, can predict and simulate how drugs behave in the body. A population PK model built using data from 109 children treated with levofloxacin in MDR-PK 1 determined that levofloxacin dosed at 20 mg/kg (recommended range: 10–15 mg/kg once daily for children more than five years of age; 15–20 mg/kg split into two doses for children five years of age or younger) achieved lower levels of exposure in children than in adults.⁵⁴ The model predicted that the 30–40 mg/kg doses required for children to achieve exposures matching those in adults would produce higher peak exposures, raising safety concerns. In MDR-PK 1, levofloxacin dosed at 15–20 mg/kg was safe and well tolerated.⁵⁵

A population PK model of moxifloxacin in children with and without HIV, built using data from 52 children in MDR-PK 1 and MDR-PK 2, determined that at currently recommended doses (range: 7.5–10 mg/kg) children achieve considerably lower moxifloxacin exposures than adults.⁵⁶ Higher moxifloxacin doses need to be explored and evaluated for safety in children.

A population PK model of linezolid in children with and without HIV, built using data from 17 children enrolled in MDR-PK 1 and MDR-PK 2, determined that at currently recommended doses (range: 10 mg/kg three times a day) children achieve linezolid exposures that approximate those achieved in adults, and that twice-daily dosing in young children may result in exposures that exceed those achieved in adults.⁵⁷ These data highlight the importance of ongoing PK and safety investigations of second-line and new TB drugs in children, especially given the potential for dose-dependent toxicities.

Data collected from participants in MDR-PK 1 treated with moxifloxacin and linezolid will be rolled into MDR-PK 2, which remains open to enrollment and will further examine the PK and safety of optimized doses of moxifloxacin, levofloxacin, and linezolid in children.⁵⁸ Simulations with these models and data will determine optimal weight-banded dosing schemes for these drugs in children. Optimal dosing strategies for clofazimine in children may also be evaluated in this project.

Data from **C232/C233** (a pediatric PK and safety study of delamanid in HIV-negative children) have informed a decision by the WHO to extend its recommendations on the use of delamanid for

the treatment of MDR-TB in adults to children six years and older and adolescents, using the adult formulation.⁵⁹ Studies with the pediatric formulation are underway: follow-up for the three- to five-year-old cohort is ongoing, and the fourth and final age cohort (children younger than 2 years old has started enrollment.⁶⁰ IMPAACT P2005 will provide complementary delamanid PK and safety data in children with MDR-TB, including those with HIV infection, in the context of all-oral regimens.⁶¹

In December 2012, the U.S. Food and Drug Administration (FDA) granted accelerated approval for bedaquiline in adults, but pediatric investigations of bedaquiline only began in March 2016. As a result, limited data are available and the WHO has not been able to make a recommendation about the use of bedaquiline in adolescents or children.⁶² However, bedaquiline is already being used to treat adolescents and children down to 12 years old in some programs under certain conditions.⁶³ At the time of writing, Janssen's pediatric PK and safety study of bedaquiline (C211) was enrolling at sites in South Africa, Russia, and the Philippines and had recruited just 15 participants to the first and second age cohorts (7- to 18-year-olds).⁶⁴ Results from the first two cohorts will be available in 2018. The site Janssen opened in Russia has so far been able to enroll only adolescents. Discussions between Janssen and the Russian regulatory authorities on the possibility of enrolling younger children are ongoing. Janssen expects a site in India to open to enrollment at the end of this year, which may help to speed up recruitment.⁶⁵ P1108, the IMPAACT network's pediatric PK and safety study of bedaquiline, including in HIV-positive children, is expected to open by mid-2017. P1108 uses model-based dosing strategies and modified age de-escalation; data will be disseminated as each cohort is enrolled.

The pretomanid-containing NiX-TB regimen has produced promising preliminary results (see TB Treatment Pipeline, in *2017 Pipeline Report*, [publishing July 2017]), and the TB Alliance is currently advancing plans for a phase III trial. FDA concern regarding testicular toxicity observed in rodents in preclinical studies stalled the initiation of pediatric investigations of pretomanid.⁶⁶ The TB Alliance has submitted male reproductive hormones data collected from participants in its phase II and III studies of pretomanid to the FDA to alleviate its concern and gain agreement that children may be dosed with pretomanid. It plans to submit a Pediatric Investigational Plan (PIP) to the European Medicines Agency (EMA) in mid-2017 and has already developed a dispersible formulation.⁶⁷

Shortened Regimens

In May 2016, the WHO issued an update to its guidelines for treating MDR-TB, recommending the use of a shortened regimen (nine months of moxifloxacin, clofazimine, ethambutol, and pyrazinamide, given with kanamycin, prothionamide, and isoniazid for the first four months) in children with confirmed rifampin-resistant or MDR-TB.⁶⁸ This recommendation was based on data collected in adults, but operational research conducted by the Union in collaboration with national TB programs in nine African countries has provided some data on the performance of, and practical experience implementing, the shortened regimen in adolescents and children.

Using the shortened regimen, the Union reported a treatment success rate of 83 percent among 47 children and adolescents (19 percent HIV-positive).⁶⁹ These findings should be interpreted with caution given the small sample size and that just five of the children enrolled were under 10 years old. While adverse events were reportedly "mild," high rates of observed gastrointestinal toxicity (74 percent) and ototoxicity (41 percent) underscore the urgent need for similarly short regimens, made up of less-toxic and better-tolerated drugs.

The paucibacillary nature of TB disease in children, and the improved MDR-TB treatment outcomes observed among children compared to adults,⁷⁰ even with observed lower exposures to key second-line drugs, suggest that it might be possible to treat MDR-TB in children using shorter and less aggressive regimens than those necessary in adults.⁷¹ The shortened regimen could be a major improvement but still requires a lot of drugs, including an injectable agent, with unacceptable toxicity. Studies to determine whether it is possible to treat MDR-TB in children using all-oral regimens that contain fewer drugs are urgently needed.

SMaRT Kids, a randomized phase III trial for which a protocol is currently under development (currently unfunded), proposes to test an all-oral, six-month regimen of delamanid, clofazimine, linezolid, levofloxacin, and pyrazinamide against the WHO-recommended shortened regimen in children younger than 13 years old with rifampin-resistant or MDR-TB. The study will evaluate six months of delamanid, clofazimine, linezolid, para-aminosalicylic acid, and pyrazinamide against 18- to 24-month individualized regimens built according to WHO recommendations in children with pre-extensively drug-resistant and extensively drug-resistant TB.⁷²

The wide spectrum of TB disease presentation in children, ranging from severe disease (e.g., miliary disease or TBM) in young children to limited pulmonary disease to cavitary disease in adolescents, makes selecting a regimen and duration of treatment appropriate for all children and adolescents difficult. A one-size-fits-all approach is likely to result in under- or overtreatment in certain groups of children with TB.⁷³ Discussions of the optimal design, regimen, and population for inclusion in SMaRT Kids continue.⁷⁴

Formulation Updates

Under the Unitaid-funded Step-TB project, implemented by the TB Alliance, appropriately dosed pediatric FDCs of first-line TB drugs were finally introduced to the market at the end of 2015. Uptake has been slow due to logistical and other challenges at the country level, but recent efforts by key organizations through their participation in the Stop TB Partnership Global Drug Facility–convened TB Procurement Market Shaping Action Team (TPMAT) have helped country programs develop and expedite plans to facilitate transition to the new formulations. A second quality-assured source necessary to ensuring market stability and competition, though anticipated, has yet to reach the market.

