2014

HIV·HCV·TB

PIPELINE REPORT

drugs, diagnostics, vaccines, preventive technologies, research toward a cure, and immune-based and gene therapies in development

ABOUT HIV i-BASE

HIV i-Base is a London-based HIV treatment activist organization. HIV i-Base works in the United Kingdom and internationally to ensure that people living with HIV are actively engaged in their own treatment and medical care and are included in policy discussions about HIV treatment recommendations and access.

www.i-base.info

ABOUT TAG

Treatment Action Group (TAG) is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS. TAG works to ensure that all people with HIV receive lifesaving treatment, care, and information.

www.treatmentactiongroup.org

2014 PIPELINE REPORT

HIV, HEPATITIS C VIRUS (HCV), AND TUBERCULOSIS (TB) DRUGS, DIAGNOSTICS, VACCINES, PREVENTIVE TECHNOLOGIES, RESEARCH TOWARD A CURE, AND IMMUNE-BASED AND GENE THERAPIES IN DEVELOPMENT

By Polly Clayden, Simon Collins, Colleen Daniels, Mike Frick, Mark Harrington, Tim Horn, Richard Jefferys, Karyn Kaplan, Erica Lessem, Lindsay McKenna, and Tracy Swan

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This report is dedicated to Marvin Oscar Shulman

May 17, 1932–January 15, 2014

Photo: Thomas M. Keane

Marvin pictured, seated, second from left.

A fierce AIDS warrior, principled leader, and beloved friend, Marvin Shulman was an activist's activist. He dedicated himself completely to the fight against AIDS, first as a member of ACT UP/NY, where he served as treasurer and as a member of the coordinating committee, and later as the first treasurer of TAG. His years of work for both organizations, without ego or fanfare, made possible historic actions leading to changes that continue to save lives today. Without Marvin, there would have been no "Storm the NIH," no "Seize Control of the FDA," no giant condom on Jesse Helm's house…and none of the lifesaving drugs that have changed the landscape of the epidemic in the ensuing years.

Marvin was fiercely loyal to his friends and a man of legendary generosity in his personal life as well as in his activism. He was loving, blunt, savagely funny, and deeply courageous. He saved many situations with his ability to call bulls**t for the greater good. He was the best kind of activist because he cared—first, last, and always—about the work. Marvin wanted the AIDS crisis to end. He wanted the ignorance and injustice underlying the crisis to end. He didn't care who took the credit. And so he just did great things. And so can we all. And so must we all.

Marvin's life and his approach to work were and are a model for other activists, including his colleagues at TAG. Marvin leaves a tremendous legacy. We thank him, and we miss him greatly.

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Introduction and Executive Summary

By Polly Clayden and Mark Harrington

INTRODUCTION

Last year we wrote:

> [Getting] the best drugs to the most people as quickly as possible… requires that the compounds and combination products be:
>
> - Discovered and developed in a high-quality research program;
> - Approved by a national or multinational regulatory authority;
> - Recommended by national or multinational guidelines groups;
> - Available in formulations suitable for use in the proposed population;
> - Affordable to public-sector programs and through private insurance; and
> - Accessible to patients through local health systems.[1]

One year later, the research, regulatory, and access landscape for people with HIV, hepatitis C virus (HCV), or tuberculosis (TB) remains one of stark contrasts among the three diseases, and between people with access to affordable health care—whether they live in rich or developing countries—and those without. The research pipelines described in this year's report show substantial progress in new treatments and preventive interventions against HIV. Revolutionary changes are afoot in the treatment of HCV, which allow—for the first time—the prospect of universal cure and disease eradication—if only cost and access barriers can be overcome. But, in the case of TB, few new diagnostics, even fewer new drugs, poor access, and declining political will create a pipeline woefully underpopulated, slow-moving, and resource-deprived.

Here we highlight the first of the essential requirements outlined above, the requirement that new interventions be "discovered and developed in a high-quality research program."

A quick scan of worldwide trials data maintained by the U.S. National Institutes of Health (NIH) at clinicaltrials.gov reveals many disparities between research

and development programs for treatments of HIV, HCV, and TB. Newly approved drugs for the three diseases—dolutegravir (for HIV), sofosbuvir (for HCV), and delamanid (for TB)—have respectively 61, 67, and 6 clinical trials registered to investigate their use.

The 61 studies of dolutegravir cover: treatment-naive and -experienced patients (including those with resistance to other integrase inhibitors); comparisons, use, and interactions with the most commonly used antiretrovirals (and a couple of investigative ones); interactions with potential concomitant medicines that include studies with methadone, rifampin, and oral contraceptives; an investigation into how the drug performs in women; use in people with hepatic and renal impairment; pregnancy pharmacokinetics; a pediatric investigation program down to four weeks of age conducted by the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) network; and pharmacokinetics of the pediatric granule formulation. This list is not exhaustive. Despite the limitations of the registrational studies, with the usual underrepresentation of women, people with coinfections, etc., by the time all the studies are completed as well as several in the planning stage that are not yet registered, we will have a pretty good idea how the drug will perform across a diverse population (Polly Clayden looks at some of these that will help with our understanding of how the drug will perform in low- and middle-income settings in her chapter on antiretroviral dose optimization).

Registered sofosbuvir trials are also abundant and include patients with varying treatment experience, liver disease stage, and genotypes. But a closer look reveals limited investigations into regimens with other sponsors' drugs, nothing in pregnant women or children, few in HIV coinfection (and nothing in other comorbidities), and just one (not yet recruiting) in people who inject drugs. As yet there are very few trials registered by independent investigators (and notably these are usually HIV networks or centers). Tracy Swan details the shortcomings of HCV trial enrollment in her chapter.

The tally for delamanid trials is a paltry 10 percent of those for the other two recently approved agents. It is at least encouraging that two of these trials will provide information for use in children with multidrug-resistant TB (MDR-TB). However, approval of delamanid by the European Medicines Agency (EMA) was delayed due to confusingly presented results from the phase II program, which included a two-month study, a six-month study, and an open-label study. The sponsor claimed a mortality benefit for those treated for six rather than two

months, but neglected to mention that those not surviving or lost to follow-up between the two- and six-month endpoints were excluded from this survival analysis—producing a biased readout.[2] The sponsor's inexperience and the lack of validated treatment options in multidrug-resistant (MDR) TB cannot excuse the poor design and presentation of this phase II program. A phase III study, now fully enrolled, may shed more light on delamanid's use.

The other recently approved drug to treat MDR-TB, Janssen's bedaquiline, had stronger evidence of efficacy at two and six months, but in the "placebo-controlled C208 trial, however, an imbalance of all-cause mortality has been observed with more deaths reported in the bedaquiline group (10/79 versus 2/81 in the placebo group in C208 Stage 2). Causes of death were varied and all but one occurred after the treatment period with bedaquiline."[3]
The U.S. Food and Drug Administration (FDA) carried out a thorough review of each death in the phase II program and could not rule out an association with bedaquiline,[4] resulting in a black box warning on the label and a requirement that Janssen open a U.S. patient registry to monitor safety post-marketing.[5]
The excess mortality seen in phase II should have induced Janssen to accelerate its confirmatory phase III study, which has not yet even begun. Rather than mounting its own phase III study, Janssen is trying to piggyback onto an ongoing USAID/British Medical Research Council (BMRC) study of a modified so-called Bangladesh regimen compared with standard of care (SOC). Janssen does not want to compare SOC with or without bedaquiline—which would be the clearest and simplest confirmatory study—but rather wants to compare a bedaquiline-containing modified Bangladesh regimen to one without.
This way lies madness. The low standards for TB clinical trials leading to these accelerated (FDA) and conditional (EMA) approvals must be improved in future licensing efforts.

Throughout this report, the authors will be pointing out the need for better-quality research in order to more clearly define how to use new interventions. We will be writing in more detail on the challenges of improving research quality over the coming year.

EXECUTIVE SUMMARY

HIV

The 2014 adult antiretroviral pipeline is robust. As Tim Horn and Simon Collins note, antiretrovirals in late-stage development include a handful of new fixed-dose combinations (FDCs) and coformulations including dolutegravir/abacavir/lamivudine (DTG/ABC/3TC), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (EVG/COBI/FTC/TAF), darunavir (DRV)/cobicistat/FTC/TAF, TAF/3TC, cenicriviroc/3TC, dolutegravir/rilpivirine, and a once-daily regimen of raltegravir (RAL). Five compounds are in phase II including doravirine, BMS-663068, and the long-acting injectables S/GSK1265744 LAP, rilpivirine-LA, and PRO 140. As noted in previous pipelines, another six compounds, some of which hold serious potential for people living with HIV that is cross-class resistant to current antiretrovirals, continue to languish in earlier phases with no relevant development advances since 2013.[6]

The past year saw FDA and EMA registration of the new, low-molecular weight, once-daily integrase inhibitor DTG (Tivicay, ViiV Healthcare), one of the most remarkable new antiretroviral drugs in memory. The sponsor's development program is one of the most comprehensive ever. DTG as an anchor drug proved robustly noninferior, possibly superior, to regimens containing efavirenz (EFV), atazanavir/ritonavir (ATV/r), DRV/r, or RAL. This led the U.S. Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents to recommend use of DTG as a preferred first-line antiretroviral with a background of either tenofovir disoproxil fumarate (TDF)/FTC or—in those without HLA-B*5701—ABC/3TC. However, if ABC/3TC is used with efavirenz or with ATV/r it is recommended only when baseline viral load is below 100,000 copies/mL.[7]

The sponsor's new drug application package included adolescents 12 years or older, enabling DTG's approval for that population alongside adults, and a pediatric development program, including a granule formulation for infants and young children, is well under way. Although the drug is unjustifiably expensive in the United States at $16,926/year at 50 mg/day, $33,852/year for those with prior integrase inhibitor resistant or when taken with EFV, fosamprenavir/ritonavir, or tipranavir/ritonavir,[8] the sponsor has entered into a broad licensing agreement with the Medicines Patent Pool (MPP), allowing generic drug manufacturers to make lower-cost DTG in countries where over 90 percent of adults and children with HIV live.[9] Thus, though the price in rich countries

remains an issue, the sponsor has set a new standard for phase III development in adults, rapid pediatric advancement, and global licensing to allow low-cost generics access. Since FDA approval, the drug has been registered in nine other countries: Canada, Chile, Switzerland, Australia, Japan, Brazil, Uruguay, Argentina, Israel, as well as in the European Union.

Activists, researchers, and providers are interested in the potential of a once-daily combination pill containing DTG, generic 3TC, and TDF, which will become generic in the coming years. This FDC could provide potency, durability, low cost, and increased tolerability if licensing and intellectual property considerations don't get in the way—and could warrant use of integrase inhibitor–based first-line therapy globally, especially if data continue to support a low risk of resistance. This would displace EFV-based regimens and their neurotoxicity, and allow protease inhibitor–based therapies to remain in second-line recommended regimens. When TAF is approved, an even-lower-molecular-weight DTG/3TC/TAF pill would be possible.

Polly Clayden reports encouraging progress on treatment optimization,[10] noting that ENCORE1 showed 400 mg/day of EFV to be noninferior to the currently recommended 600 mg dose; potentially, this could mean a lower cost first line with slightly fewer adverse effects. Further research is needed to bring us closer to the optimal safe, effective, tolerable, durable, universal, and affordable ideal antiretroviral regimen for all.

To recommend DTG-based regimens as preferred global first line we need a bit more information. DTG has been studied in several treatment scenarios and regimens, but so far not in key populations who would be treated with DTG in low- and middle-income countries, such as pregnant women and people with TB coinfection. The registrational trials for DTG were about 80% men, had few non-white participants, and hardly anyone coinfected with other diseases (a few hepatitis B and none with TB or malaria). People with baseline NRTI resistance were excluded.

Clayden describes several planned investigator- and sponsor-led trials that should generate data to fill in some of the gaps. This research needs to be prioritized, funded, and conducted in a timely and coordinated fashion so that the time lag between recommendations and adoption in treatment programs does not take over half a decade between rich and poor countries.

Besides the 12-and-up approval of DTG noted above, Clayden shows how two additional new pediatric formulations have recently been approved, for the youngest age group with the least options: RAL for infants over four weeks of age and ATV for those at least three months old. Global pediatric HIV treatment remains far from ideal, however, with recently updated World Health Organization (WHO) recommendations "not very simple and somewhat aspirational," with several missing suitable, child adapted formulations of currently approved antiretrovirals including AZT/3TC/lopinavir (LPV)/r, ABC/3TC/LPV/r, ABC/3TC/EFV, DRV/r, ritonavir granules. As with adults, DTG (in kids below 12), cobicistat, and TAF might offer improvement on current options. The UNITAID, Drugs for Neglected Diseases Initiative (DNDi), and the Medicines Patent Pool–cosponsored Paediatric HIV Treatment Initiative provide one granule of hope that these needed new pediatric drugs and formulations will be developed and brought to market more quickly without intellectual property barriers.[11]

Tim Horn and Richard Jefferys present a synoptic overview of recent developments in HIV preventive technologies, including antiretroviral therapy (ART) and vaccine development.[12] Significant research, growing indications of effectiveness, considerable excitement and controversy accompany the newer field of preventive ART, with at least 10 agents being studied as oral or parenteral preexposure prophylaxis (PrEP), vaginal microbicides, tablets, or gels as single drugs (dapivirine, GSK1265744, ibalizumab, maraviroc, rilpivirine-LA, TDF) or in combination (TDF/FTC, already FDA-approved for this use; maraviroc/TDF, maraviroc/dapivirine).

Despite FDA approval of TDF/FTC in mid-2012, uptake has been slow, with fewer than 10,000 people in the U.S. being prescribed PrEP[13] while, over the same period, over 100,000 Americans became infected with HIV. In mid-May 2014, the CDC issued the first comprehensive U.S. PrEP guidelines, which suggest that PrEP may be appropriate for as many as 500,000 Americans.[14] Complementing this, and helping to provide guidance on who would benefit most from PrEP, Susan Buchbinder of the University of California, San Francisco, and colleagues, published an analysis of the iPrEx PrEP study in gay men and transgender women that assessed which baseline characteristics were most associated with HIV acquisition and with PrEP efficacy. Using these data they determined the population attributable fraction (PAF) of new infections and the number needed to treat based on baseline risk factors. A history of receptive anal intercourse without a condom in the three months before enrollment had

the highest PAF (64% of new infections). Individuals most likely to benefit from PrEP in iPrEx included these, as well as those with a history of recent sexually transmitted infection (STI), syphilis, or cocaine use.[15] Much work remains to be done to scale up use of effective preventive approaches including PrEP.

Horn and Jefferys note that an effective preventive HIV vaccine "remains frustratingly elusive" and show how ill-prepared the HIV vaccine field was to respond to success, citing the RV144 trial in Thailand and the underwhelming advancement of its findings, largely due to the need to produce a new envelope protein boost to replace the discontinued AIDSVAX.

