

# 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.”<sup>1</sup>

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."<sup>2</sup> 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.<sup>3</sup> 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 18–30<sup>4</sup>. 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/mm<sup>3</sup>), 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/rifapentine 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 rifapentine 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  $\leq 5$  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 2004<sup>5</sup> 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  $\leq 5$  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  $\leq 5$  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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