In contrast to first-line TB drugs, just five of 14 second-line TB drugs are available in pediatric formulations, and even these are inadequate. Existing oral suspensions (syrups) of linezolid and levofloxacin are difficult to dose accurately, are bulky and difficult to ship and store, and are not widely available.⁷⁵ Moxifloxacin (only available in a 400 mg tablet), which is not scored and bitter when crushed, and clofazimine (only available in soft gel capsule form) are core components of MDR-TB treatment, including the WHO-recommended shortened regimen, but are hard to give in appropriate doses to children with existing adult formulations. Pediatric formulations of moxifloxacin, clofazimine, and other key second-line TB drugs are an urgent priority.

Encouragingly, Macleods has been working to develop dispersible levofloxacin, moxifloxacin, linezolid, and ethionamide and a minicapsule of cycloserine. Macleods' scored dispersible 100 mg levofloxacin formulation, currently undergoing PK and acceptability testing in children, will be piloted in the TB-CHAMP trial. With support from the U.S. National Institute of Allergy and Infectious Diseases Small Business Initiative for Research Program, Luna Innovations has been working to create pediatric gummy formulations of ethambutol, isoniazid, moxifloxacin, and clofazimine. They have created gummies in FDCs of isoniazid, rifampin, and pyrazinamide (HRZ) and isoniazid and rifampin (HR). Luna Innovations is currently working with the IMPAACT network to perform stability testing and hopes to initiate animal studies in 2018.⁷⁶ Pediatric formulations in development or new to the market are summarized in Table 2.

Table 2. Pediatric Formulations in Development or New to Market

Drug	Dose	Formulation	Company	Status
First-line drugs				
Fixed-dose combinations	HRZ: 50/75/150 mg HR: 50/75 mg	Dispersible tablet	Macleods	Passed GF ERP; in distribution; PQ dossier under assessment*
	HRZ: 50/75/150 mg HR: 50/75 mg	Dispersible tablet	Lupin	Status unknown
	HRZ: 50/75/150 mg HR: 50/75 mg	Gummy	Luna Innovations	In preclinical development; undergoing stability testing
	HRZ: 50/75/150 mg HR: 50/75 mg	Dispersible tablet	Sandoz	Status unknown
	HRZ: 50/75/150 mg HR: 50/75 mg HP: 150/150 mg	Dispersible tablet	Sanofi	HRZ/HR: Status unknown HP: Product developed; soon to be in clinical trial
	HRZ: 50/75/150 mg HR: 50/75 mg	Dispersible tablet	Svizera	Status unknown
Ethambutol	100 mg	Dispersible tablet	Macleods	Status unknown
	50 mg	Gummy	Luna Innovations	In preclinical development; undergoing stability testing
Isoniazid	100 mg	Dispersible tablet	Macleods	Status unknown
	50 mg	Gummy	Luna Innovations	In preclinical development; undergoing stability testing
Pyrazinamide	150 mg	Dispersible tablet	Macleods	PQ granted; distribution status unknown
Rifapentine	100 mg	Dispersible tablet	Sanofi	Product developed; soon to be in clinical trial
Second-line and new drugs				
Bedaquiline	20 mg	Dispersible tablet	Janssen	Product developed; soon to be in clinical trial
Clofazimine	10 mg	Gummy	Luna Innovations	In preclinical development; undergoing stability testing
Cycloserine	125 mg	Mini capsule	Macleods	Passed GF ERP; distribution status unknown
Delamanid	20 mg 5 mg	Dispersible tablet	Otsuka	Undergoing clinical trial
	125 mg	Scored dispersible tablet	Macleods	PQ granted; distribution status unknown
Ethionamide	125 mg	Scored dispersible tablet	Lupin	Status unknown
Levofloxacin	100 mg	Scored dispersible tablet	Macleods	Passed GF ERP; distribution status unknown
Linezolid	150 mg	Dispersible tablet	Macleods	Status unknown
Moxifloxacin	100 mg	Scored dispersible tablet	Macleods	Status unknown
	50 mg	Gummy	Luna Innovations	In preclinical development; undergoing stability testing
Pretomanid	50 mg 10 mg	Dispersible tablet	TB Alliance	Product developed; soon to be in clinical trial
*The status of this formulation is speculative and based on available information, as the WHO does not provide information linking PQ dossiers under assessment to manufacturers. The manufacturer was contacted to confirm the status listed here but did not respond.				

GF ERP: Global Fund Expert Review Panel
H: isoniazid

P: rifapentine
R: rifampin

PQ: Prequalification
Z: pyrazinamide

Box 1. TB Research Updates for Pregnant Women

Despite substantial clinical need for TB prevention and treatment, pregnant women remain neglected by research initiatives. In recent years, pregnant women have started to see modest representation in TB clinical trials.

Table 3. Ongoing and Planned TB Prevention and Treatment Studies in Pregnant Women

Trial	Phase	TB type	Study purpose
PREVENTION			
IMPAACT P1078 (TB APPRISE) NCT01494038*	IV	DS-TBI	To evaluate antepartum vs. postpartum isoniazid preventive therapy in HIV-positive women
IMPAACT P2001 NCT02651259*	I/II	DS-TBI	To evaluate the pharmacokinetics and safety of once-weekly rifapentine and isoniazid in pregnant and postpartum women with and without HIV
TREATMENT			
IMPAACT P1026s NCT00042289*	IV	DS-/DR-TB	To evaluate the pharmacokinetics of first- and second-line TB drugs with and without ARVs in pregnant women
ACTG A5338 NCT02412436*	IV	DS-TB	To evaluate the pharmacokinetic interactions among depo-medroxyprogesterone acetate, rifampin, and efavirenz in women co-infected with HIV and TB
THSEPISO	IV	DS-TB	To study the impact of TB/HIV coinfection in pregnancy on maternal and infant outcomes and to evaluate the pharmacokinetics of first-line TB drugs in pregnant and postpartum women
TB pregnancy registry	IV	DS-/DR-TB	To evaluate maternal and infant treatment and safety outcomes from clinical research databases (planned)
*U.S. National Institutes of Health clinical trial identifiers; for more information, go to ClinicalTrials.gov .			