They suggest that the greatest hope might lie in pursuing development of antigens based on the accumulating number of broadly neutralizing antibodies (bNAbs) that have been discovered, and recent advances in understanding both how these bNAbs are generated by the human immune system and how they interact with the HIV envelope to accomplish neutralization. They write: "A vaccine capable of inducing bNAbs remains the holy grail for the HIV vaccine field, and these developments suggest that it is possible."[16]

Thirty-eight preventive vaccination approaches are in clinical trials, and Horn and Jefferys say there are reasons to be optimistic about long-term prospects, but a licensed product is not on the immediate horizon.

Jefferys provides a clear, concise overview of the growing activity in research toward an HIV-1 cure and sometimes-related immune-based therapies.[17] Research toward the goal of curing HIV infection has rapidly assumed a central role within the overall scientific portfolio, but funding has not swelled at the same pace, although there have been signs of change over the past year. The number of clinical trials under way has increased substantially since 2013, as has the diversity of approaches being evaluated.

Efforts are under way to replicate the apparent cures seen in Timothy Ray Brown after his CCR5-Δ32 heterozygous stem cell transplant, and in the so-called Mississippi baby, now a child. One early transplant recipient has died, while two others rebounded virologically 12 and 32 weeks after stopping ART; both had received wild-type rather than CCR5-Δ32-mutated transplants. IMPAACT network study P1115, funded by the NIH, will attempt to treat immediately "babies infected with HIV because their mothers failed to receive appropriate prevention of mother-to-child transmission (PMTCT). While the possibility of sparing these newborns a lifelong burden of ART needs to be pursued," notes

Jefferys, "the goal of ensuring that no HIV-positive mother lacks access to PMTCT remains paramount."[18]

Jefferys notes updates on Sangamo BioSciences' SB-728-T autologous ex vivo disrupted CCR5 CD4 cell reinfusion therapy studies of cyclophosphamide to deplete CD4 cells, allowing greater growth space for reinfused gene-modified cells, latency-reversing agents, therapies targeting PD-1, exciting basic science research on broadly neutralizing HIV antibodies, therapeutic HIV vaccines, and immune-based therapies including the ill-starred interleukin-7 (IL-7), gut-targeted approaches to reduce immune activation, and a panoply of anti-inflammatories.

"The development of widely accessible interventions capable of curing the majority of HIV-positive people remains a stern challenge with no solution imminent," he writes. And he stresses the continued need for advocacy to ensure that this work continues, funding support grows, and the understanding of the science among the HIV/AIDS community and broader public is enhanced.

The immune-based therapy field, he concludes, in contrast, remains fallow, with meager commercial interest. A broader dialogue among activists, scientists, funders, pharmaceutical companies, and other interested parties might be needed in order to assess whether the problems in this area can be solved—notably, the incomplete immune reconstitution and extra morbidity seen among immunologic nonresponders and excess morbidity associated with residual immune activation.[19]

Hepatitis C Virus (HCV)

Tracy Swan brilliantly summarizes the exploding universe of new HCV treatment and cure regimens, a boon for the 185 million people who have been infected with hepatitis C.[20] In April 2014, the WHO issued its *Guidelines for the Screening, Care and Treatment of Persons with Hepatitis C Infection*.[21] While the *Guidelines* support the use of these new regimens in low- and middle-income countries (LMICs), drug pricing has once again become the major barrier to access and the hope of global eradication of HCV.

> A hefty pipeline will increase HCV treatment options, especially for people with genotype 1, by mid-to-late 2014. Cure rates

> above 95 percent—after only 12 weeks of treatment—have become commonplace in HCV clinical trials. DAAs [direct-acting antivirals] have been miraculous for people with cirrhosis, HIV/HCV coinfection, and before and after liver transplantation.
>
> But the outrage about sky-high DAA prices is quickly overtaking excitement about these wonder drugs. Advocates and clinicians are forced to fight for access to outrageously expensive drugs for people who cannot wait for affordable options—or watch people die from a curable infection.
>
> Gilead's nucleotide polymerase inhibitor, sofosbuvir—the backbone of most DAA regimens—is US$1,000 per tablet. Such a price limits access to this lifesaving drug, even in high-income countries...
>
> Global eradication of HCV is possible, if pharmaceutical companies will allow generic DAA production in LMICs....DAAs can be produced inexpensively, according to an analysis from the University of Liverpool (using molecular weight, chemical structure, complexity, dose, and cost of comparable HIV antiretroviral agents). The actual production cost for 12 weeks of a single DAA ranges from US$10 to US$270, assuming an annual volume of 1–5 million treatment courses.[22,23]

Clearing the way through a daunting forest of data, Swan identifies the key elements of an ideal HCV curative regimen—affordable, safe, highly effective against all HCV genotypes, tolerable, simple to administer and undergo, with limited drug-drug interactions—and matches these characteristics with nine of the most advanced regimens studied to date.[24] Swan points out the lack of data on these regimens in people who use and inject drugs and in children; in addition, sponsors have failed to provide disaggregated data by gender in many studies.

Swan observes that HCV research has been undermined by commercial competition. Gilead has refused to continue promising clinical collaborations with Janssen and BMS, which has delayed or complicated access to promising DAA combinations. In phase II trials, simeprevir/sofosbuvir cured more than 90% of participants after 12 weeks of treatment—even prior null responders

with compensated cirrhosis. Although sofosbuvir (Sovaldi) and simeprevir (Olysio) are licensed, this combination remains off-label; Janssen is supporting phase III trials. In a phase II trial, the combination of daclatasvir and sofosbuvir cured 100% of people with HCV genotype 1 (regardless of treatment experience), 92% of people with genotype 2, and 89% of people with genotype 3.[25] BMS is supporting phase III trials of this combination in pre- and-post transplantation, HIV/HCV coinfection, and genotype 3. Approval of daclatasvir in the United States and the European Union is expected later this year. Gilead is developing its own daclatasvir analogues, ledipasvir and GS-5816, which will be co-formulated with sofosbuvir in FDCs, whose price one can only shudder to imagine.

The DAA era has been good news for people coinfected with HIV. They have experienced SVR rates similar to the monoinfected when an HCV protease inhibitor was added to pegylated interferon and ribavirin. Now, several interferon-free regimens have demonstrated proof of concept in HIV/HCV coinfection, with SVR rates equivalent to those in HCV monoinfection. Drug interactions between HCV and HIV regimens remain a concern, since they may limit antiretroviral treatment options during HCV treatment.

Swan criticizes the underenrollment of African Americans in U.S.-based HCV trials (below 20% in all but one industry-sponsored study), as well as people of other races and ethnicities. Gender differences are not broken out by race/ethnicity in many studies, limiting our understanding of possible differences in safety, toxicity, or efficacy.

Research and treatment access for people who inject drugs—who make up 80 percent of new HCV infections in developed countries and 10–15 million of the world's 185 million people with HCV—remain abysmal.

Pregnant and nursing women are excluded from HCV clinical trials because ribavirin is highly teratogenic. At least 60,000 new infant infections occur each year; the advent of ribavirin-free regimens facilitates much-needed research to interrupt vertical HCV transmission. A search on clinicaltrials.gov reveals just nine open intervention studies for children with HCV, most of them with standard therapy with or without already-approved and quite toxic HCV protease inhibitors.

As Swan says, "[t]he hard work—transforming the HCV treatment cascade from scarcely a dribble into a waterfall—is just beginning." Now that HCV treatment

has become simple, safe, and highly effective, governments "must not continue to ignore HCV; it is time for national plans to address the epidemic. People with HCV and their allies, people who inject drugs, epidemiologists, medical providers, researchers," policy makers, donors, and industry need to work together.

Activists have launched an ambitious global campaign to achieve universal access to HCV prevention, diagnostics, care, and treatment, which Karyn Kaplan and Tracy Swan summarize in their global brief.[26] They have collaborated with allies around the world on the "Missing" campaign—targeting WHO Director–General Margaret Chan and highlighting the WHO's tardy and underresourced response to HCV; the first HCV World Community Advisory Board meeting in Bangkok, Thailand; and the first-ever demonstration at the European Association for the Study of the Liver meeting, protesting the price of sofosbuvir, a DAA that costs less than US$136 to manufacture for a 12-week treatment course, yet costs US$1,000 a pill.

These are the opening moves in a long and hard-fought struggle for global, affordable HCV DAAs, with the potential to save hundreds of millions of lives.

Tuberculosis (TB)

TB Diagnostics

Tuberculosis research and development (R&D) continues to present a disappointing landscape compared with the healthy diversity of HIV R&D and the explosive advances in HCV treatment. Where HIV research combines substantial long-term public-sector investment with diverse pharmaceutical involvement, and HCV research is primarily driven by profit-seeking drug companies with a dearth of public-sector investment, TB research suffers from scant and falling public-sector investment and industry fleeing for the exits. The view is not pretty.

TB diagnostics research has not advanced much in the past year, with the exception of a vigorous ongoing series of implementation science studies connected with the rollout of the GeneXpert MTB/RIF DNA polymerase chain reaction (PCR) system for detection of *Mycobacterium tuberculosis* and rifampin resistance, and—to a lesser extent—advances in our understanding of the usefulness of the Alere Determine LAM urine dipstick for diagnosis of TB in

people with advanced immunosuppression (including HIV-positive people with CD4 counts below 100/mm^3 and children). A hoped-for wave of "fast follower," putatively cheaper, and possibly portable molecular tests has failed to materialize, and the ideal instrument-free, cheap, and accurate point-of-care TB diagnostic test remains as elusive as ever. Seven molecular tests advanced in the past year, alongside two nonmolecular technologies (including LAM) and a single culture-based technology. Anemic investment—just US$43 million was spent on TB diagnostics R&D in 2012, versus the Global Plan to Stop TB's target of US$340 million per year—has brought research in this area to a virtual standstill—a fragmented landscape with promising technologies stuck in early development with little funding and no cohesive strategy to bring them forward.[27]

TB Treatment

The last eighteen months have seen the first approvals—accelerated approval by the FDA in December 2012 of Janssen's bedaquiline (Sirturo)[28] and conditional approval by the EMA in November 2013 (reversing its previous rejection) of Otsuka's delamanid (Deltyba)[29]—of new anti-TB drugs from new therapeutic classes in forty years. Nonetheless, as Erica Lessem points out in her 2014 TB treatment pipeline review, "with limited access to these drugs, and with no data on how they can be used to shorten or otherwise optimize MDR-TB treatment regimens, this is more an incremental step than a leap forward." She describes the slow progress toward identifying shorter and better regimens for treating drug-sensitive TB, noting that "there are no validated options for treating TB infection in contacts of people with MDR-TB."

The scant TB drug pipeline features only six compounds from four different classes; the handful of novel drugs in phase II studies is slowly creeping forward, followed by a gaping hole of drugs in phase I studies.

Investments in TB drug research are paltry; several companies have departed from TB drug R&D in the past year; and pharmaceutical investments in TB R&D—which fell by 22 percent in 2012—are likely to drop further.

Because the new MDR-TB drugs have been studied as add-ons to existing, expensive, often difficult to obtain MDR-TB treatment combinations, they are likely to add cost to underfunded TB programs until phase III/IV studies can sort out whether these agents allow shorter treatment duration or fewer coadministered drugs. Unfortunately, however, Janssen has yet to begin its

phase III study of bedaquiline, while current published data on delamanid—as the EMA noted tartly and deservedly in its November 2013 conditional recommendation—are limited to two months of a rigorous randomized comparison, with open-label follow-up on a subset of the original study population out to six months. Otsuka's phase III study is fully enrolled and first results are expected later this year. The EMA requires a pediatric investigational plan, so Otsuka has a pediatric study under way, while Janssen has just pulled out of a planned collaboration with IMPAACT.[30] Access to either new drug remains limited, with bedaquiline approved in just a handful of countries, while a compassionate use program continues. Otsuka has refused until quite recently to open compassionate use, which remains unduly restrictive. A preliminary analysis conducted for the WHO, however, indicates that adding bedaquiline to MDR-TB treatment is likely to be cost-effective, and potentially even cost-saving, at a price of US$900 for Global Fund–eligible countries and US$3,000 for other countries[31] (the price in the United States is $30,000 for six months).

TB research has experienced a depressing series of market exits by big pharma in the past two years, including that of Pfizer, who licensed the oxazolidinone sutezolid to Sequella, a private Maryland-based company with no publicly available annual reports or visible capital, followed by AstraZeneca, which states that it is committed to developing its compound from the same class, AZD5847, through phase II and no further.

Due to the pharmaceutical exodus, the NIH and the Global Alliance for TB Drug Development are now supporting most current activity in TB treatment research. The NIH, through the National Institute of Allergy and Infectious Diseases (NIAID), supports a comprehensive TB treatment research agenda including adults and children, drug-sensitive and drug-resistant TB, active and latent infection, as well as TB/HIV and drug-drug interaction (DDI) and PK studies important to advancing new drugs and regimens, such as the long-delayed bedaquiline-delamanid DDI/PK study now in development.

The TB Alliance has conducted some of the most important and innovative TB regimen research in the past years, including combinations such as PA-824 (a drug in the same class as delamanid), moxifloxacin (an approved fluoroquinolone), and pyrazinamide, which is moving into phase III, as well as an earlier phase bedaquiline/PA-824/pyrazinamide combination, which is moving into phase IIb. Results from REMox, a potentially treatment-shortening study including moxifloxacin in first-line therapy, are expected imminently. The Alliance plans to begin enrolling in NIX-TB, an open-label study of a new

combination for extensively drug-resistant TB, later in 2014. Thanks to support from UNITAID, the Alliance has begun efforts in pediatric TB drug development (see below).

The dearth of new anti-TB agents has led to a fairly broad re-examination of existing anti-TB agents including the rifamycins—rifampin, rifabutin, and rifapentine—for treatment of both active and latent disease, as well as formerly fifth-line drugs such as clofazimine and linezolid, which are now being evaluated in various combinations, mostly in drug-resistant disease. A handful of studies are evaluating shorter-course treatment for latent TB infection, including a proposed ACTG/IMPAACT adult/pediatric collaboration of preventive therapy for household contacts of people with MDR-TB, a group for whom no effective preventive therapy exists.

Lessem's conclusions are sobering and her recommendations urgent: TB treatment research needs greater investment by industry and the public sector. Drug companies, nonprofit sponsors, and publicly funded clinical trial groups must collaborate more closely. Study populations must include all those affected by TB including those with drug-resistant, TB/HIV-associated, and pediatric disease. Sponsors should expand community involvement. Regulators must assure that postmarketing requirements are enforced. Sponsors must work with global and national authorities to streamline and accelerate rollout of pre- and postapproval access to new treatments and regimens. New drugs and regimens must be affordable to public-sector programs everywhere.