ARV: antiretroviral
 DR-TB: drug-resistant tuberculosis
 DS-TB: drug-sensitive tuberculosis

DS-TBI: drug-sensitive tuberculosis infection
 TB: tuberculosis

An evaluation of 87 women who became pregnant while participating in two studies comparing three months of weekly rifapentine (900 mg) and isoniazid (900 mg) to nine months of daily isoniazid (300 mg) found that the combination regimen (3HP) was not associated with adverse pregnancy outcomes.⁷⁷ Further safety and PK investigations of 3HP are necessary in pregnant and postpartum women and are planned in **IMPAACT P2001**, which opened to accrual in the first quarter of 2017. Investigators should attempt to collect safety and other data in women who become pregnant while participating in TB research studies to help inform the prevention and treatment of TB in pregnant and postpartum women in the time between when interventions are formally tested in nonpregnant versus pregnant populations.

IMPAACT P1078, a phase IV study to evaluate the safety and toxicity of isoniazid preventive therapy (IPT) administered during pregnancy (second or early third trimester) or three months postpartum, has enrolled 950 mother-infant pairs from eight countries. Primary results are expected by the end of 2017. The study will provide information about the safety and optimal timing of IPT in pregnancy, PK and interactions between isoniazid and antiretroviral therapy, and TB-specific immune responses in pregnancy and postpartum.⁷⁸

Samples from 34 pregnant and postpartum women enrolled in the **TSHEPISO** study, previously analyzed to characterize PK and DDIs for rifampin, isoniazid, and efavirenz,^{79,80} are now undergoing further analyses and are expected to produce additional information regarding the PK of ethambutol and pyrazinamide.⁸¹ A publication describing the impact of TB/HIV coinfection in pregnancy on maternal and infant outcomes is expected in 2017.⁸²

P1026s, the IMPAACT network study to evaluate the PK of first- and second-line TB drugs with and without antiretrovirals in pregnant women, has enrolled 10 women. An abstract with interim results regarding the PK of isoniazid and rifampin has been accepted for presentation at the International AIDS Society Conference on HIV Science in July.⁸³

A recently established cross-network TB and Pregnancy Research Working Group (TBPWG) has fostered collaborations among researchers and networks to enable data sharing between THSEPISO and P1026s to better characterize the PK of first-line TB drugs in pregnant and postpartum women. A population PK model combining PK, safety, and outcomes data from THSEPISO and P1026s is planned and will be proposed to the IMPAACT network in 2017. The TBPWG has also submitted a concept sheet to the TBTC's Core Science Group proposing an observational study of TB treatment in pregnant and postpartum women who screen out of TBTC S31/ACTG 5349—a phase III study evaluating whether rifapentine-containing regimens can shorten treatment for DS-TB (see TB Treatment Pipeline, in *2017 Pipeline Report*, [publishing July 2017]).

Despite these encouraging advancements and collaborative efforts, there is still an urgent need to support the earlier inclusion of pregnant women in TB drug trials.^{84,85}

Recommendations

Pediatric TB treatment R&D has come a long way in recent years. Studies to fill longstanding PK and safety data gaps are producing results, and those to evaluate shortened and simplified prevention and treatment regimens are already underway or are soon to open. Yet much work remains to simplify and improve the treatment of DR-TB in children and to bring pediatric formulations of new and second-line TB drugs to market.

For researchers

- Determine whether exposures achieved using recommended doses of first-line drugs in children result in good outcomes, even if they do not match the levels of exposure achieved in adults. This evidence is crucial in the context of shortened regimens and for treatment of the wide spectrum of TB disease seen in children.

- Include children with TB in pediatric studies of new antiretrovirals and children with HIV in pediatric TB studies. PK substudies in TB/HIV-coinfected children are needed to evaluate safety and DDIs to inform appropriate dosing.
- Determine optimal regimens and doses to improve outcomes in children treated for TBM, which have remained abysmal and unchanged for the past 50 years.⁸⁶

For drug and study sponsors

- Expedite the investigation of new drugs and regimens in children. Pediatric investigation of new TB drugs and regimens should begin as soon as indications of efficacy and safety have been established in adults (phase IIb studies); cohorts for PK and safety studies in children should be recruited in parallel. Adolescents aged 10 years and older should be included in adult TB drug trials phase IIb and later as a matter of urgency.⁸⁷

For regulatory authorities

- Ensure the timely and comprehensive collection and submission of pediatric data to inform the safe and appropriate use of new TB drugs in children.

For policy makers

- Incorporate emerging data into guidelines for children more rapidly, especially those for new and second-line TB drugs in children. Given the amount of data on the PK of second-line TB drugs that have emerged since 2006 (the first and last time the WHO recommended doses for second-line TB drugs in children), the WHO should immediately take steps necessary to issue updated dosing guidelines for second-line TB drugs in children.

For donors

- Increase investments in pediatric TB drug R&D to support the progressively full roster of studies necessary to improve the treatment of all forms of TB in children. Global investments in pediatric TB drug R&D totaled just \$16.1 million in 2015.⁸⁸
- Unitaid, whose investments led to the market introduction of appropriately dosed pediatric FDCs of first-line TB drugs, should fund a similar project to expedite development and market introduction of pediatric second-line TB drugs. Pediatric DR-TB is a small and fragile market, for which medicines vital to catalyzing better treatment of DR-TB in children are highly unlikely to be developed without external incentives.

ACKNOWLEDGEMENTS

Many thanks to Dr. Anneke Hesseling for her generosity in time and attention paid to editing this chapter year after year. My gratitude also goes to Dr. Norbert Heinrich for his comments on the diagnostics section of this chapter. Input from multiple other researchers and sponsors who responded to queries for this report is greatly appreciated.

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HCV Pipeline: DAAs and Diagnostics in the Pangenotypic Era

By Annette Gaudino

INTRODUCTION

The continued development of direct-acting antivirals (DAAs) against hepatitis C virus (HCV) has brought both multigenotypic and pangenotypic regimens to market, with more on the horizon. These simpler-to-prescribe regimens potentially eliminate the need for genotype testing, have shown improved efficacy in previously difficult-to-treat patients, and hold the promise of massive scale up of treatment in primary care settings with nonspecialist providers, such as general internists and non-physicians, including nurse practitioners and physician assistants, as well as community pharmacists prescribing these therapies. Progress towards reliable, streamlined diagnostics that provide rapid confirmatory ribonucleic acid (RNA) testing has also continued, with manufacturers pursuing the goal of one-step point-of-care testing suitable for resource-limited settings. To effectively address the rising incidence of HCV among those who actively inject drugs, punitive approaches to drug use must be abandoned in favor of a public health approach, with people who use drugs at the center of the response.

Unless and until we can rapidly identify and treat chronically infected individuals, concrete progress towards the World Health Organization (WHO) targets on the elimination of HCV as a public health threat by 2030 will remain an elusive goal.¹ Despite possessing highly effective short-course curative treatments that are the envy of those combatting HIV and TB, without unprecedented investment in implementation of strategic public health actions against HCV, we stand to miss a historic opportunity to wipe this deadly infectious disease from the face of the earth.

Global commitments are needed to end the HCV epidemic:

- National action plans with secure, multi-year funding for HCV treatment for everyone without restrictions, including treating reinfections;
- Sustainable global funding for generics, including multigenotypic and pangenotypic DAAs, and diagnostics in low- and middle-income countries;
- R&D for more options in point-of-care RNA assays to fill critical gaps in screening programs and put more patients on treatment;
- R&D for comprehensive diagnostic technologies that ensure rapid test results in a single visit, inform treatment regime choice, and confirm curative rates in patients;
- Research to develop a new class of DAAs to cure in four weeks;
- Continued funding for research towards a HCV vaccine that shows efficacy in people at risk for HCV infection because they inject drugs; the ability to elicit immune response in people living with HIV who are not at high risk for HCV infection; and safety in combination with HIV vaccine administration in healthy volunteers;
- R&D for dosage and effective treatment regimens for infants and children (aged 3-12 years) and weighing less than 35 kilograms (77 pounds);
- Post-treatment studies on the efficacy and long-term health effects for sofosbuvir and sofosbuvir/ledipasvir in adolescents (aged 12-17 years);

- Expanded risk based screening beyond the birth cohort (1945-1965 in the U.S.; different ranges outside the U.S.)
- Decriminalization of drug use and centering the needs of those most at risk for infection.

Beyond blockbuster prices: adding tools to the toolkit

The arrival of highly effective, interferon-free, single daily dose DAAs in 2014 led to remarkably increased public awareness of HCV, but hasn't led to a comprehensive response to the epidemic. The eye-popping price of Gilead's essential compound sofosbuvir (Sovaldi) generated countless headlines and outrage as the latest example of corporate greed in the pharmaceutical industry. However, focus on the high price of HCV cures has dominated the public response to the epidemic, only slowly and haltingly generating movement on the public health challenge posed by HCV infection. Although calls to address the high price of pharmaceutical drugs have frequently used HCV cures as the exemplars of everything wrong with the status quo, the movement for drug-pricing reform has, overall, rarely engaged directly in the struggle for HCV treatment access. A broad coalition bringing together activists for patent law and drug development reform, drug user health and harm reduction, and those living with HCV could be a powerful force to demand action.

As advocates fight to be heard, recent approvals of multigenotypic and pangenotypic treatments continue to add tools to our anti-HCV toolkit. New and soon-to-be available options from multiple manufacturers not only benefit patients, especially those with advanced disease, co-morbidities, and difficult-to-treat genotype 3, but also offer payers needed flexibility when choosing regimens for their formularies. Drugs in the development pipeline, most notably AbbVie's pangenotypic combo glecaprevir/pibrentasvir (Maviret), will go head to head with Gilead's sofosbuvir/velpatasvir (Epclusa).

In high-income countries, Merck's Zepatier (grazoprevir/elbasvir) and AbbVie's Viekira Pak have been used as alternative, more-affordable regimens in patients with genotype 1 and 4. Viekira Pak is offered as a multi-pill twice daily regimen, and is not approved for patients with genotype 4 and cirrhosis. Zepatier requires pre-treatment NS5A-resistance testing in patients with genotype 1a. A new once daily formulation of AbbVie's four-drug combination, Viekira XR, was approved in July 2016, and appears to be a more attractive option for patients and providers. Gilead's drugs are not currently available through state AIDS Drug Assistance Programs (ADAP) for HIV/HCV co-infected patients in the U.S., potentially allowing AbbVie to leverage their position in ADAP formularies for their new pangenotypic combo G/P when it hits the U.S. market.

Pending drugs in the pipeline: the dawn of the pangenotypic era

AbbVie, Gilead, Merck, and Janssen have presented data at international congresses on efficacy across the six major genotypes; in difficult-to-treat populations, including patients with genotype 3 and cirrhosis; and patients with advanced kidney disease. Gilead also recently received approval for previously untreated adolescents, and presented data on ongoing clinical trials in young children. It would not be hyperbole to state that science has solved chronic HCV infection for all but individuals with decompensated cirrhosis—yet another powerful argument for early treatment. It must be noted that, as historically has been the case, all clinical trial data is based on majority male patient populations, with few people of color, particularly African Americans, taking part in clinical trials.

Table 1 (below) summarizes the latest multigenotypic and pangenotypic DAAs in the pipeline.

Table 1. Multigenotypic and Pangenotypic Treatments

TREATMENT	FDA STATUS	MANUFACTURER	PAN GENOTYPIC	STUDY NAME	STUDY DESIGN	TREATMENT DURATION	EVALUATED IN HIV COINFECTED	RIBAVIRIN	SVR AND AE OUTCOMES
Glecaprevir + pibrentasvir (G/P) (300 mg/120 mg)	NDA submitted Dec 2016	AbbVie	YES	EXPEDITION-1 ^{2,3,4}	Single arm, open-label study; N=146 patients with GT1, 2, 4, 5, or 6 and compensated cirrhosis.	12 weeks	NO	NO	99% SVR; one GT1a relapse. No serious treatment-related AEs.
				EXPEDITION-2 ⁵	Open-label study comparing 8 (without cirrhosis)-and 12 weeks (with cirrhosis) G/P. N=153 HIV/HCV coinfecting patients, GT1-6 (N=16 with cirrhosis); treatment naïve or not cured with prior treatment.	8 or 12 weeks	N=153	NO	98% SVR without cirrhosis, 93% SVR with cirrhosis. No serious treatment-related AEs
				EXPEDITION-4 ⁶	Single-arm, open-label evaluation of 12 weeks G/P in patients with chronic disease (CKD); N=104 with GT1-6 and stage 4 or 5 CKD.	12 weeks	N=0	NO	98% (102/104) SVR12; , no serious treatment related AE or treatment discontinuations reported, grade 3 or higher lab abnormalities were rare
				ENDURANCE-1 ^{7,8,9}	Randomized comparisons of 8 and 12 weeks G/P. N=703 patients with GT1 and without cirrhosis; treatment naïve or not cured with prior treatment.	8 or 12 weeks	N=33	NO	95% SVRs in 12- and 8-week groups; no serious treatment-related AEs.
				ENDURANCE-3 ¹⁰	Randomized comparison of 12 weeks G/P vs. sofosbuvir/daclatasvir (SOF/DCV), with additional 8-week G/P non-inferiority comparison with 12-week G/P. N=505 treatment-naïve patients with GT3 and without cirrhosis.	8 or 12 weeks	NO	NO	Non-inferior to SOF/DCV; 95% SVRs in 12- and 8-week G/P groups; no serious treatment-related AEs