One area of (relative) progress is the renewed—or more accurately, unprecedented—effort now under way in pediatric TB treatment research, as Lindsay McKenna demonstrates; the need is great, as many TB drugs were developed over a half-century ago and still lack evidence-based doses in children. The WHO only released evidence-based pediatric dosing guidelines for first-line drugs in 2010. Four years later, we are still waiting for appropriately dosed child-friendly FDCs. The current treatment of MDR-TB in children is very much a guessing game, and treatment practice is guided by findings extrapolated from adult data.

As mentioned above, Otsuka has initiated pediatric studies of delamanid, and is enrolling the second age-banded cohort, while Janssen has yet to start pediatric studies of bedaquiline and, as mentioned above, has just pulled out of a planned collaboration with IMPAACT.

McKenna recommends that, whenever possible, studies in children be initiated earlier and adolescents over 10 years old be included in phase III trials. For studies in children younger than 10 years old, cohorts should be recruited in parallel, as sequential enrollment does not necessarily offer any additional protection for the younger age groups, whose physiology differs from that of older children.

A pediatric TB treatment research agenda that looks at ongoing and planned studies in adults, and identifies missing data in children and trials where adolescents can be included, is urgently needed, as are substantially increased funding and a push from regulatory authorities.

TB Vaccines

The failure of the candidate TB vaccine MVA85A in a phase IIb study published in spring 2013 stimulated researchers in the field to renew their exploration of fundamental scientific questions regarding the relationship between infection with *Mycobacterium tuberculosis* and the susceptible and infected human host. This "back to basics" approach is explored by Mike Frick in his 2014 TB vaccines pipeline update. Research is needed to better understand the interaction between the human immune system and TB—in those who are susceptible as well as those infected. The predictive value of animal models used in preclinical development needs to be explored. Clinical trialists are developing innovative designs with earlier endpoints, which in turn depend on better surrogate markers of protection. As Frick notes, "[f]indings from basic research have cast doubt on the core assumptions that steered TB vaccine R&D from its revitalization in 2000, when the pipeline sat empty, to the present day, when the pipeline now has 16 candidates or vaccine combinations under active clinical development." (see "The Tuberculosis Vaccines Pipeline," table 1, p. 234.)[32]

Key recommendations include prioritizing basic science, improving use of animal models, promoting innovative trial designs, striving to validate new surrogate endpoints, expanding community involvement—sadly deficient in TB vaccine R&D compared with TB drug development—and mobilizing the full complement of resources—scientific, political, financial, and community-based—needed to fully realize the promise of new TB vaccine discovery, development, and dissemination.

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The Antiretroviral Pipeline

By Tim Horn and Simon Collins

Introduction

By 2024, antiretroviral treatment (ART) could be as different from that used today as triple therapy in 1997 was from AZT monotherapy in 1987, or as dramatically evolved as the once-daily and single-pill regimens of 2014 compared with the multidose, multipill regimens of 1997. A lot can be achieved in 10 years, though new developments are ultimately dependent on both ambitious goals and adequate resources to enable them to come to fruition.

This will require pushing technology: using rational design to manufacture new compounds that not only are effective at controlling HIV, but also have fewer toxicities, less complicated dosing, and reduced risk of drug resistance. Novel therapies also need to be brought to market at prices that are affordable, whatever the setting.

Although progress toward a cure might be edging forward, HIV is likely to require lifelong treatment for the 40 million people living with the virus for years to come. The near future of scale-up therefore needs to be just as dramatic as the 2013 World Health Organization (WHO) estimate that roughly 10 million people in low- and middle-income countries were on ART by the end of 2012, an increase from less than a million people 10 years earlier.[1]

Glimpses of the future of ART are provided in this year's antiretroviral (ARV) treatment pipeline chapter, including the arrival of the integrase inhibitor dolutegravir; the evolving potential of two long-acting drugs to revolutionize treatment dosing; and what may prove to be a kinder, gentler version of tenofovir. Missing, however, is the advancement of agents with potential for people with multiclass-resistant HIV, an important subpopulation of individuals living with the virus for whom novel drugs and regulatory pathways are essential.

Drug Pricing and Access: Cost Effectiveness versus Affordability

Though the approval of dolutegravir (Tivicay) in 2013 was welcomed, its U.S. Average Wholesale Price (AWP) of $16,920 annually (as of January 2014) made it the most expensive single component recommended for first-line therapy in the *U.S. Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*.[2] This price is doubled for people requiring twice-daily dosing due to either drug resistance or drug interactions.[2]

In Europe, ongoing price negotiations are likely to lead to prices closer to other widely used first- and second-line drugs. For most public health systems, already squeezed by budget freezes year after year since 2011, the option to use new drugs outside anything other than a highly restricted minority of patients is increasingly dependent on a realistic approach to pricing. Even with advantages in efficacy and tolerability, premium pricing is no longer an effective model anywhere in the world.

As an example of these financial constraints, patients using commonly prescribed fixed-dose combinations (FDCs) such as Atripla (efavirenz/TDF/FTC) are likely to be changed to generic efavirenz plus Truvada (TDF/FTC) if this results in lower costs. In some countries, boosted protease inhibitor (PI) monotherapy (principally darunavir/ritonavir) is already widely used due to similar efficacy compared with three-drug regimens and the opportunity to save the costs of the dual-nucleoside reverse transcriptase inhibitor (NRTI) component.[3]

U.S. Access to Antiretroviral Therapy

The upward trend in drug pricing is widely considered to be a key driver of inequitable access to treatment in the United States, particularly under the private Qualified Health Plans (QHPs) in the health insurance exchanges established by the Affordable Care Act (ACA).

For example, many QHPs are engaging in discriminatory practices by placing prescription medications for HIV in high "specialty drug" tiers (Tier 4 or 5), which impose exorbitant out-of-pocket (OOP)

costs in the form of co-insurance that requires paying a percentage of retail prescription drug costs, rather than a flat co-payment.

Under some QHPs, people are paying as much as 40 to 50 percent of their prescription costs. Though ACA requires QHPs to cap their OOP costs (individuals may be required to pay up to $6,350 in annual copayments, co-insurance, or deductibles) many people with HIV would incur the maximum OOP for their medications, likely in the first few months of each annual cycle—prohibitive dollar amounts for most.

Worsening matters, pharmaceutical company co-payment assistance programs do not necessarily cover all out-of-pocket expenses. Advocacy efforts are now under way, demanding that these programs offer 100 percent coverage of OOP expenses. Yet the future of co-payment assistance programs for HIV is hazy because of an interim final rule from the U.S. Centers for Medicaid and Medicare Services (CMS) that both discourages third-party payment programs and encourages QHPs to reject payments from these programs.[4]

Though professional and community comments have been submitted to the CMS urging that this language be struck—notably for drugs without generic equivalents, which include many preferred components of antiretroviral therapy (e.g., dolutegravir, efavirenz, darunavir, and atazanavir)—the future of the final rule and, by extension, the programs themselves remains uncertain.

What also remains uncertain is the cost of three co-formulations now under review by the FDA: Janssen's darunavir plus Gilead's cobicistat, Bristol-Myers Squibb's atazanavir plus cobicistat, and ViiV's FDC containing darunavir, abacavir, and 3TC. Cobicistat has already been associated with lucrative sales as a component of Stribild (annual average wholesale price [AWP]: US$35,378[2]), with sales of more than US$200 million in the fourth quarter of 2013 and nearly US$540 million for the entire year.[5] A lingering concern is that the prices set for the cobicistat-inclusive FDCs will surpass those of darunavir/ritonavir and atazanavir/ritonavir (approximate annual AWP for both: US$20,000[2]), considering that, 1) the AWP of ritonavir was barbarically inflated by 400 percent in 2003, soon after

it became clear that ritonavir's primary role was that of a boosting agent and not as a protease inhibitor in its own right, and 2) any potential safety advantages of cobicistat over ritonavir have not been borne out in clinical trials completed so far.

With respect to the pricing of ViiV's dolutegravir/abacavir/3TC FDC, having two components off patent (abacavir and 3TC are available as generics in the U.S. and other markets) could have significant leverage against FDCs from Gilead: competition may yet prove advantageous in the United States. Though annual AWPs for these generic agents in the U.S. average $7,224 and $5,148 (roughly 85 to 90 percent of the originator drug price), their annual retail prices are as low $1,950 and $2,550, respectively. An FDC containing all three drugs may be preferable to prescribers and people living with HIV. But data from well-designed clinical trials concluding that it is superior to a once-daily regimen consisting of multiple tablets have not yet materialized. Treatment advocates will be hard pressed to convince both public and private payers to cover the FDC, without preauthorization requirements, in preference to dolutegravir plus generic abacavir and 3TC, without clear scientific evidence of need.

ViiV has the potential to further challenge Gilead's market dominance by competitively pricing its FDC to reflect reduced prices of generic abacavir and 3TC. The DHHS guidelines once again list abacavir and 3TC as a recommended NRTI backbone for first-line treatment—primarily in combination with dolutegravir, but also in combination with efavirenz and ritonavir-boosted atazanavir for people with pretreatment viral loads <100,000 copies/mL.[2] The still-patent-protected tenofovir DF (TDF)/FTC is generally recommended otherwise, though with an undeniable recognition of the need to balance use of branded and generic treatment to maximize cost savings without worsening health outcomes, the guidelines note the suitability of replacing FTC with generic 3TC.

As other DHHS-recommended ARVs come off patent in the next four to five years, cost will continue to be a critical factor in the selection of treatments. The pharmaceutical industry must be aware of this, not as a threat, but as a reality of cost-contained health care delivery.

SUMMARY OF PIPELINE PROGRESS

A summary of key developments since the *2013 Pipeline Report* is included in table 1. Several of the compounds, notably those with new data or development advances over the past year, are discussed in more detail below.

Table 1. Summary of Pipeline Compounds in 2014

Compound	Company	Class/Type	Status	Comments
cobicistat	Gilead	PK booster	Approved in E.U.; NDA refiled for U.S. approval	In September 2013, European Commission approved cobicistat as a pharmacokinetic booster of atazanavir 300 mg once daily or darunavir 800 mg once daily as part of a complete ART regimen in adults
elvitegravir	Gilead	INSTI	Approved in E.U.; NDA refiled for U.S. approval	In November 2013, European Commission approved elvitegravir for use in combination with ritonavir-boosted PIs for individuals without evidence of resistance to elvitegravir
darunavir plus **cobicistat** (co-formulation)	Janssen	PI plus PK booster	Application filed in E.U.; NDA filed in U.S.	EMA application filed October 2013; NDA filed April 2014
atazanavir plus **cobicistat** (co-formulation)	BMS	PI plus PK booster	NDA filed in U.S.	NDA filed April 2014
darunavir plus **abacavir** plus **3TC** (co-formulation)	ViiV Healthcare	INSTI plus two NRTIs	NDA filed in U.S.; application filed in E.U.	U.S. and E.U. applications filed in October 2013
tenofovir alafenamide (TAF, GS-7340)	Gilead	NtRTI (tenofovir prodrug)	Phase III	In development as FDC component with elvitegravir, cobicistat, and FTC for treatment-naive and –experienced patients. Also as a component of FDC with darunavir, cobicistat, and emtricitabine. FDC with emtricitabine, as follow-up to Truvada, also in development
raltegravir (once-daily formulation)	Merck	INSTI	Phase III	PK data from phase I once-daily formulation (2 x 600 mg tablets) studies presented at EACS 2013 and CROI 2014. A phase III study is expected to begin in 2014

Compound	Company	Class/Type	Status	Comments
dolutegravir plus **rilpivirine** (co-formulation)	ViiV Healthcare, Janssen	ISNTI plus NNRTI	Phase II/III	Clinical trials evaluating the safety and efficacy of the FDC as two-drug maintenance therapy are expected to begin in early 2015.
darunavir plus **cobicistat** plus **FTC** plus **TAF** (co-formulation)	Gilead	PI plus PK booster plus NtRTI and NRTI	Phase II	Phase II study has been completed. A phase III study of the FDC has not yet been announced
apricitabine	Avexa	NRTI	Phase II	3TC-like molecule, stalled at phase IIb with no new studies listed since a phase III study was halted in 2009. A potential role for multiclass-resistant HIV. Partnership announced in December 2013 with NextPharma
BMS-663068	BMS	Attachment inhibitor (gp120)	Phase II	Phase II data presented at CROI 2014
cenicriviroc (TBR-652)	Tobira	CCR5 inhibitor (also active against CCR2)	Phase II	Phase II study results reported at EACS 2013. Tobira plans to study FDC of cenicriviroc plus 3TC in combination with third drug in phase III program
doravirine (MK-1439)	Merck	NNRTI	Phase II	Phase II data reported at CROI 2014
PRO 140	CytoDyn	CCR5-specific humanized monoclonal antibody	Phase II	No new data since 2010. Phase III trials, including treatment substitution protocol, are planned by CytoDyn
ibalizumab (TMB-355; formerly TNX-355)	TaiMed Biologics	CD4-specific humanized IgG4 monoclonal antibody	Phase II	No data from treatment studies in several years; potential as long-acting preexposure prophylaxis
S/GSK1265744 oral and long-acting parenteral (LAP) formulations	ViiV Healthcare	INSTI (follow-up to dolutegravir)	Phase II	Preliminary data supporting daily oral dosing as maintenance therapy, paired with oral rilpivirine, presented at CROI 2014. Demonstrates potential for once-monthly dosing with rilpivirine-LA
rilpivirine-LA (long-acting formulation)	Janssen	NNRTI	Phase II	Preliminary data supporting daily oral dosing as maintenance therapy, paired with oral S/GSK1265744, presented at CROI 2014. Demonstrates potential for once-monthly dosing with S/GSK1265755 LAP

Compound	Company	Class/Type	Status	Comments
OBP-601 (formerly BMS-986001)	Oncolys	NRTI	Phase II	d4T-like molecule in phase II, with no new clinical data reported since 2012. Licensing agreement between Oncolys and BMS has been terminated and the compound returned to Oncolys for continued development
albuvirtide	Chongquing Biotechnologies	Long-acting fusion inhibitor	Phase I	No new data or studies announced since 2013 Pipeline Report
CMX157	Merck	NtRTI (similar to TAF)	Phase I	No new data or studies announced since 2013 Pipeline Report
EFdA	Merck	NRTI	Phase I	No new data or studies announced since 2013 Pipeline Report

BMS: Bristol-Myers Squibb; CROI: Conference on Retroviruses and Opportunistic Infections; EACS: European AIDS Conference; E.U.: European Union; FDA: U.S. Food and Drug Administration; FDC: fixed-dose combination; GSK: GlaxoSmithKline; IM: intramuscular; INSTI: integrase strand transfer inhibitor (integrase inhibitor); MDR-HIV: multidrug-resistant HIV; NDA: new drug application; NRTI: nucleoside reverse transcriptase inhibitor; NtRTI: nucleotide reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PK: pharmacokinetic; PI: protease inhibitor; STR: single-tablet regimen; U.S.: United States

NEW APPROVALS AND CURRENT SUBMISSIONS

Dolutegravir

The most important approval since HIV i-Base and Treatment Action Group's joint publication of the *2013 Pipeline Report* is ViiV Healthcare's dolutegravir (Tivicay). Dolutegravir is an integrase strand transfer inhibitor (INSTI) that can be used once a day (for treatment-naive and INSTI-naive patients) without dietary requirements or a need for boosting. Phase III studies were notable for reporting superiority results over many commonly recommended combinations, generally driven by higher adverse event–related discontinuations in the comparator arms. The low-milligram dosage has led to a co-formulated FDC with ViiV's abacavir and 3TC. It is also being co-formulated with rilpivirine as an FDC for potential use as two-drug maintenance therapy.