TREATMENT	FDA STATUS	MANUFACTURER	PAN GENO-TYPIC	STUDY NAME	STUDY DESIGN	TREATMENT DURATION	EVALUATED IN HIV COINFECTED	RIBAVIRIN	SVR AND AE OUTCOMES
				MAGELLAN-1, Part 1 ^{11,12}	Randomized comparison of 12 weeks G/P 200/80 mg (Group A; discontinued), G/P 200/120 mg plus 800 mg ribavirin (Group B), or 300/120 mg without ribavirin (Group C). N=50 GT1 patients with history of failure with NS3/4A \geq 1 NS3/4A PI or NS5A inhibitor	12 weeks	NO	Yes	SVRs of 100% in Group A, 95% in Group B, and 86% in Group C; no improvement associated with addition of ribavirin. Virologic failure in 1 patient each in Groups B and C.
				MAGELLAN-1, Part 2 ¹³	Randomized comparison of 12 and 16 weeks G/P; N=91 with GT1, 4, 5, or 6 with history of failure with \geq 1 NS3/4A PI or NS5A inhibitor (N=27 with compensated cirrhosis)	12 or 16 weeks	NO	No	Overall SVR: 89% (12 weeks) and 91% (16 weeks); 79–81% in pts. with PI + NS5A experience; 88–94% with NS5A experience only; 100% with PI experience only
sofosbuvir/velpatasvir/voxilaprevir (400 mg/100 mg/100 mg)	NDA submitted Dec 2016	Gilead	YES	POLARIS-1 ¹⁴ , -4 ¹⁵	Phase III multicenter randomized double-blind, placebo-controlled study in GT1-6 TE patients with/without previous NS5A inhibitor exposure, N=445	12 weeks	NO	NO	97% (241/248) SVR12 TE with NS5A inhibitor 99% (168/169) SVR12 TE without NS5A inhibitor; positioned as salvage treatment; mild GI upset reported with voxilaprevir
				POLARIS-2 ¹⁶	Phase III multicenter randomized, open label, active comparator trial, GT1-6 TN patients +/- cirrhosis, 8 weeks sof/vel/vox in vs 12 weeks sof/vel, stratified by GT, cirrhosis and TE, N=941	8 weeks	NO	NO	95% (476/501) SVR12 with 8 weeks sof/vel/vox 98% (432/440) SVR12 with 12 weeks sof/vel

TREATMENT	FDA STATUS	MANUFACTURER	PAN GENOTYPIC	STUDY NAME	STUDY DESIGN	TREATMENT DURATION	EVALUATED IN HIV COINFECTED	RIBAVIRIN	SVR AND AE OUTCOMES
				POLARIS-3 ¹⁷	Phase III multicenter randomized open label active comparator trial, GT3 +/- cirrhosis, 8 weeks sof/vel/vox vs 12 weeks sof/vel, stratified by TE, N=219	8 weeks	NO	NO	96% (106/110) SVR12 with 8 weeks sof/vel/vox 2 relapse, 1 withdrawal of consent, 1 non treatment related death 96% (105/109) SVR12 with 12 weeks sof/vel 1 treatment failure, 1 relapse, 1 discontinued due to AE, 1 lost to follow up
uprifosbuvir/ grazoprevir/ ruzasvir (225 mg/50 mg/30 mg)	Phase II/III	Merck (MK3)	GT1, 2, 3	C-SURGE ¹⁸	Multicenter open label randomized trial of GT1 patients who previously failed LDV/SOF or EBR/GRZ, stratified by GT1 a/b and cirrhosis, N=94	16/24 weeks	NO	YES with 16 weeks	GT1 TE 16 weeks + RBV 98% (43/44) SVR8 24 weeks 100% (30/30) SVR8; Neither cirrhosis, RBV, nor baseline NS3 or NS5A resistance affected SVRs.
				C-CREST B & C ¹⁹	Multicenter open label randomized trial, N=675; participants treatment-naïve to DAAs; GT3 pegIFN/RBV treatment-experienced patients included.	8/12/16 weeks	NO	YES in all arms	GT1 8 weeks 94% (83/88) SVR24, 12 weeks 94% (83/88) SVR24 GT2 8 weeks 86% (54/63) SVR24, 12 weeks 97% (60/62) SVR24, 16 weeks 100% (26/26) SVR24 GT3 8 weeks 93% (96/103) SVR24, 12 weeks 96% (153/159) SVR24, 16 weeks 96% (72/75) SVR24 GT4 8 weeks 100% (7/7) SVR12 GT6 12 weeks 100% (4/4) SVR12 1 discontinued due to AE, 1 reinfection GT1 8 weeks

TREATMENT	FDA STATUS	MANUFACTURER	PAN GENOTYPIC	STUDY NAME	STUDY DESIGN	TREATMENT DURATION	EVALUATED IN HIV COINFECTED	RIBAVIRIN	SVR AND AE OUTCOMES
AL-335 (NS5B nuc)/odasvir (NS5A) +/- simeprevir (PI) (800 mg/50 mg/75 mg)	Phase II	Janssen (JNJ-4178)	GT1, 3	OMEGA-1 NCT02765490 ²⁰	International Phase IIb multicenter, randomized, open-label study of GT1, 2, 4, 5 and 6 without cirrhosis, fully enrolled	6/8 weeks	NO	NO	GT1 TN* 6 or 8 weeks 100% SVR, GT3 TN 12 weeks 77% SVR
sofosbuvir/velpatasvir (400 mg/100 mg)	Approved	Gilead (Epclusa)	YES	ASTRAL-1 ²¹ , -2 ²² , -3 ^{23,24}	Phase 3, multicenter, randomized, double-blind, placebo-controlled study	12 weeks	YES	With decompensated cirrhosis	>90% SVR except GT3 TE with decompensated cirrhosis* 89% SVR
sofosbuvir/ledipasvir (400 mg/90 mg)	Approved	Gilead (Harvoni)	GT1, 4, 5 & 6			12 weeks, consider 8 weeks with low viral load	YES	GT1, GT4 TE with decompensated cirrhosis	Approved for use post-transplant with RBV; >90% SVR except GT1 with decompensated cirrhosis*
dasabuvir/paritaprevir/ritonavir/ombitasvir (600 mg/150 mg/100 mg/25 mg)	Approved new QD formulation	AbbVie (Viekira XR)	GT1, GT4 w/out cirrhosis			12 weeks, 24 weeks in GT1 with cirrhosis	GT1	GT1a, GT4	>90% SVR; Can cause resistance to HIV ARVs
grazoprevir/elbasvir (100 mg/50 mg)	Approved	Merck (Zepatier)	GT1, 4			12 weeks, 16 weeks TE	YES	With NS5A resistance or GT4 TE	>90% SVR except GT1 TE with protease inhibitor resistance
sofosbuvir/daclatasvir (400 mg/60 mg)	Approved components	Gilead (Sovaldi), BMS (Daklinza)	GT1, 3	REDEMPTION trials ²⁵ ; ALLY-1 , 2, 3, 3+ ^{26,27}	Phase 3 open label, non randomized, parallel assignment study; few GT4, GT5, or GT6 patients enrolled.	12 weeks	YES	GT1 decompensated cirrhosis or post transplant	GT1 96% SVR, GT2 100% SVR, GT3 87% SVR, GT4 91% SVR, GT5/6 100%
sofosbuvir/ledipasvir (400 mg/90 mg) for >12 yrs, >35kg	Approved supplemental application	Gilead (Harvoni)	GT1, 4, 5, 6	Gilead Long Term Follow-up Registry ²⁸	Observational prospective cohort study (5 years)	12 weeks	NO	NO	approved on previous data

TREATMENT	FDA STATUS	MANUFACTURER	PAN GENOTYPIC	STUDY NAME	STUDY DESIGN	TREATMENT DURATION	EVALUATED IN HIV COINFECTED	RIBAVIRIN	SVR AND AE OUTCOMES
sofosbuvir (400 mg) + ribavirin for >12 yrs, >35kg	Approved supplemental application	Gilead (Sovaldi)	GT2, 3	Gilead Long Term Follow-up Registry ²⁹	Observational prospective cohort study (5 years)	12 weeks, 24 weeks	NO	YES	GT2 100% SVR, GT3 97% SVR, No serious treatment related AE, most common AE were fatigue, headache, nausea
sofosbuvir/ledipasvir (200 mg/45 mg) +/- ribavirin for ages 6-11 yrs	Phase III	Gilead (Harvoni)	GT1, 3, 4	Gilead Long Term Follow-up Registry ³⁰	Observational prospective cohort study (5 years) for ages 6-11; international multi-site open label trial with children aged 3-6 ongoing	12 weeks, 24 weeks	NO	With cirrhosis	12 weeks 99% SVR, 24 weeks 100% SVR, 24 weeks + RBV 100% SVR All patients received 12 weeks except GT3 (n=2) and GT1 TE patient with cirrhosis (n=1); No treatment related AE or treatment discontinuations reported

AE: adverse events.

NDA: new drug application.

QD: once daily.

TE: treatment experienced.

TN: treatment naive.

*decompensated cirrhosis defined as Child-Pugh B/C

Treatment duration: how short can we go?

Shortening treatment duration has been of interest to patients and providers since the development of interferon-based treatments. Cost is usually understood as the unstated reason for seeking to go shorter. For example, cost savings may have motivated recent real-life studies of eight-week courses of ledipasvir/sofosbuvir at the Veterans Administration.³¹ However, drug prices are not based on the costs of pill production,³² so the clinical benefits of shorter treatment courses must be clear and significant. Policy makers and providers perceive that adherence to daily oral treatment over 12 weeks will be too challenging for patients who lack stable housing, or are actively using illicit substances. In practical terms, reducing treatment length from 12 to eight or six weeks still requires a return trip to the pharmacy, as DAAs are typically dispensed in 30-day supplies. Thus, the ability to reliably achieve SVR12 with 4 weeks/28 days would be a significant breakthrough for some vulnerable patients.

The current class of drugs have similar chemical kinetics, suggesting that a new class of compounds would be needed to achieve SVR12 with only four weeks of DAA treatment.³³ Viral load at four weeks of treatment is strongly correlated with SVR12 post-treatment.³⁴ According to some experts, one bottle—and one trip to the pharmacy—is likely the physiological limit to eliminate HCV.³⁵ Results for new compounds from Gilead and Merck demonstrate that reliably successful eight-week treatments are here, particularly for patients without cirrhosis. However, 6-week treatment courses have not yet demonstrated high SVR12 rates. Researchers should continue to explore shorter treatment courses with the goal to achieve SVR12 greater than 90% with four weeks of treatment.

Glecaprevir/Pibrentasvir

A new drug application for the fixed dose, once daily combination glecaprevir/pibrentasvir (G/P; Maviret) was submitted by AbbVie in December of 2016³⁶ with FDA approval anticipated in Quarter 3 2017. Registration trials in genotypes 1-6 demonstrated uniformly high 12-week sustained virologic response (SVR12) rates of 95% with eight weeks of treatment in treatment-naïve patients without cirrhosis.³⁷ Difficult-to-treat patients with genotype 3, with and without cirrhosis, and patients with chronic kidney disease had SVR12 rates of 93-100%.³⁸ Among patients with previous DAA failure due to baseline resistance associated substitutions (RASs) SVR12 was 94% with G/P.³⁹

AbbVie has lagged in the number of patients treated behind Gilead and Merck, as well as generic formulations based on Gilead and Bristol-Meyers Squibb (daclatasvir) developed compounds in high-income countries.⁴⁰ Pricing for G/P will ultimately determine treatment uptake for this promising new treatment.

Sofosbuvir/Velpatasvir/Voxilaprevir

While AbbVie was aiming at Gilead's dominant treatments, Gilead was targeting salvage treatment for genotype (GT) 1–4 patients who had previously failed a DAA- or interferon-based regimen. The addition of a new NS3/4A protease inhibitor to sofosbuvir/velpatasvir resulted in SVR12 in 98% these patients with eight or 12 weeks of treatment (POLARIS trials).⁴¹ However, this new triple therapy, to be branded as Vosevi, has not been adequately tested in patients with decompensated cirrhosis. Mild gastro-intestinal upset, including nausea and diarrhea, were reported, but were not severe enough to discontinue treatment.

April 2017 saw the FDA approval for the use of Gilead's Sovaldi and Harvoni in adolescents aged 12-17 years old, weighing more than 35 kilograms (77 pounds) without cirrhosis or with compensated cirrhosis.⁴² Sovaldi (sofosbuvir) in combination with weight-based ribavirin is indicated for adolescents with genotypes 2 and 3, also without cirrhosis or with compensated cirrhosis. Harvoni (sofosbuvir/ledipasvir) is indicated for adolescents with genotypes 1, 4, 5 and 6, providing effectively pangenotypic treatment for this population with Gilead's products. Clinical trials for children aged 3-12 years and weighing less than 35 kilograms are ongoing.⁴³

Uprifosbuvir/Grazoprevir/Ruzasvir

Phase II data on a novel triple combination consisting of NS5B polymerase inhibitor uprifosbuvir (formerly known as MK-3682), approved protease inhibitor grazoprevir (component in Zepatier) and novel NS5A inhibitor ruzasvir (formerly MK-8408) have been presented by Merck.⁴⁴ Also known as MK3, this once daily fixed-dose combination was studied against genotypes 1, 2 and 3 in treatment durations ranging from eight weeks to 24 weeks. GT1 patients achieved SVR12 at a rate of 95% (84/88, GT1a and GT1b) with 8 weeks and 98% (45/46) with 12 weeks of treatment, respectively. GT2 had limited

response to eight weeks of treatment, with 86% (54/63) achieving SVR12. GT2 patients receiving 12 weeks of MK3 had 97% (60/62) and 100% (26/26) SVR12. Finally, GT3 patients responded with 95% (98/103) SVR12 with eight weeks, 97% (155/159) with 12 weeks and 96% (72/75) with 16 weeks. In summary, treatment duration of at least 8 weeks was sufficient to achieve high SVR12 rates with the exception of patients with genotype 2, who required 12 weeks.⁴⁵ Significantly, neither the addition of ribavirin nor the presence of compensated cirrhosis impacted treatment outcomes.