Dolutegravir was approved by the U.S. Food and Drug Administration (FDA) on August 12, 2013,[6] Health Canada on November 4, 2013,[7] and the European Commission on January 21, 2014.[8] For adults, the indication is based on data

from two treatment-naive trials (SPRING-2 and SINGLE), one trial that enrolled treatment-experienced but integrase inhibitor–naive subjects (SAILING), and another study that enrolled treatment-experienced patients with resistance to raltegravir or elvitegravir (VIKING-3).

The dose for treatment-naive and INSTI-naive adults is 50 mg once daily; for INSTI-experienced patients, it is 50 mg twice daily. Although there are limited clinical data on the resistance profile for dolutegravir, efficacy is clearly reduced in patients with Q148 integrase mutations plus two or more additional INSTI-associated mutations, including: L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R. This requires early switching from raltegravir- or elvitegravir-containing combinations if viral load is not maintained below detectable levels.

Treatment-naive patients appear to have such a low risk of developing resistance to dolutegravir that, if early results are supported with additional studies, this could warrant broad use in first-line therapy. One mechanism may involve the drug's extremely long intracellular half-life, which could minimize the risk of suboptimal concentrations times associated with selective pressure and the emergence of resistance. Another could be the dramatic reduction that the integrase mutation R263K has on enzymatic activity, especially in the presence of secondary mutations, as this seems to impair viral fitness to a degree that may become incompatible with viral survival.[9]

Clarifying dolutegravir's reduced potential for resistance should become a research priority, especially for use in resource-limited settings where heavy reliance on non-nucleoside reverse transcriptase inhibitor (NNRTI)–based treatment, compounded by limited access to viral load testing or resistance assays, contributes to extensive drug resistance, even in the context of good adherence.[10]

Twice-daily dosing is also required when combining dolutegravir with efavirenz, ritonavir-boosted fosamprenavir, ritonavir-boosted tipranavir, or rifampin.

Though dolutegravir's indication allows for dosing with or without food, its levels are increased when taken with a meal, especially with a higher fat content (AUC increased by 33, 41, and 66 percent when administered with low-, moderate-, or high-fat meals, respectively, compared with fasting).[11] This may have potential clinical benefit for INSTI-experienced patients requiring higher concentrations to overcome drug resistance, though this has not been formally studied.

The FDC tablet, containing dolutegravir, abacavir, and 3TC (Triumeq, 572-Trii) has already been submitted by ViiV to the FDA and the European Medicines Agency (EMA) for regulatory review.[12,13] An approval decision, at least from the FDA, is expected in August of this year.

Clinical trials evaluating the safety and efficacy of the FDC containing dolutegravir and rilpivirine as two-drug maintenance therapy are expected to begin in early 2015.[14]

Cobicistat and Elvitegravir

Gilead's pharmacokinetic (PK) booster cobicistat (Tybost) and its INSTI elvitegravir (Vitekta) were approved by the European Commission on September 25 and November 18, 2013, respectively.[15,16] New drug applications (NDAs) for both agents have been refiled with the FDA, with U.S. decisions anticipated by October of this year.[17] The original NDAs, filed in June 2012, were rejected by the agency in April 2013, due to "deficiencies in documentation and validation of certain quality testing procedures and methods that were observed during inspections."[17]

The European Union (EU) indication for elvitegravir is for use in combination with a ritonavir-boosted protease inhibitor (PI/r) and other antiretrovirals in individuals without evidence of HIV resistance to elvitegravir. Approval was based on 96-week data from a phase III study in which once-daily elvitegravir was found to be noninferior to twice-daily raltegravir (47.6% vs. 45.0% with viral loads <50 copies/mL through week 96; difference: 2.6%, 95% CI: 4.6% to 9.9%), each combined with an optimized background regimen that included a fully active boosted PI in treatment-experienced, INSTI-naive patients.[18] Elvitegravir is available as an 85 mg tablet, for use with atazanavir/ritonavir or lopinavir/ritonavir, and a 150 mg tablet, for use in combination with ritonavir-boosted darunavir or fosamprenavir.

Elvitegravir has cross-resistance with raltegravir, but its mutation profile suggests that patients are likely to remain sensitive to dolutegravir if resistance is detected early and patients are promptly switched.[19]

Cobicistat, available as a 150 mg tablet, is indicated in Europe as a booster for atazanavir (300 mg once daily) and darunavir (800 mg once daily). Approval is based on results from a phase III study in which cobicistat was

found to be noninferior to ritonavir at boosting atazanavir (85.2% vs. 87.4% with viral loads <50 copies/mL through week 48; difference: −2.2%, 95% CI: −7.4% to 3.0%), with a similar side-effect profile, along with additional pharmacokinetics data indicating that cobicistat produces comparable boosting of darunavir, compared with ritonavir.[20] Of note, cobicistat is not always interchangeable with ritonavir. It has a selective pharmacokinetic mechanism that is sometimes very different—for example, it cannot be used to boost tipranavir.

In collaboration with Gilead, Bristol-Myers Squibb (BMS) has developed a co-formulation containing both cobicistat and atazanavir. A recent pharmacokinetics evaluation in 62 HIV-negative individuals concludes that atazanavir administered in the FDC tablet is bioequivalent to coadministration of stand-alone atazanavir and cobicistat, when taken with a light meal.[21] Although not prespecified, cobicistat in the FDC also met the criteria for bioequivalence to coadministration of the individual components. An NDA was filed with the FDA on April 4, 2014.[22]

An NDA supporting a combined formulation containing cobicistat and darunavir was submitted to the FDA for approval on April 1, 2014; a marketing authorization application was submitted to the EMA on October 15, 2013.[23,24] The filing is supported, in part, by the results of a 133-person pharmacokinetics evaluation in which co-formulated darunavir/cobicistat was bioequivalent to darunavir and cobicistat, administered as single agents, under fed and fasted conditions.[25] As a food effect was observed with darunavir, similar to that reported with darunavir/ritonavir, the investigators concluded that the darunavir/cobicistat FDC should therefore be taken with food.

UPDATE ON COMPOUNDS WITH PHASE II AND PHASE III RESULTS

Several compounds with exciting early data are steadily progressing, and several co-formulations are in advanced phase III studies.

The pipeline can be categorized broadly as “advanced,” “progressing,” and “trailing.”

Advanced: generally phase III

- New FDCs
    - dolutegravir/abacavir/lamivudine
    - elvitegravir/cobicistat/FTC/TAF
    - darunavir/cobicistat/FTC/TAF
    - TAF/FTC
    - cenicriviroc/FTC
    - dolutegravir/rilpivirine
- raltegravir formulation for once-daily dosing

Progressing: generally in active phase I or phase II

- doravirine
- BMS-663068
- Long-acting injections:
    - S/GSK1265744 LAP
    - rilpivirine-LA
    - PRO 140

Trailing: generally little or no progress irrespective of development phase

- apricitabine
- OBP-601
- ibalizumab
- CMX157
- EFdA
- albuvirtide

Tenofovir alafenamide fumarate (TAF, formerly GS-7340)

Tenofovir alafenamide fumarate (TAF) is a prodrug formulation of tenofovir. Development as an FDC component—rather than as a stand-alone new drug—is being prioritized. This is an activist concern, especially for people with HIV resistant to TDF. The current leading FDC combines TAF with elvitegravir, cobicistat, and FTC (E/C/F/TAF)—a follow-up to Stribild. A replacement

for Truvada, in which TAF will be paired with FTC, is in later development—potentially explained by TDF's remaining patent-protected until 2017. Though a stand-alone TAF formulation is being developed, it is being evaluated exclusively for the treatment of chronic hepatitis B virus.

Unlike the currently approved 300 mg TDF, another prodrug converted in the blood to the active drug tenofovir diphosphate and then taken up into cells, TAF is primarily metabolized and converted to tenofovir diphosphate inside 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 seven times higher.[26,27] The reduced systemic elimination has the potential for fewer renal- and bone-related toxicities compared with TDF.

Forty-eight-week results from a phase II evaluation of E/C/F/TAF, compared with Stribild-containing TDF, were reported at the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in October 2013.[28] The study randomized 170 treatment-naive individuals (2:1) to either E/C/F/TAF (N = 112) or Stribild (N = 58). Because cobicistat boosts TAF levels, the four-drug FDC uses a 10 mg TAF dose.

Baseline median CD4 and viral load were approximately 400 cells/mm^3 (15% were <200 cells/mm^3) and 40,000 copies/mL (17–28% were >100,000 copies/mL). As with previous studies using cobicistat and TDF, entry criteria included normal or mild impairment of kidney function, defined as an estimated glomerular filtration rate (eGFR) >70 mL/min (median baseline levels were 115 mL/min).

The primary endpoint of virologic suppression (<50 copies/mL) at 48 weeks was reported for 88.4% vs. 87.9% in the TAF vs. TDF arms, albeit with a very wide confidence interval (weighted difference: −1.0%, 95% CI: −12.1 to +10.0; P = .84). CD4 increases were similar (+177 vs. +204 cells/mm^3). Of note, the study wasn't powered to evaluate differences in antiviral activity. Even in larger studies, it may be difficult to document differences in potency, given the high level of efficacy associated with TDF.

Adverse events, occurring in ≥10 percent of study subjects, were similar. These included nausea (21% vs. 12%), diarrhea (16% vs. 16%), upper respiratory tract infection (15% vs. 21%), fatigue (14% vs. 9%), headache (10% vs. 14%), and cough (10% vs. 10%)—all TAF vs. TDF, respectively.

As for laboratory abnormalities, both arms had a reduction in eGFR related to use of cobicistat. These occurred by week 2 but then stabilized by week 48. Reductions in eGFR were less pronounced in the TAF arm (−5.5 mL/min vs. −10.0 mL/min; P = .041). These findings jibe with recent in vitro data suggesting that, unlike TDF, TAF does not undergo active renal secretion via organic anion transporters, which can lead to higher exposure of renal proximal tubules to tenofovir and a resulting increased risk of kidney toxicity.[29]

Reductions in bone mineral density (BMD) were less pronounced in the TAF arm for both spine (−1.00% vs. −3.37%; P = .001) and hip (−0.62% vs. −2.39%; P < .001). No decrease in hip BMD was documented in 32 percent in the E/C/F/TAF arm, compared with 7 percent in the TDF arm (P < 0.001). These results are consistent with in vitro data presented at the 53rd ICAAC, indicating that TAF had no discernible effects on osteoblasts, the cells responsible for the synthesis and mineralization of bone, using concentrations comparable to those that would be achieved as a result of human dosing.[30]

Although grade 3 or 4 increases in LDL cholesterol were more common in those in the TAF arm, compared with those receiving TDF, HDL cholesterol also increased among TAF recipients, resulting in comparable HDL: total cholesterol ratios in both arms.

A phase II/III clinical trial evaluating the PK, safety, and antiviral activity of E/C/F/TAF in treatment-naive adolescents ages 12 to 17 is currently under way.[31]

In light of TAF's ability to achieve intracellular concentrations that are substantially higher than those associated with TDF, it is active against virus with the TDF-associated K65R mutation, the multinucleoside/nucleotide T69S and Q151M mutations, and up to three thymidine analog mutations (TAMs).[32] Gilead is evaluating E/C/F/TAF in treatment-experienced (including TDF-experienced) patients. Further development of resistance, even in the presence of K65R, appears to be limited in vitro.[33]

Study 292-0117 will evaluate the efficacy of TAF versus placebo added to a failing regimen for 10 days, followed by treatment with atazanavir plus E/C/F/TAF.[34] The primary endpoint is viral-load reduction of $\geq$0.5 log copies/mL at day 10. The trial will recruit 100 patients with detectable viral loads (with a broad range between 500 copies/mL and 100,000 copies/mL) on current treatment with NRTI resistance. This is defined either as one to three TAMs or K65R, plus M184V, and at least one major NNRTI or PI mutation.

A clinical trial is also looking at a five-drug regimen of E/C/F/TAF plus darunavir (Study 292-0119) as a switch strategy in treatment-experienced patients who are stable on their current antiretroviral therapy.[35] Volunteers must have a history of at least two prior antiretroviral regimens, along with a history of resistance to at least two different drug classes, and be virally suppressed on a regimen containing darunavir. Entry criteria require current use of raltegravir, elvitegravir, or dolutegravir (50 mg once daily, but not twice daily), or documentation showing no evidence of resistance to these INSTIs. The cost-effectiveness analysis from this study will be worth noting.

Finally, a phase III trial (Study 311-1089) will randomize 660 patients to either remain on Truvada or switch this component to TAF/FTC. Other drugs will not be switched.[36] Allowed third agents include: atazanavir/ritonavir, lopinavir/ritonavir, darunavir/ritonavir, efavirenz (as individual agent only), rilpivirine (as individual agent only), nevirapine, raltegravir, dolutegravir, or maraviroc. Combination tablets containing FTC and either 10 mg or 25 mg TAF will be evaluated in the study. The TAF dose will depend on the third drug used and will be based on the results from pharmacokinetic studies, the results of which have not yet been reported or published.

Doravirine (MK-1439)

Doravirine is a once-daily NNRTI being developed by Merck. It has in vitro activity against common NNRTI resistance mutations (K103N, Y181C, G190A, and E138K) and selects for distinct mutations in vitro (V106A, F227L, and L234I), suggesting limited cross-resistance to rilpivirine or etravirine.[37]

Phase I studies have noted multiple doses up to 750 mg were generally well tolerated with minimal food effects (after 50 mg dosing);[38] primary metabolism is by CYP3A4, but without having an inducer or inhibitor effect.[39] Doravirine produced a median 1.3 log viral-load decline in a seven-day monotherapy evaluation using 25 mg and 200 mg once-daily oral dosing.[40]

First results from an ongoing two-part phase II dose-finding study in treatment-naive patients have been reported.[41] Part one of the study, presented at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI), was a five-arm dose-ranging assessment with 40 patients in each arm. Doravirine doses of 25 mg, 50 mg, 100 mg, and 200 mg were compared in four arms, along with a standard dose of efavirenz in the fifth arm. All study volunteers also received TDF and FTC.

Median CD4 count and viral load at study entry was approximately 380 cells/mm^3 (range: ~80–1,140 cells/mm^3) and 4.6 log copies/mL (range: 2.8–6.1 log copies/mL), with 30 percent having viral load >100,000 copies/mL. Distribution was roughly similar between arms, although a higher percentage of people with CD4 counts <200 cells/mm^3 were in the 25 mg doravirine group (17.5% vs. 7–12.2% in the other arms).