AL-335/Odalasvir/Simeprevir

Development of a novel NS5B nucleoside analogue (AL-335) in combination with odalasvir (NS5A inhibitor), with and without simeprevir (protease inhibitor Olysio), continues as the result of a partnership between Achillion and Janssen. The triple combination is known as JNJ-4178, and preliminary Phase II results in treatment-naïve and treatment-experienced patients without cirrhosis have been presented.⁴⁶ Treatment-naïve patients with genotype 1 and without cirrhosis who were treated with the triple combo for six or eight weeks resulted in 100% SVR24 (20/20 in each arm). Of patients with genotype 3 who relapsed during eight weeks of treatment, 77% achieved SVR12 when extended to 12 weeks. However, eight weeks of treatment was insufficient for GT3 patients, with only 77% (10/13) achieving SVR12 even when extended to 12 weeks on the triple combo.⁴⁷ A Phase IIb study of efficacy in non-cirrhotic patients with genotypes 2, 4, 5, and 6 is ongoing.⁴⁸

Injectables

Data on a proof-of-concept injectable micro-RNA (miRNA) based treatment from Merck was expected at the 67th Meeting of the American Association for the Study of Liver Diseases (AASLD) in 2016; however, the poster was withdrawn prior to the conference.⁴⁹ The market viability of injectable treatments based on difficult-to-produce miRNA technology is questionable given the efficacy of current oral treatments, and the future development of this treatment route is unclear.

Generic DAAs

Real-world data on generic DAAs, most extensively sofosbuvir and daclatasvir in fixed-dose combination, have consistently demonstrated SVR12 rates comparable to those of drugs manufactured by originator companies (REDEMPTION trials).⁵⁰ Patients accessing generics manufactured in Bangladesh, China, and India achieved an average SVR12 rate across all genotypes. As with branded sofosbuvir/daclatasvir, GT3 continued to be difficult-to-treat, achieving an SVR12 rate of only 94%. National health ministries should implement generic-based treatment for everyone wherever voluntary licenses are registered. Unfortunately, registration with national regulatory bodies continues to be a major barrier to treatment uptake in low- and middle-income countries, with expanded registration being a top priority among global treatment activists. Real-time data on registration is available at mapCrowd.org, a collaboration between Médecins du Monde and Treatment Action Group.

Real World Data in People Who Use Drugs

Transmission of HCV among people who inject drugs continues to be the main driver of the global epidemic. Stigmatization, discrimination and myths that active drug users cannot adhere to daily treatment regimens have resulted in treatment restrictions and other policies that further marginalize those we need to engage the most. However, post-marketing studies of DAA treatment in active drug users and those in opioid substitution therapy (OST) demonstrate that HCV cure rates comparable to those in clinical trials can be achieved among people who inject drugs.

The SIMPLIFY trial, a Phase IV open-label multicenter international trial of sofosbuvir/velpatasvir in people with injection drug use in the prior six months and compensated liver disease, resulted in 94% of participants achieving SVR12 (96/99; four participants were lost to follow up).⁵¹ Participants were recruited from March through October 2016 with no relapse or reinfection observed to date.

The C-EDGE CO-STAR trial, a Phase III randomized double blind parallel group trial of grazoprevir/elbasvir in patients in OST for minimum of three months, consisted of two arms: 12 weeks of treatment versus placebo for 12 weeks followed by 12 weeks of treatment (starting at week 16).⁵² Both arms achieved high SVR12 rates: 96% (189/198) and 97% (85/88), respectively. Follow up continued to SVR24, with 96% (175/186) and 97% (82/85) of patients maintaining cure. The six reinfections which occurred are equivalent to 3.4 per 100 person years.

These data support treatment for everyone without restriction.

Finding people with chronic HCV infection: diagnostics for elimination

Globally, less than 5% of individuals chronically infected with viral hepatitis have been diagnosed, and estimates of the global burden of chronic HCV are 71–80 million individuals (POLARIS Observatory data).⁵³ Modeling studies indicate that 5–10% of the global infected population must be treated each year from 2018–2030 to achieve the targeted 90% reduction in viral hepatitis incidence and 65% reduction in associated mortality. To screen and diagnose the hundreds of millions of individuals at risk of infection, diagnostic technologies and algorithms will need to be rethought, streamlined, and implemented across a range of settings outside of tertiary hospital or even primary care community clinic sites. To meet this tremendous need, technologies will need to be affordable, provide results in a single visit, sufficiently inform regimen choice, and confirm cure.

As concisely described by John Dillon, MD, Professor of Hepatology and Gastroenterology, University of Dundee, the minimal inputs for confirmed cure of HCV are blood for an RNA confirmatory test, DAAs, and blood to confirm SVR12. Ideally, blood could be collected as a dried blood spot. Building clinic infrastructure and deploying new technologies appropriate to acquire the blood inputs are critical priorities for the next three to five years. It is particularly important to deploy low-cost solutions in resource-limited settings across high-, middle-, and low-income countries, specifically where people who inject drugs receive harm reduction, opioid substitution, and other services; in jails and prisons; to migrants regardless of legal status; and where pregnant women receive care. In high-income countries, including the U.S., emergency rooms have been shown the potential of capturing new infections, particularly among young people outside of the baby boomer birth cohort (1945–1965 in the U.S.),⁵⁴ but lack both the payer mechanisms and clinic flow to inform and link infected individuals to care in a timely manner. Rapid point-of-care RNA assays could fill critical gaps in screening programs and provide opportunities to effectively bring more into treatment.

The only point-of-care rapid diagnostic HCV antibody test available in the field and recognized as reliable by regulatory bodies is the Oraquick test from OraSure. Although not yet WHO prequalified, the assay is CE marked (Conformité Européenne; accepted as quality assured in the European Union) and provides results with both capillary blood and oral swabs. However, with pricing ranging from USD\$8 to over USD\$10, price remains a barrier to wide-scale deployment in limited resource settings. The work of Andrew Hill, University Liverpool, has shown that generic DAAs can be produced for less than USD\$200 per treatment course, including 50% mark up.⁵⁵ In countries with voluntary licensing, generic prices continue to fall, approaching Hill's model. Ironically in those circumstances, pre- and post-treatment diagnostics can cost USD\$500–600,⁵⁶ with little or no support for patients. As a result, out-of-pocket diagnostic costs are often a greater barrier to treatment access than the price of DAAs.

The Foundation for Innovative New Diagnostics (FIND), the leading non-profit organization advocating for appropriate diagnostics in low- and middle-income countries, has developed target product profiles (TPPs) for HCV diagnostics. The following table compares point-of-care tests currently in the field and in the pipeline to FIND's TPP (see Table 2).