Rates of primary efficacy—the percentage with viral suppression <40 copies/mL at week 24—were 80.0% in the 25 mg doravirine group, 76.2% in the 50 mg group, 71.4% in the 100 mg group, and 78.0% in the 200 mg group. In the efavirenz group, 64.3% had viral loads <40 copies/mL at week 24.

Viral-load suppression rates were more pronounced in patients with baseline viral loads ≤100,000 copies/mL, compared with those with viral loads >100,000 copies/mL, according to an ad hoc analysis. Among those in the lower viral-load strata, between 83 and 89 percent of those receiving doravirine, compared with 74 percent of those receiving efavirenz, had viral loads <40 copies/mL at week 24. Among those in the higher viral-load strata, between 58 and 91 percent of those receiving doravirine, compared with 54 percent of those receiving efavirenz, had viral loads <40 copies/mL.

Median CD4 increases were similar between arms: +137 cells/mm^3 in the combined doravirine groups, compared with +121 cells/mm^3 in the efavirenz arm.

Fewer patients discontinued because of adverse events in the doravirine arms, compared with the efavirenz arm (2.5% vs. 4.8%, respectively). The incidence of at least one central nervous system–related adverse event was higher in the efavirenz-treated patients compared with the doravirine-treated subjects (33.3% vs. 20.5%, respectively). Lipid-related profiles and liver enzyme (ALT/AST) elevations were also less common in those receiving doravirine.

Despite the lack of associations between the doses used and either efficacy or tolerability in part 1 of the study, the investigators have selected 100 mg once-daily doravirine for part 2 of the trial, which will compare doravirine/TDF/FTC and efavirenz/TDF/FTC in 120 patients for a total of 96 weeks.

Cenicriviroc

Cenicriviroc is a CCR5 inhibitor that is also active against CCR2. This compound has been in development in various formulations by Tobira for several years (previously as TBR-652). Forty-eight-week results from a randomized, double-blind, placebo-controlled phase IIb study in treatment-naive patients were presented at the 14th European AIDS Conference (EACS) in Brussels in October 2013.[42]

The study used a 50 mg formulation of cenicriviroc and randomized 143 patients 2:2:1 to either 100 mg or 200 mg of cenicriviroc twice daily compared with 600 mg of efavirenz once daily, all with matching placebo and open-label TDF/FTC. This required participants to take six pills twice daily, using a 50 mg formulation of cenicriviroc taken in the morning with breakfast and efavirenz taken in the evening.

Baseline characteristics included approximate median baseline CD4 and viral load of 400 cells/mm^3 (range: 77–1,090 cells/mm^3) and 25,000–40,000 copies/mL (14–25% had viral loads >100,000 copies/mL).

At week 24, viral suppression (<50 copies/mL) was achieved by 68 percent and 64 percent in the 100 mg and 200 mg cenicriviroc arms, compared with 50 percent in the efavirenz arm—all significantly lower than the week-24 results report at CROI 2013 (78, 73, and 71 percent, respectively). It is most unusual for efavirenz to show such poor efficacy.

Protocol-defined virologic failure was documented in 4 (7%), 6 (11%), and 1 (4%) patients in the 100 mg and 200 mg cenicriviroc arms and the efavirenz arm, respectively. Five patients in the cenicriviroc arms developed an NRTI-associated resistance mutation (M184I/V), and two patients in the 200 mg cenicriviroc arm developed an NNRTI-associated mutation (V108I/V). No resistance-associated mutations were documented in the one individual who experienced virologic failure in the efavirenz arm. One patient in the 200 mg cenicriviroc arm also experienced an HIV tropism shift to dual-mixed.

The number of patients with at least one treatment-related adverse event was lower in the cenicriviroc arms compared with the efavirenz arm (50% and 44% vs. 71%, respectively). Rates of abnormal dreams, insomnia, rash, and nausea were all higher in the efavirenz arm.

Grade 3 or 4 laboratory abnormalities were more common among those in the 200 mg cenicriviroc group (21%) compared with those in the 100 mg group (12%) and the efavirenz group (14%). Creatine phosphokinase increases were the most notable difference, occurring in 16%, 5%, and 7%, respectively. As for lipid changes from baseline, mean total cholesterol, LDL, triglycerides, and HDL all decreased or remained stable in the cenicriviroc arms, compared with increases in the efavirenz group.

Levels of soluble CD14 (sCD14)—an immune activation biomarker that is independently associated with mortality—decreased through week 24 in the cenicriviroc groups, but returned to baseline by week 32. This compared with a steady increase of sCD14 in the efavirenz group throughout the 48-week observation period. The clinical significance of these findings requires further investigation.

A PK analysis of 24-week data from this study suggests that the 200 mg dose is less likely to result in a Cmin <50 ng/mL, which was found to be associated with virologic failure and the emerging NRTI-associated mutations in the study.[43] The 200 mg dose has therefore been selected for phase III development.

Instead of exploring cenicriviroc as the leading drug to be combined with a standard NRTI backbone, Tobira's phase III program will evaluate a dual-formulation tablet containing 200 mg cenicriviroc and 300 mg 3TC. This will be compared with TDF/FTC, each combined with preferred third components.

Cenicriviroc may also be active against HIV-2 in CCR5-tropic patients.[44]

BMS-663068

BMS-663068 (BMS-068) is a prodrug of BMS-626529, which is an HIV attachment inhibitor that is active against both CCR5- and CXCR4-tropic HIV, but not subtype AE and Group O.[45,46] Unlike enfuvirtide, an injectable peptide that inhibits the gp41-mediated fusion of HIV to CD4 cells, BMS-068 is an oral drug that binds directly to gp120, causing conformational changes that block attachment to the CD4 receptor.

Eight days of BMS-068 monotherapy in treatment-naive and -experienced patients in a phase I proof-of-concept study resulted in substantial declines in viral load (1.21 to 1.73 log copies/mL) and was generally safe and well tolerated.[47]

Results from an international phase II dose-ranging study were reported at CROI 2014.[48] Treatment-experienced patients—all of whom had virus susceptible to raltegravir, TDF, and atazanavir—were assigned to receive BMS-068 at doses of 400 mg twice daily, 800 mg twice daily, 600 mg once daily, and 1,200 mg once daily, compared with atazanavir/ritonavir, all in combination with raltegravir and TDF. There were 50 people in each arm, including 10 patients in each arm using seven days of BMS-068 monotherapy. Sensitivity to BMS-626529 was an entry requirement (IC50 <100 nM); approximately 5 percent of study volunteers did not meet this criterion for enrollment.

Mean CD4 counts and viral loads at entry were approximately 250 cells/mm^3 (roughly 40% had <200 cells/mm^3) and 4.7 log copies/mL (approximately 40% had >100,000 copies/mL). Roughly 30 percent of patients had one or more resistance mutation to one or more available drug classes.

Discontinuations ranged from 11 percent in the 400 mg twice-daily BMS-068 arm to 22 percent in the 800 mg twice-daily BMS-068 arm, though these were primarily due to withdrawal of consent, loss to follow-up, pregnancy, or poor adherence. Few discontinuations were due to lack of efficacy or side effects.

Viral response rates of monotherapy were dose-related. Unlike other antiretroviral classes, a transient small increase in viral load was observed during the first two days of treatment prior to a decline averaging −0.69 logs (400 mg twice daily) to −1.47 logs (1,200 mg twice daily) on day eight of the monotherapy substudy.

At week 24, viral-load suppression to <50 copies/mL was achieved by 80, 69, 76, and 72 percent of patients in the 400 mg twice-daily, 800 mg twice-daily, 600 mg once-daily, and 1,200 mg once-daily BMS-068 arms, respectively, compared with 74.5% in the atazanavir/ritonavir arm. Patients with pretreatment viral loads ≥100,000 copies/mL, with the exception of those in the 1,200 mg once-daily group, had at least 15 to 20 percent lower response rates, compared with patients with baseline viral loads <100,000 copies/mL. CD4 increases were similar across all arms.

In the BMS-068 arms, none of the 15 serious adverse events documented in 13 study volunteers were attributed to the study drugs. Four adverse events led to study discontinuation: nonspecific EKG changes in a person with a history of illicit drug use, two TB cases, and one case of acute renal failure associated with TDF use.

There was, however, a high rate of resistance to raltegravir, which developed in four of eight people who experienced virologic failure while receiving BMS-068 plus raltegravir and TDF.[49]

All participants on BMS-068 have now been rolled over to the twice-daily 1,200 mg dose for continued follow-up. Jay Lalezari, MD, who presented the data on behalf of the study team, noted that this is not necessarily the dose that will be employed in future safety and efficacy evaluations of the drug.

Raltegravir (Once-Daily Formulation)

Once-daily dosing of Merck's INSTI is not recommended based on the results of the QDMRK trial, which failed to show that once-daily dosing of raltegravir (800 mg) was noninferior to twice-daily dosing (400 mg) when used in people starting first-line therapy.[50]

A new formulation has been developed by Merck to allow for once-daily dosing, although current data suggest that this will involve both an increase in the total daily dose and a requirement to take the new formulation with food.

At EACS 2013, investigators reported preliminary results from an open-label study comparing the single-dose (1,200 mg) pharmacokinetics of the reformulated and older formulations of raltegravir. The former was given as two 600 mg tablets, the latter as three 400 mg tablets. Pharmacokinetics evaluations included fasted, low-fat-fed, and high-fat-fed states.[51] Following a low-fat meal, the area under the plasma drug concentration-time curve (AUC) of raltegravir was reduced by 40 percent using the reformulated tablet, compared with more than 70 percent using the older tablet. And whereas a high-fat meal increased the AUC of raltegravir by 26 percent using the older tablet, it remained relatively stable using the reformulated tablet.

Results of a multiple-dose, three-period (five days), crossover study were reported at CROI 2014.[52] Twenty-four HIV-negative men and women received 1,200 mg (3 x 400 mg tablets) of the original raltegravir formulation, once daily; 1,200 mg (2 x 600 mg tablets) of the newer formulation, once daily; and standard doses (400 mg) of the older formulation, twice daily. All doses were taken without food. Data were used to develop a PK/PD viral-dynamics model to assess the feasibility of 1,200 mg once-daily dosing. According to Merck's calculations, the probability of the standard and new formulation of raltegravir,

dosed at 1,200 mg once daily without food, achieving noninferiority to 400 mg twice-daily raltegravir, is 89 and 86 percent at week 24, and 92 and 87 percent at week 48, respectively. The investigators also suggested that due to a smaller food effect on the pharmacokinetics of reformulated raltegravir, simulated efficacy is less dependent on meal type than for standard once-daily 1,200 mg raltegravir.

Clinical results, not just pharmacokinetics data, appear to be a requirement of once-daily dosing approval. A phase III randomized and double-blind trial (onceMRK) comparing once-daily and twice-daily formulations of raltegravir in treatment-naive patients is currently under way.[53]

Long-Acting Formulations

The development, approval, and scale-up of highly effective combination antiretroviral therapy have led to marked improvements in HIV-related morbidity and mortality. Yet several factors continue to work against ART's acceptability and durability, including daily oral dosing, strict timing for combinations vulnerable to drug resistance, and other adherence challenges including variable pharmacokinetics and adverse effects.

Long-acting drug formulations allowing monthly or less frequent dosing are a potential solution, whether administered in the clinic or at home. Intramuscular or subcutaneous injections may also have reduced gastrointestinal and other side effects. Additionally, they may be cheaper to produce, given that much less active pharmaceutical ingredient is used and could potentially overcome a key global concern of stock-outs in resource-limited settings.

There are two long-acting formulations in advanced development: the INSTI S/GSK1265744 and the NNRTI rilpivirine. Both of these ARVs are already being combined in phase II/III clinical trials. They use nanoformulation technologies to overcome bioavailability, water solubility, and stability weaknesses of oral antiretrovirals. Long-acting formulations are already approved and widely used for other indications, such as depot paliperidone for schizophrenia and depot medroxyprogesterone to prevent pregnancy.[54,55]

Alternatives to taking daily pills have a high level of patient interest. Potential advantages include reducing complications of adherence for people who find this difficult, including children and adolescents; reducing the stigma associated with medication and HIV disclosure; and "normalizing" life.[56]

These formulations also have an exciting potential for use as preexposure prophylaxis (PrEP). Macaque data for GSK-744 is at least as impressive as initial animal data for tenofovir for both vaginal and rectal protection, and the considerable complications of adherence for oral PrEP are overcome by perhaps needing an injection only every three months. This research should be fast-tracked as an urgent priority. (See "Preventive Technologies," p. 55, for details.)

Challenges remain, however. First, in the absence of an antidote for both drugs, oral lead-in dosing will be necessary to safeguard against serious adverse events, including rare but life-threatening hypersensitivity reactions. Lead-in dosing with a standard oral combination may also be necessary to achieve an undetectable viral load before using the dual long-acting combination as maintenance therapy. Second, it is unclear how best to manage drug interactions after long-acting antiretrovirals have been given (e.g., rifampin-inclusive treatment for TB if it is diagnosed later). Third is the challenge of the pharmacokinetic "tail" at the end of the dose, when drug concentrations fall below their inhibitory concentrations and increase vulnerability to drug resistance, especially if the subsequent dosing is missed due to adherence or supply issues, and an oral regimen is not started promptly. Fourth, it is uncertain if the volume of injections for both drugs, given by multiple injections, will affect their acceptability by people living with HIV.

A new collaborative research group, to be centralized at the Johns Hopkins University School of Medicine in Baltimore, is hoping to bridge regulatory, manufacturing, research, and community interests in the field (both authors of this chapter will serve on its executive committee).

S/GSK1265744

S/GSK1265744 (GSK-744) is an INSTI and an analog of dolutegravir. It is being developed as a formulation for long-acting parenteral administration (GSK-744 LAP) and as an oral tablet for once-daily dosing.

Two phase I placebo-controlled evaluations of oral GSK-744 have been reported.[57,58] In both trials, HIV-positive individuals received 5 mg or 30 mg GSK-744 once daily for 10 days. Mean viral-load decreases of 2.2–2.5 log copies/mL were observed, and the drug was well tolerated.

Data are also available from phase I evaluations of long-acting GSK-744. In a single-dose study, 56 HIV-negative adults received 100, 200, 400, or 800 mg intramuscular injections of GSK-744 LAP, or 100, 200 or 400 mg subcutaneous injections of GSK-744 LAP.[58] The half-life of GSK-744 ranged from 21 to 50 days, compared with 30 to 40 hours for the oral drug, with drug detectable in plasma for up to a year. The 200, 400, and 800 mg intramuscular doses and 400 mg subcutaneous dose were associated with sustained concentrations, for at least 24 weeks, similar to that associated with viral-load reductions of 2.5 log copies/mL seen using 30 mg oral dosing. Injection-site reactions were the most common adverse event, with erythema and nodules being more common among those receiving subcutaneous doses of the drug.

A second phase I trial randomized 47 HIV-negative volunteers to one of four cohorts.[59] All study participants first took 14 days of 30 mg of daily oral GSK-744. After a seven-day washout period, all volunteers received an 800 mg of GSK-744 LAP (two 400 mg intramuscular injections). At week four, one cohort received 200 mg subcutaneous GSK-744 LAP, with injections repeated at weeks 8 and 12; the second cohort received 200 mg intramuscular GSK-744 LAP, also repeated at weeks 8 and 12, with 1,200 mg long-acting rilpivirine (rilpivirine-LA) coadministered at week 8, and 900 mg coadministered at week 12; the third cohort received 400 mg intramuscular GSK-744 LAP at weeks 4, 8, and 12, along with 600 mg rilpivirine-LA at week 12. In the fourth cohort, a second 800 mg intramuscular injection of GSK-744 LAP was administered at week 12.

Plasma concentrations of GSK-744 and rilpivirine remained well above the IC90, comparable to the 30 mg oral dose of GSK-744. All regimens were well tolerated. Two discontinuations were due to dizziness and a transient rash. Though most study participants experienced injection-site reactions, such as pain, tenderness, and nodules, they were mostly mild in intensity, although more common in volunteers receiving subcutaneous, compared with intramuscular, injections.

Encouraging results on the efficacy and safety of this dual combination as maintenance therapy using oral formulations are already available, with 48-week data from the phase II LATTE study presented at CROI 2014.[60]

The LATTE study enrolled 243 treatment-naive HIV-positive individuals generally in early infection. Median baseline CD4 count was 410 cells/mm^{3,} and only

15 percent of participants entered the study with viral loads above 100,000 copies/mL. Patients were randomized to a six-month lead-in course of three-drug therapy consisting of either GSK-744 (10, 30, or 60 mg) or efavirenz plus TDF/emtricitabine or abacavir/lamivudine. At week 24, if viral loads were <50 copies/mL, those receiving GSK-744 substituted their NRTIs for 25 mg oral rilpivirine; those in the efavirenz arm continued their NRTI backbone.

At week 24, viral load was <50 copies/mL in 87 percent of those in the GSK-744 arms compared with 74 percent in the efavirenz arm. In the primary endpoint week-48 analysis, which included those who did and did not meet the maintenance therapy requirement, 82 percent of those in the GSK-744 arms, compared with 71 percent of those in the efavirenz arm, had viral loads <50 copies/mL.

Limiting the analysis to the 47 patients in the efavirenz arm and 160 patients in the GSK-744 arms who met the viral-load criteria for continuing in the maintenance phase of the study, between 91 and 96 percent maintained on GSK-744 plus rilpivirine, compared with 94 percent of those continuing efavirenz plus two nucleoside analogues, had viral loads <50 copies/mL at week 48. Rates of virologic failure in the maintenance population averaged 6 percent in the combined GSK-744 arms, compared with 4 percent in the efavirenz arm.

One patient with persistently low GSK-744 and rilpivirine plasma concentrations developed treatment-emergent INSTI and NNRTI mutations during the study.

As for adverse events, central nervous system effects were more commonly seen in the efavirenz arm. Headache was more common in the GSK-744 arms (22% percent vs. 11% in the efavirenz arm). Most adverse events were mild to moderate in intensity.

The LATTE study will continue for 96 weeks of follow-up. The phase II long-acting maintenance therapy trial, dubbed LATTE 2, is expected to begin this year.

Long-Acting Rilpivirine

As reported in the *2013 Pipeline Report*, a phase I, open-label, two-cohort, single-sequence crossover study looking at the effects of oral coadministration

of rilpivirine with S/GSK1265744 or dolutegravir found no clinically significant interaction, supporting coadministration of the drugs.[61] Rilpivirine-LA is also being evaluated as a potential PrEP agent, as described in "Preventive Technologies," p. 55.

The clinical development of long-acting rilpivirine for therapeutic purposes is being conducted primarily by ViiV Healthcare, in collaboration with Janssen Pharmaceuticals.

NEW TARGETS AND COMPOUNDS OF INTEREST

Monoclonal Antibodies

PRO 140, originally developed by Progenics and now owned by CytoDyn, is a monoclonal antibody targeting CCR5. Phase I and phase II studies exploring single-dose intravenous infusions of PRO 140 at doses of 5 mg/kg or 10 mg/kg reported mean maximum viral-load reductions of 1.8 log copies/mL in the absence of other antiretrovirals.[62,63] Weekly (162 mg and 324 mg) and biweekly (324 mg) subcutaneous administration has also been evaluated, yielding mean viral-load reductions of 1.37 log to 1.65 log copies/mL and no serious adverse events.[64]

Though no new PRO 140 data have been reported since 2010, phase IIb studies are planned in collaboration with Drexel University College of Medicine in Philadelphia.[65] In addition to PRO 140's potential for people with multiclass-resistant HIV, CytoDyn is focusing on a treatment substitution strategy that calls for alternating between daily oral dosing of standard antiretrovirals and PRO 140 administration (i.e., three months of daily oral antiretroviral treatment followed by three months of weekly injections of PRO 140, followed by a return to daily oral antiretrovirals).[66]

Ibalizumab (TMB-355) is an HIV-neutralizing monoclonal antibody that binds to CD4 and blocks HIV entry postattachment. It is being developed, albeit slowly, by TaiMed Biologics, after passing through the hands of Biogen, Tanox, and Genentech. Phase Ia data were published in 2004,[67] phase Ib data were published in 2009,[68] phase IIa data were reported in 2006,[69] and phase IIb data (exploring ibalizumab 800 mg every two weeks or 2,000 mg ever four

weeks in treatment-experienced patients) were reported in 2011.[70] Mean viral-load reductions of −0.95 to −1.96 were reported, with no severe drug-related adverse events reported among the 247 study volunteers who have received the drug, via intravenous administration, thus far.

No additional phase II or phase III treatment protocols have been announced, other than an ongoing investigator-sponsored protocol that allows for those in the phase IIb clinical trial to continue receiving ibalizumab with optimized background therapy.[71] TaiMed reports that the monoclonal antibody has been reformulated for intravenous or subcutaneous administration and that safety and tolerability data from an evaluation of subcutaneous ibalizumab are anticipated at ICAAC 2014 in September. Trials to determine the optimal dosing of subcutaneous ibalizumab are planned for 2014 and 2015.

Ibalizumab's slow development is disconcerting, given its potential for people with multiclass-resistant HIV and at the end of their therapeutic rope. It would behoove TaiMed, along with other manufacturers with compounds with the potential for targeted roles in the management of multiclass-resistant HIV, to explore orphan drug status with the FDA and other regulatory agencies.

As the efficacy and tolerability barrier becomes increasingly raised for the development of first-line antiretroviral therapy, compounds that could be highly effective for people with drug resistance risk being left on the shelf.

Luckily, extensive drug resistance affects only a small minority of people. The low numbers clearly support an option for development under orphan-drug regulations. The risk–benefit ratio for a drug with clear efficacy against multiclass-resistant HIV is very different from that of compounds for first- or second-line use: pill count, convenience of dosing, and even tolerability become less essential compared with viral activity. We noted this opportunity in our *2010 Pipeline Report*.[72]

Another neutralizing monoclonal antibody in phase I studies is VRC01, being developed by the Vaccine Research Center of the U.S. National Institutes of Health.[73,74] How VRC01 will continue to be developed as ARV therapy remains unclear. Its potential as a broadly neutralizing antibody to prevent mother-to-child transmission has been well characterized,[75] though plans to conduct clinical trials in low-income settings where monoclonal antibodies may remain out of reach due to their anticipated expense remain controversial.[76]

Maturation Inhibitors

Maturation inhibitors target the final stage of HIV Gag processing that inhibits release of fully formed capsid, and as a new class would overcome currently drug-resistant HIV. Early studies focused on the compound beviramat (PA-457), and have been featured in our earlier pipeline reports. Beviramat was acquired by Myriad Pharmaceuticals from Panacos in 2009 and was ultimately discontinued by Myriad in June 2010.

Second-generation maturation inhibitors, including DFH-055 and DFH-110, are to be developed by DFH Pharma—founded in 2011 by the former chief scientific officer and a senior vice president of Panacos—in collaboration with the Hetero Group in Hyderabad, India. No additional details have been made available since the original partnership announcement in April 2013.[77]

A maturation inhibitor being developed by GlaxoSmithKline is GSK2838232. A phase I study has been completed, though no results have been reported or published. The study evaluated the initial safety, tolerability, and pharmacokinetics profile following single doses of 5, 10, or 20 mg GSK2838232, along with the effects of food and ritonavir on the drug's bioavailability and pharmacokinetics in HIV-negative individuals.[78]

Transcription Factors: RNase H Inhibitors

After reverse transcriptase has copied RNA into DNA, ribonuclease H (RNase H) must degrade the HIV RNA that remains attached to the newly created DNA so that HIV's genetic material can be successfully integrated into the host cell's genome.[79] The critical role of RNase H in the HIV life cycle makes it an ideal target, and the development of high-throughput screening assays has enabled an increased development pace for inhibitors of the enzyme's activity.

Though numerous small molecules with good inhibitory potency against RNase H have been published since 2003, the discovery of compounds with potential for animal and human dosing remains in its infancy.[80]

Transcription Factors: Regulatory and Accessory Protein Inhibitors

HIV regulatory proteins (Tat and Rev) and accessory proteins (Nef, Vpu, Vpr, and Vif) all play critical roles in the HIV life cycle and replication process,

rendering them candidates as drug targets. Compounds with inhibitory potential against these translation factors are in various stages of preclinical development.

Cellular Factors: LEDGF/p75

There has been growing interest in lens-epithelial-derived growth factor (LEDGF/p75), a cellular protein that binds to HIV integrase and is needed for replication. Inhibitors of this interaction, a series of compounds dubbed LEDGINs, were first described in 2010 and remain in preclinical development.[86] LEDGINs may be synergistic with approved integrase inhibitors and are active against integrase inhibitor–resistant strains of HIV, and therefore hold promise for further clinical development.[87]

One of the more promising non-catalytic inhibitors of HIV integrase is BI 224436.[81] Unfortunately, plans for a phase I study in humans was withdrawn last year.[82] Encouragingly, though, almost all major pharmaceutical companies active in HIV research and development have taken significant interest in the class, and inhibitors may soon enter clinical trials.[83]

CONCLUSION

The antiretroviral pipeline continues to produce compounds with the potential to further improve HIV treatment with highly efficacious, safe, and easy-to-use drugs.

The development of new long-acting formulations is particularly exciting. The research and development of new products and formulations must remain a priority, along with scientifically rigorous evaluations of patient acceptability.

Dolutegravir's robust drug resistance profile demonstrated in studies completed to date warrants more intensive support to determine whether this could overcome one of the most significant inadequacies associated with NNRTI-based treatment in settings where viral load testing and resistance assays are more rarely available.

The lack of prioritized drug development for people with multiclass-resistant HIV is worrisome. Though the prevalence of HIV resistant to multiple classes

of available antiretrovirals is decreasing, at least in Western Europe (extensive three-class resistance peaked at 4.5% in 2005 and decreased thereafter),[84] this is ultimately of little comfort to those who are dependent on new drugs as lifesaving treatment. Using the existing regulatory option of granting orphan-drug status to compounds to be used for this indication will be an important incentive for the research and development of therapies with potential efficacy against multiclass-resistant HIV.

With respect to the continued development of drugs with potential as both first- and second-line therapy, the pharmaceutical industry in general should increase its focus on the large untapped markets, including in the United States, where the majority of people living with HIV are not being effectively linked to, or retained in, clinical care and therefore have not yet commenced (or been well maintained on) antiretroviral therapy. Robust support of existing, evidence-based programs intended to facilitate access to care and treatment must feature prominently in industry product launch, marketing, sales, and community support plans.

Pressure is likely to increase for the development of a two-tier system of access, even within the wealthiest countries—based on lower-cost generics. We warned of this in the conclusion of last year's antiretroviral chapter, and we feel compelled to repeat that this needs to be resisted. Even at current prices, antiretroviral therapy is one of the most economical medical interventions. We want it to become even better, and for these advances to become widely available to all.

It is critical to prepare the U.S., European, and other wealthy markets for the increasing use of generic versions of antiretrovirals recommended by the U.S. Department of Health and Human Services as highly effective components of treatment regimens, with the potential for significant cost savings to people living with HIV and to health care systems.

Pharmaceutical companies developing and marketing originator products should price their existing and future products based on the changes in economic realities facing health care systems in rich countries, including the challenge from generics. This is dependent on next-generation drugs having an evidence base that proves significant advantages over older off-patent antiretrovirals.

ENDNOTES

CROI: Conference on Retroviruses and Opportunistic Infections
EACS: European Conference on AIDS
ICAAC: Interscience Conference on Antimicrobial Agents and Chemotherapy
IAC: International AIDS Conference (World AIDS Conference)
IAS: IAS Conference on HIV Pathogenesis, Treatment and Prevention

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Preventive Technologies: Antiretroviral and Vaccine Development

By Tim Horn and Richard Jefferys

The U.S. Food and Drug Administration (FDA) approval of co-formulated tenofovir DF and emtricitabine (Truvada) as preexposure prophylaxis (PrEP) has transformed the HIV prevention landscape, though perhaps more in theory than reality. Uptake of PrEP has been slow, including among men who have sex with men (MSM), but a gradual uptick in U.S. prescriptions is expected with the recent publication of U.S. Public Health Service guidelines providing critical information to help health care providers and at-risk individuals evaluate the suitability of PrEP and to ensure that those who choose this prevention method have the comprehensive and coordinated support they require to remain HIV-negative.[1]

Clinical trials of tenofovir DF and emtricitabine have indicated significant efficacy as PrEP—if it is taken daily as prescribed. Adherence has been described as "the single biggest Achilles heel in all the PrEP studies," as has been evident in the highly variable results from clinical trials reported to date.[2] There are also toxicity, drug resistance, and cost considerations. As a result, there is profound interest in antiretrovirals in the preventive technologies pipeline, including additional agents for oral use, long-acting injectables, and a robust portfolio of products for vaginal and rectal administration: gels, tablets, rings, films, and nanofibers.

An effective preventive HIV vaccine also remains highly desirable, but frustratingly elusive. The surprising—albeit slight—efficacy seen with a poxvirus vector prime/protein boost (ALVAC/AIDSVAX) in the RV144 trial in Thailand exposed how ill-prepared the HIV vaccine field was to respond to success.[3] The RV144 results were announced in 2009, but as yet no confirmatory trials have been launched, largely due to the need to produce a new envelope protein boost to replace the discontinued AIDSVAX.