Table 2. Target Product Profiles for HCV Diagnostics

Assay Name	Optimal spec	Minimal spec	Assay TPP Specification Result						
			Xpert HCV RNA	Truenat HCV	Architect core Ag	Realtime HCV	Alere q RNA	HCV Qual/Quant	HCV RNA POC
Developer/manufacturer			Cepheid	Molbio/bigTech	Abbott	Abbott	Alere/SD	Roche	Genedrive
Registrational status			Approved	Pipeline	Approved	Approved	Pipeline for HCV	Approved	Pipeline
Target users	Community workers	Health-care workers	Minimal	Optimal	Minimal	Minimal	Minimal	Minimal	Optimal?
Setting	Community centers	District hospitals (II)	POC, but somewhat centralized	Optimal	Minimal	Minimal	Optimal	Minimal	Both
Analytical sensitivity	200 IU/mL	1,000–3,000 IU/mL	Minimal	?	Minimal	Minimal	?	Optimal for quantitative	Yes
Diagnostic sensitivity	>99%	>98%	Minimal	?	Minimal	Minimal	?	Optimal	TBD
Polyvalency	Platform allows HCV, HBV, HIV tests	Platform allows HCV, HBV, HIV tests	Yes	HIV	HIV	HIV, HCV genotyping	HIV	HIV	TBD
Quantitation	Quantitative	Qualitative	Optimal	Optimal	Minimal	Optimal	Optimal	Both	Approximate quantitative results
Specimen type	Capillary blood	Venous blood/plasma	Both	Both	Both	Both	Both	Both	Both
Steps	<2	2	Cartridge based	?	Cartridge based	Cartridge based	Cartridge based	1, precision pipetting required	~4
Time to result	<15 min	<60 min	105 min	60 min	36 min	5+ hrs (batch processing)	?	5-8 hrs (batch processing)	<90 min
Instrument cost	<2,000 USD	<20,000 USD	17,000 USD	9,000 USD	?	207,000 USD	?	150,000 USD	?
Assay price	<5 USD	<15 USD	<20 USD	14 USD	25–50 USD	13–35 USD	15–25 USD?	Depends on country	?

POC: point-of-care.

Courtesy of FIND⁵⁷, MSF Access Campaign⁵⁸, Genedrive⁵⁹.

HCV TREATMENT RECOMMENDATIONS

Next steps: getting where we want to go

Elimination of viral hepatitis C as a public health concern is feasible. Although we currently lack reliable, affordable diagnostics and nonspecialist provider capacity, those can be developed with time and commitment. Curative oral therapies continue to improve, and, as disease progression and sobriety restrictions fall, scaled up treatment and competition will contribute to driving prices down for branded and generic drugs.

Decades of research into the virus has yielded a promising vaccine candidate (see Box: A vaccine for HCV?) and real-world data on treatment adherence and shortened treatment duration suggests that it is possible to further cut costs and improve the efficiency of public health strategies. Implementation science on how to intervene successfully to prevent reinfection and support the most vulnerable patients—active injection drug users, the homeless, and other marginalized communities—will be critical in this phase of the fight.

Concrete, concerted action is needed to move forward:

- National governments must develop HCV action plans in consultation with affected populations, especially people who use drugs, people co-infected with HIV, and women;
- National governments must use every available legal tool, including TRIPS flexibilities, compulsory licenses, and patent opposition, to secure affordable DAAs;
- Generic producers and diagnostics manufacturers must partner to develop bulk procurement proposals in low- and middle-income countries;
- Public and private payers must make multi-year commitments to fund HCV diagnosis and treatment;
- Diagnostic technologies and algorithms will need to be rethought, streamlined, and implemented across a range of settings outside of tertiary hospital or even primary care community clinic sites;
- More options for point-of-care RNA assays are needed to fill critical gaps in screening programs and facilitate putting more patients on treatment.
- Diagnostic technologies will need to be affordable for low- and middle-income countries and provide results in a single visit, sufficiently inform regimen choice, and confirm curative rates in patients;
- Sustainable funding for vaccine research to show efficacy in people at risk for HCV infection because they inject drugs; the ability to elicit immune response in individuals living with HIV who are not at high risk for HCV infection; and safety in combination with HIV vaccine administration in healthy volunteers;
- Researchers must pursue four-week treatment courses that match current SVR12 rates of 90% or greater across genotypes, levels of disease severity, and comorbidities and infections, including HIV/HCV co-infection.

Science has brought us to the brink of winning the biochemical battle with HCV. How far and how fast we move towards elimination will depend on evidence-based solutions to battles outside of the liver—the incoherence between intellectual property and the human right to health, the lack of global funding streams for viral hepatitis, the deadly war against drug users, and the need to galvanize global demand for treatment for all.

With thanks to Gregory Dore (Kirby Institute, University of New South Wales Sydney), David Bernstein (North Shore University Hospital and IJ Medical Center), and Bryn Gay (Treatment Action Group).

A vaccine for HCV?

The world's first recombinant vaccine was the hepatitis B vaccine, based on hepatitis B surface antigen, and a half dozen commercial vaccines exist for hepatitis A. However, a prophylactic HCV has eluded researchers. That may be about to change.

Although HIV is a more extreme example, HCV can also be considered a master virus, supremely adapted to stay one step ahead of the human immune system. Rapidly mutating and ten times more variable than HIV in its genotypic subtypes, HCV elicits a weak immune response,⁶⁰ resulting in poor viral control and chronic infection of hepatocytes (liver cells) in most. Approximately 25% of individuals exposed to HCV spontaneously clear the virus. People who inject illicit drugs and other high-risk groups can be repeatedly exposed to HCV. Some individuals in high-risk groups infected are repeatedly able to clear the virus again and again without treatment and exhibit a broadening of their adaptive antibody-mediated immune response with repeated exposure to HCV.

Evidence from people who control HCV infection and primate studies suggests a potential role for broadly neutralizing antibodies (bNAbs) in effective vaccine design for HCV. bNAbs for both HIV and HCV have been identified, and how to induce bNAbs is being studied for vaccine development. However, the precise interaction of antibody and T-cell-mediated responses in protecting against infection are unknown at this time. bNAbs targeting HCV envelope proteins have been tested in healthy people.⁶¹

Further back in the pipeline, the only vaccine ever tested in high-risk individuals is an HCV prophylactic vaccine (Ad Ch3 NS/MVA NS) originated by Okairos and that is now being developed in collaboration with GlaxoSmithKline. Results are pending from Phase II trials in three groups: for efficacy in people at risk for HCV infection because they inject drugs (NCT01296451); for ability to elicit immune response in individuals living with HIV (NCT02568332) who are not at high risk for HCV infection; and for safety in combination with HIV vaccine administration in healthy volunteers (NCT02362217). These results will determine whether this candidate vaccine is effective on its own or needs to be combined or enhanced with vaccines that generate bNAbs against envelope proteins.

The high cost of curative treatments will continue to limit treatment access in the near term, and cost-driven concerns about reinfection, particularly among people who inject drugs and men who have sex with men, present considerable challenges to advocates for universal access and treatment as prevention. Primary prevention through an affordable, effective vaccine could be our most powerful tool for defeating the virus. Data generated in this upcoming year will tell us if we're one step closer to adding a preventative vaccine to our HCV toolkit.

With thanks to Andrea Cox (Johns Hopkins University).

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