Efficacy trials aiming to build on RV144 are planned, but hopes that they might begin in 2014 have not been borne out. The estimated start date is now 2016 at the earliest. In the meantime, a variety of other candidates are being evaluated for safety and immunogenicity; whether any will eventually

advance further is unclear. The greatest promise for the future may lie in the accumulating number of broadly neutralizing antibodies (bNAbs) that have been discovered, and recent advances in understanding both how these bNAbs are generated by the human immune system and how they interact with the HIV envelope to accomplish neutralization. A vaccine capable of inducing bNAbs remains the holy grail for the HIV vaccine field, and these developments suggest that it is possible.

ANTIRETROVIRALS FOR PREVENTION

Table 1. PrEP and Microbicides Pipeline 2014

Agent	Class/Type	Delivery	Manufacturer/Sponsor(s)	Status
Truvada (tenofovir DF/emtricitabine) oral PrEP demonstration projects	Combined nucleoside and nucleotide reverse transcriptase inhibitors	Oral	Gilead/U.S. Centers for Disease Control and Prevention	Phase IV
Truvada (tenofovir DF/emtricitabine) intermittent/as-needed dosing	Combined nucleoside and nucleotide reverse transcriptase inhibitors	Oral	HIV Prevention Trials Network, French National Agency for Research on AIDS and Viral Hepatitis	Phase III
dapivirine	Reverse transcriptase inhibitor	Vaginal ring	International Partnership for Microbicides/Microbicide Trials Network	Phase III
tenofovir	Nucleotide reverse transcriptase inhibitor	Vaginal gel	CONRAD	Phase III
tenofovir	Nucleotide reverse transcriptase inhibitor	Rectal gel	CONRAD	Phase II
maraviroc, maraviroc + tenofovir DF, maraviroc + emtricitabine	CCR5 inhibitor	Oral	HIV Prevention Trials Network, AIDS Clinical Trials Group	Phase II
GSK1265744	Integrase strand transfer inhibitor	Long-acting injectable	ViiV Healthcare, HIV Prevention Trials Network	Phase II
rilpivirine	Non-nucleoside reverse transcriptase inhibitor	Long-acting injectable	PATH, HIV Prevention Trials Network	Phase II
dapivirine	Reverse transcriptase inhibitor	Vaginal gel	International Partnership for Microbicides	Phase I/II
tenofovir	Nucleotide reverse transcriptase inhibitor	Vaginal tablets	CONRAD	Phase I

Agent	Class/Type	Delivery	Manufacturer/Sponsor(s)	Status
tenofovir/emtricitabine	Combined nucleoside and nucleotide reverse transcriptase inhibitors	Vaginal tablets	CONRAD	Phase I
tenofovir	Nucleotide reverse transcriptase inhibitor	Vaginal ring	CONRAD	Phase I
tenofovir DF	Nucleotide reverse transcriptase inhibitor	Vaginal ring	Albert Einstein College of Medicine	Phase I
maraviroc	CCR5 inhibitor	Vaginal ring	International Partnership for Microbicides/Microbicides Trials Network/NIAID/National Institutes of Mental Health (NIMH)	Phase I
maraviroc + dapivirine	CCR5 inhibitor, reverse transcriptase inhibitor	Vaginal ring	International Partnership for Microbicides/Microbicides Trials Network/NIAID/NIMH	Phase I
MZC (MIV-150/zinc acetate/carrageenan) vaginal gel	Non-nucleoside reverse transcriptase inhibitor	Vaginal gel	Population Council	Phase I
dapivirine	Reverse transcriptase inhibitor	Thin film polymer	International Partnership for Microbicides	Phase I
ibalizumab	Monoclonal antibody	Long-acting injectable	TaiMed/Aaron Diamond AIDS Research Center	Phase I

Oral Preexposure Prophylaxis (PrEP)

Following FDA approval of co-formulated tenofovir DF and emtricitabine as PrEP in July 2012, two broad objectives have emerged:

- continued development and implementation of demonstration projects,[4] cost-benefit analyses, guidelines to shepherd prescribing and follow-up practices in a variety of clinical care and community-based settings,[5] and affordable scale-up in the United States and other countries where PrEP has been identified as a potentially useful prevention modality; and
- ongoing research and development of agents and optimized delivery mechanisms to further minimize safety concerns and to maximize adherence and, ultimately, effectiveness.

Tenofovir DF and Emtricitabine

Topline results from the five clinical trials reviewed by the FDA's Antiviral Drugs Advisory Committee in May 2012 recommending the approval of tenofovir DF/emtricitabine as PrEP against sexual transmission of HIV are summarized in our *2013 Pipeline Report*. Three trials demonstrated protective efficacy: iPrEx, which enrolled MSM and transgender women, primarily in Peru and Ecuador; Partners PrEP, involving HIV-serodiscordant heterosexual couples in Uganda and Kenya; and TDF2, a U.S. Centers for Disease Control and Prevention (CDC) study that enrolled single heterosexual men and women in Botswana.[6,7,8] Two studies, both of which were limited to women, failed to demonstrate protective efficacy: the FEM-PrEP trial, conducted in Kenya, Malawi, South Africa, and Tanzania; and the VOICE study, the largest of all five studies and conducted in South Africa, Uganda, and Zimbabwe, with final results reported in March 2013.[9,10]

Results from a clinical trial evaluating daily tenofovir DF as PrEP for people who inject drugs were published soon after the *2013 Pipeline Report* went to press. Though the CDC–sponsored Bangkok Tenofovir Study demonstrated a statistically significant reduction in risk of HIV acquisition of 49 percent among 2,413 men and women who inject drugs in Bangkok, Thailand (95% CI: 9.6–72.2; P = .01)—the efficacy was 71 percent among those who opted to receive directly observed therapy (DOT) and 84 percent among those with 97.5 percent adherence, as determined by drug level measurements—the extent to which tenofovir DF truly protected against parenteral exposure to HIV remains a matter of debate.[11,12]

The Bangkok Tenofovir Study failed to demonstrate efficacy during the first three years of the trial when reported needle sharing was highest among trial participants. Only during the subsequent four years of the trial, when the number of participants presenting for follow-up dwindled and rates of needle sharing declined, was there a divergence in infection rates among those who received tenofovir compared with those on placebo. This led academics and advocacy groups—many of which had long-standing concerns about the study's ethical practices and the failures of the sponsor and investigators to address activists' concerns[13]—to question whether tenofovir's efficacy was more directly related to sexual exposure during the study's seven-year follow-up period.[14] However, in his oral review of the efficacy and additional adherence data from the trial at the 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention in July 2013 in Kuala Lumpur, Michael Martin, MD, of the

CDC noted the likelihood of a statistical fluke during the first three years of the study, created in part by the very low HIV incidence in the tenofovir and placebo arms.[12] Additionally, according to a multivariate analysis presented at the conference, sharing needles, a history of incarceration, or being under 30 years of age were the only risk factors associated with HIV infection in the study.[15] Reporting sex with domestic, casual, or same-sex partners was not associated with HIV infection.

Aside from ongoing tenofovir DF/emtricitabine PrEP demonstration projects, two closely watched clinical trials—the HIV Prevention Trials Network (HPTN) ADAPT study and the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) IperGay study—are exploring the efficacy of intermittent dosing of Truvada.[16,17]

Maraviroc

CCR5-tropic HIV—virus that utilizes the CCR5 coreceptor on CD4 cells to gain entry and establish infection—is responsible for more than 95 percent of new sexually transmitted infections of the virus.[18,19] In turn, there has been interest in studying the CCR5 antagonist maraviroc (Selzentry) for potential use as PrEP. Compared with tenofovir and emtricitabine, maraviroc may be associated with a reduced risk of adverse events, such as kidney toxicity and bone mineral density depletion. Because its mechanism involves blockade of cellular rather than viral protein functioning, maraviroc may also minimize the risk of developing drug resistance. The drug, administered systemically, also penetrates and concentrates well in cervical, vaginal, and rectal tissues.[20,21]

Results from preclinical studies involving animals have been mixed. Oral maraviroc prevented HIV infection in a humanized mouse model involving vaginal challenge with the virus.[22] In a study involving macaques, however, maraviroc failed to protect against rectal challenges with simian/human immunodeficiency virus (SHIV), despite high concentrations of the drug in rectal tissue.[23]

Three human studies are under way. The first is NEXT-PrEP, a phase II clinical trial being conducted by the HIV Prevention Trials Network (HPTN 069) and the AIDS Clinical Trials Group (A5305).[24] It has an estimated enrollment of 600 HIV-negative MSM and at-risk women, with an anticipated completion date of July 2015. NEXT-PrEP is primarily a safety and tolerability trial comparing four arms: maraviroc, maraviroc plus emtricitabine, maraviroc plus tenofovir DF, and tenofovir DF plus emtricitabine.

Another study, MARAVIPREX, is being conducted by the Fundació Lluita contra la SIDA in Barcelona and is evaluating the capacity of maraviroc to protect against HIV in samples of rectal mucosa from HIV-negative volunteers.[25] The third trial is MVC-PREP, which is being conducted at Emory University and is evaluating concentrations of maraviroc in the blood and genital tracts of HIV-negative women.[26]

Long-Acting Formulations

A significant challenge in the oral PrEP clinical trials completed to date was adherence, which has been demonstrated to be directly related to levels of protection. For example, in Partners PrEP, the intention-to-treat (ITT) efficacy of tenofovir/emtricitabine was 75 percent, and the estimated adherence, determined using blood measures of drug concentrations, was 75 to 80 percent. In iPrEx, which yielded a more moderate tenofovir DF/emtricitabine efficacy of 44 percent in the ITT analysis, the estimated adherence rate was 51 percent. In the VOICE study, which found that tenofovir DF/emtricitabine wasn't efficacious, adherence was estimated at 29 percent.[27]

Improving the acceptability of PrEP is one approach to strengthening adherence rates among populations at risk for HIV infection. A particular focus is the development of long-acting parenteral nanosuspensions of antiretrovirals with PrEP potential, which may allow for monthly or quarterly, rather than daily, dosing. The two long-acting drugs furthest along this development path are GSK1265744 (GSK744 LA), ViiV Healthcare's integrase strand transfer inhibitor (and dolutegravir analog), and rilpivirine (Edurant; RPV LA), Janssen's non-nucleoside reverse transcriptase inhibitor.

Data from a study evaluating the protective effects of GSK744 LA in macaques rectally challenged with simian-human immunodeficiency virus (SHIV) were presented at the 21st Conference on Retroviruses and Opportunistic Infections (CROI) in March 2014 in Boston. Chasity Andrews of the Aaron Diamond AIDS Research Center in New York administered single injections of GSK744 LA to 12 macaques (four received placebos) and challenged the animals with SHIV on a weekly basis.[28] Whereas monkeys that received placebo injections all became infected within seven weeks, the GSK744 LA–treated macaques were protected for six to 17 weeks. No animals were infected as long as the GSK744 drug levels remained three times the concentration inhibiting 90 percent of viral replication (IC90). Interpreting these results in tandem with those from a human pharmacokinetics study presented previously,[29,30] Andrews noted that 800 mg

injections maintained plasma levels three times the IC90 for 12 to 16 weeks, indicating that quarterly administration should result in high-level protection.

Also presented at CROI 2014 were data from a CDC study that treated six female macaques with GSK744 LA and six with placebo.[31] Three injections, once a month, were administered. Whereas the six placebo-treated monkeys were all infected by week 11 (all but one within five weeks), none of the GSK744 LA–treated macaques were infected during the twelve-week study. Gerardo García-Lerma, presenting for the CDC, cautioned that concentrations of GSK744 were lower in both vaginal (20% lower) and rectal tissues (50% lower) compared with plasma, though he also noted that GSK744 LA's protection is likely dependent on both systemic and tissue concentrations of the drug.

Encouraging phase I data from a study evaluating the pharmacokinetics of RPV LA in plasma, the genital tract in females, and the rectum in males were reported at the 19th CROI in Seattle.[32]

A phase II study of GSK744 LA is under way. ÉCLAIR, being conducted in the U.S. by ViiV Healthcare, is enrolling 120 at-risk men (60% MSM).[33] Volunteers will receive 30 mg daily oral dosing or placebo for four weeks. Following a one-week washout period, intramuscular (IM) injections of 800 mg GSK744 LA, or placebo, will be administered every 12 weeks for a total of three injections. A second study, HPTN 077, is in development and will enroll 160 at-risk women (60%) and men in the United States, South America, and sub-Saharan Africa.[34] The primary objective of both studies is to assess the safety, tolerability, and acceptability of GSK744 LA.

The safety, tolerability, and acceptability of RPV LA are to be evaluated in a phase II clinical trial: HPTN 076. Following an oral lead-in period, 132 HIV-negative women will receive IM injections of 1,200 mg RPV LA or placebo, once every eight weeks, over a 44-week period.[35] The study is to be conducted at four sites in the United States, South Africa, and Zimbabwe.

Another long-acting agent being explored for its preventive potential is ibalizumab, a monoclonal antibody being developed by TaiMed in collaboration with the Aaron Diamond AIDS Research Center and the Bill & Melinda Gates Foundation. A phase I clinical trial, involving 24 HIV-negative volunteers and evaluating a newly developed subcutaneous formulation of the monoclonal antibody with potential for large-scale administration over the currently available intravenous formulation, has been completed.[35]

Microbicides: Vaginal and Rectal Gels

A gel containing one percent tenofovir continues to undergo confirmatory testing as a vaginal microbicide, following the completion of one clinical trial (CAPRISA 004) demonstrating a 39 percent reduced risk of acquiring HIV—along with a 51 percent reduction in the risk of acquiring herpes simplex virus 2 (HSV-2)—and another trial (VOICE) that failed to demonstrate a statistically significant benefit, likely because of poor adherence.[36,37]

FACTS 001, a pivotal phase III placebo-controlled clinical trial being conducted by CONRAD in collaboration with the Follow-on African Consortium for Tenofovir Studies (FACTS) and the U.S. Agency for International Development (USAID), has an estimated enrollment of 2,900 HIV-negative women in South Africa, including 899 women in a high-incidence area of KwaZulu-Natal, with preliminary data anticipated by the end of 2014.[38] As with CAPRISA 004, volunteers are being instructed to use the tenofovir gel or matching placebo within 12 hours before and 12 hours after intercourse (BAT-24 regimen). If the results of FACTS 001 are affirmative, applications for approval are likely to be submitted to regulatory agencies.

There is also CAPRISA 008, an open-label study providing additional safety data and an evaluation of the feasibility and effectiveness of providing one percent tenofovir gel to HIV-negative women through family planning clinics.[39] The trial is open to CAPRISA 004 participants and women from communities in which the trial was conducted.

A reduced-glycerin one percent tenofovir gel for rectal use is in a phase II study. The new formulation developed by CONRAD has an improved osmolarity profile, meaning that it contains fewer sugars and salts relative to epithelial cells and therefore prevents tissues from purging too much water. This, in turn, may prevent damage to the structural integrity of the rectum's lining and also help minimize gastrointestinal side effects.[40] The phase II Microbicide Trials Network (MTN) 017 trial is evaluating the safety and acceptability of daily or episodic (applied before and after receptive anal intercourse) reduced-glycerin one percent tenofovir gel, compared with daily oral tenofovir/emtricitabine, in roughly 186 HIV-negative MSM and transgender women in Peru, South Africa, Thailand, Puerto Rico, and the United States.[41]

The Population Council is developing a combination gel containing the non-nucleoside reverse transcriptase inhibitor MIV-150, zinc acetate, and carrageenan (MZC). In initial studies of the MZC gel, a single application provided eight hours of protection to macaques challenged vaginally with SHIV.[42,43] Gels containing zinc acetate and carrageenan have also been shown to protect against HSV-2 vaginal and rectal challenges in mice.[44] Additionally, carrageenan has activity against human papillomavirus (HPV) infection.[45,46,47,48]

Most recently, a modified MZC gel—containing buffers, co-solvents and preservatives suitable for human trials—protected macaques against SHIV infection when applied up to eight hours prior to vaginal challenge.[49] The gel was also protective against rectal challenges in mice, but not in macaques. Protection against HSV-2 as well as HPV-16 (one of the two most common strains associated with precancerous and cancerous cervical and anal disease) has also been documented among MZC gel-treated mice challenged vaginally and rectally.

A phase I safety, pharmacokinetics, and acceptability evaluation of an MZC gel was announced in early 2014 and is expected to begin enrolling approximately 35 HIV-negative women this year.[50]

Microbicide gels in preclinical stages of development for vaginal or rectal use include:

- one percent raltegravir gel, which recently showed potential for postexposure protection of macaques from vaginal SHIV infection in a study conducted by the CDC in collaboration with Merck;[51]
- a gel containing 0.25% IQP-0528, a pyrimidinedione analog in development by ImQuest Biosciences;[52]
- a gel containing griffithsin, an HIV entry inhibitor with activity against CXCR4- and CCR5-tropic virus, being developed by the Population Council;[53]
- a maraviroc-based gel for rectal use, being developed by the International Partnership for Microbicides; and[54]
- three combination gels, also being developed by the IPM.[55] For vaginal use: maraviroc plus dapivirine, and the protease inhibitor darunavir plus dapivirine; for rectal use: maraviroc plus tenofovir.

Microbicides: Vaginal Rings

As with the oral PrEP, ITT efficacy data in clinical trials of microbicide gels have been hobbled by poor adherence rates. In turn, there has been considerable interest in easy-to-administer technologies that can slowly release protective antiretrovirals over the course of weeks or months. Polymeric vaginal rings, 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 clinical and preclinical development.

The most clinically advanced candidate is a silicone elastomer vaginal matrix ring containing 25 mg dapivirine (TMC120), a non-nucleoside reverse transcriptase inhibitor licensed to the International Partnership for Microbicides (IPM) by Janssen Pharmaceuticals. Following the IPM's successful evaluation of dapivirine in 14 phase I/II safety and acceptability studies, the vaginal ring is now in two large efficacy studies.

Preliminary results from the phase III ASPIRE study, sponsored by the Microbicide Trials Network (MTN 020), are anticipated in late 2014.[55] The study is randomizing 3,500 HIV-negative women to receive the dapivirine ring or matching placebo, replaced once a month for a year. The trial is being conducted at sites in Malawi, South Africa, Uganda, Zambia, and Zimbabwe. The Ring Study, a phase II/III evaluation, is comparing the dapivirine ring to a placebo ring, inserted once every week over 24 months, in 1,650 HIV-negative women in South Africa and Rwanda.[56] Data are anticipated in early 2015.

A rationale for developing rings that combine dapivirine with antiretrovirals using different mechanisms—in order to increase the breadth of protection and limit the emergence of drug-resistant HIV—has been established.[57] Results from an IPM and MTN phase I study (MTN 013/IPM 026) evaluating vaginal rings containing 100 mg maraviroc, both with and without 25 mg dapivirine, are mixed.[58] Though all of the rings used in the study of 48 HIV-negative women were generally safe, well tolerated, and acceptable (roughly one in five women said they would prefer not to use the ring during menstruation), only four of the 24 women randomized to receive rings containing maraviroc alone or both drugs had detectable maraviroc in cervical tissue samples. Plasma levels of maraviroc were also below the limits of quantification in most women. The IPM is currently redeveloping the combination ring to achieve protective vaginal and systemic concentrations of maraviroc, with a second phase I study slated for 2015.

Other compounds being evaluated in preclinical and early clinical studies for extended release via vaginal rings include:

- tenofovir DF, currently in a phase I safety and pharmacokinetics study, being conducted by Albert Einstein College of Medicine in New York;[59]
- tenofovir, which achieves protective vaginal concentrations in sheep, and to be developed further by CONRAD;[60]
- griffithsin and MIV-150, being developed by the Population Council;
- DS003, a gp120-binding entry inhibitor developed by Bristol-Myers Squibb that has been licensed to the IPM; and[55]
- dapivirine plus the protease inhibitor darunavir, also in the preclinical stages of development by the IPM.[55]

Microbicides: Vaginal Tablets and Films

A number of groups are evaluating the potential utility of dissolvable films and tablets, both of which may be easier to use and associated with reduced manufacturing costs compared with vaginal gels.

CONRAD is evaluating the potential utility of rapidly disintegrating vaginal tablets containing tenofovir and tenofovir plus emtricitabine. Preclinical testing in rabbits and macaques has demonstrated favorable vaginal tissue and fluid concentrations of both drugs.[61,62] A phase I placebo-controlled safety and pharmacokinetics evaluation of vaginal tablets containing, tenofovir, emtricitabine, and a combination of both drugs in 48 HIV-negative women at Albert Einstein College of Medicine and Eastern Virginia Medical School has been completed, the results of which have not yet been reported.[63]

Preliminary results from a phase I clinical trial (FAME-02) comparing the safety, drug absorption, and drug distribution of a dapivirine film to dapivirine gel were reported at CROI 2014.[64] Plasma levels of dapivirine were comparable across the film and gel arms, suggesting that both products can deliver drugs in a similar manner. While the levels of dapivirine in vaginal tissue were higher in gel users than in those who used film, ex vivo laboratory viral-challenge studies demonstrated that both the film and gel protected against HIV.

Vaginal films in preclinical development include:

- a film dosed with 0.1 percent IQP-0528, being developed by ImQuest;[65]
- a film containing EFdA, a nucleoside reverse transcriptase inhibitor, being evaluated by the Magee Women's Research Institute at the University of Pittsburgh;[66]
- vaginal films containing maraviroc plus tenofovir and maraviroc plus dapivirine; and[55]
- a vaginal tablet containing DS003, also being developed by the IPM.[55]

Multipurpose Prevention Technologies

Male and female condoms are the only prophylactic technology available to protect against pregnancy, HIV, and other sexually transmitted infections (STIs). As has been well documented in the development of oral PrEP and microbicides, however, there is a need for options that women can easily control and do not require the cooperation, consent, or knowledge of their sexual partners. In turn, there is tremendous interest in the development of multipurpose prevention technologies (MPTs) that can double as contraception and biomedical prevention against STIs.

Products currently in preclinical development can be categorized as either long-acting or on-demand. Long-acting MPTs include vaginal rings; on-demand products include gels that can be used around the time of intercourse.

At least three vaginal ring MPTs—all of which employ the contraceptive hormone levonorgestrel, a synthetic progestogen with extensive clinical experience and suitable for formulation in matrix rings—are being developed and are in various stages of preclinical testing:

- A dual-reservoir ring that can release steady levels of tenofovir, with its established activity against HIV and HSV-2, and the hormonal contraceptive levonorgestrel over a 90-day period.[67] It is being developed by CONRAD.
- A 30-day ring containing MIV-150, zinc acetate, carrageenan, and levonorgestrel (MZCL) to protect against pregnancy, HIV, HSV-2, and human papillomavirus (HPV). Prototype development and preclinical evaluation by the Population Council is ongoing.

- A 60-day silicone matrix ring that releases dapivirine and levonorgestrel, also in development by the Population Council.

On-demand products include:

- A reformulated one percent tenofovir gel to include sperm-immobilizing agents that can be used with the silicone single-sized SILCS diaphragm. Preclinical work and plans for early clinical development is being undertaken by CONRAD.
- A carrageenan-based gel containing MIV-150, zinc acetate, and levonorgestrel (MZL) being developed by the Population Council.

PREVENTIVE VACCINES

Table 2. HIV Vaccines Pipeline 2014

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
ALVAC-HIV vCP1521	Canarypox vector including HIV-1 CRF01_AE Env, clade B Gag, the protease-encoding portion of the Pol gene, and a synthetic polypeptide encompassing several known CD8 T-cell epitopes from the Nef and Pol proteins	Sanofi Pasteur/U.S. HIV Military HIV Research Program (USMHRP)/NIAID	Phase IIb
pGA2/JS7 DNA + MVA/HIV62	Prime: DNA vaccine Boost: MVA vector Both including Gag, Pol, and Env genes from HIV-1 clade B	GeoVax/NIAID	Phase IIa
HIVIS 03 DNA + MVA-CMDR	Prime: HIVIS DNA including Env (A, B, C), Gag (A, B), reverse transcriptase (B), and Rev (B) genes Boost: MVA-CMDR including Env (E), Gag (A), and Pol (E) genes	Vecura/Karolinska Institutet/ Swedish Institute for Infectious Disease Control (SMI)/USMHRP	Phase II
LIPO-5	Five lipopeptides comprised of CTL epitopes from Gag, Pol, and Nef proteins	French National Institute for Health and Medical Research-French National Agency for Research on AIDS and Viral Hepatitis (Inserm-ANRS)	Phase II
VICHREPOL	Chimeric recombinant protein comprised of C-terminal p17, full p24, and immunoreactive fragment of gp41 with polyoxidonium adjuvant	Moscow Institute of Immunology/Russian Federation Ministry of Education and Science	Phase II

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
DNA-C + NYVAC-C	Prime: DNA vaccine including clade C Env, Gag, Pol, and Nef genes Boost: NYVAC-C attenuated vaccinia vector including clade C Env, Gag, Pol, and Nef genes	GENEART/Sanofi Pasteur/ Collaboration for AIDS Vaccine Discovery (CAVD)	Phase I/II
MYM-V101	Virosome-based vaccine designed to induce mucosal IgA antibody responses to HIV-1 Env	Mymetics Corporation	Phase I/II
Ad26.ENVA.01	Adenovirus serotype 26 vector including the HIV-1 clade A Env gene	Crucell/IAVI/NIAID/Beth Israel Deaconess Medical Center/Ragon Institute of MGH, MIT and Harvard	Phase I Prime-boost phase I w/ Ad35-ENVA
Ad35-ENVA	Adenovirus serotype 35 vector including the HIV-1 clade A Env gene	Crucell/IAVI/NIAID/Beth Israel Deaconess Medical Center/Ragon Institute of MGH, MIT and Harvard	Phase I Prime-boost phase I w/ Ad26.ENVA.01
Ad35-GRIN/ENV	Two adenovirus serotype 35 vectors, one including HIV-1 clade A Gag, reverse transcriptase, integrase and Nef genes, and the other including HIV-1 clade A Env (gp140)	International AIDS Vaccine Initiative (IAVI)/University of Rochester	Phase I Prime-boost phase I w/ GSK HIV vaccine 732461
Ad5HVR48.ENVA.01	Hybrid adenovirus vector consisting of a backbone of serotype 5 with the hexon protein from serotype 48; includes HIV-1 clade A Env gene	Crucell/NIAID	Phase I
Cervicovaginal CN54gp140-hsp70 conjugate (TL01)	HIV-1 clade C gp140 protein with heat shock protein 70 (Hsp70) adjvant, delivered intravaginally	St George's, University of London/European Union	Phase I
DCVax + poly ICLC	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	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	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 genes from HIV-1 CN54	Chinese Center for Disease Control and Prevention/National Vaccine and Serum Institute/ Peking Union Medical College	Phase I

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
EN41-FPA2	Gp41-based vaccine delivered intranasally and intramuscularly	PX'Therapeutics/ European Commission	Phase I
GEO-D03 DNA + MVA/HIV62B	Prime: DNA vaccine with GM-CSF adjuvant Boost: MVA vector Both vaccines include Gag, Pol, and Env genes from HIV-1 clade B and produce virus-like particles	GeoVax/NIAID	Phase I
GSK HIV vaccine 732461	Gag, Pol, and Nef proteins in proprietary adjuvant	GlaxoSmithKline	Phase I Prime-boost phase I w/ Ad35-GRIN
HIV-1 Tat/delta-V2 Env	Tat and oligomeric ΔV2 Env proteins	Istituto Superiore di Sanità/ Novartis Vaccines	Phase I
MAG-pDNA, Ad35-GRIN/ENV	Multi-antigen DNA vaccine comprising the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVAX, interleukin-12 (IL-12) pDNA adjuvant, delivered using the electroporation-based TriGrid delivery system, two adenovirus serotype 35 vectors, one including HIV-1 clade A Gag, reverse transcriptase, integrase, and Nef genes, and the other including HIV-1 clade A Env (gp140)	IAVI/Profectus Biosciences/ Ichor Medical Systems Incorporated	Phase I
MAG-pDNA, $rVSV_{IN}$ HIV-1 Gag	Multiantigen DNA vaccine comprising the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVAX, IL-12 pDNA adjuvant, attenuated replication-competent recombinant vesicular stomatitis virus (rVSV) vector including HIV-1 Gag protein	Profectus Biosciences/HVTN	Phase I
MV1-F4-CT1	Recombinant measles vaccine vector including HIV-1 clade B Gag, Pol, and Nef	Institut Pasteur	Phase I
MVA.HIVA	MVA vector including a synthetic copy of a major part of HIV's Gag gene and 25 CD8 T-cell epitopes	Impfstoffwerk Dessau-Tornau (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 mothers (PedVacc001)
MVA HIV-B	MVA vector including HIV-1 Bx08 gp120 and HIV-1 IIIB Gag, Pol, and Nef	Hospital Clinic of Barcelona	Phase I

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
PENNVAX-G DNA + MVA-CMDR	Prime: DNA vaccine including HIV-1 clade A, C, and D Env proteins and consensus Gag protein Boost: MVA-CMDR live attenuated MVA vector including HIV-1 clade CRF_AE-01 Env and Gag/Pol proteins DNA component administered intramuscularly via either Biojector 2000 or CELLECTRA electroporation device	NIAID/ USMHRP/Walter Reed Army Institute of Research	Phase I
PolyEnv1 EnvDNA	Vaccinia viruses including 23 different Env genes and DNA vaccine with multiple Env genes	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
rAd35 VRC-HIVADV027-00-VP	Adenovirus serotype 35 vector	Vaccine Research Center/NIAID	Phase I
$rVSV_{IN}$ HIV-1 Gag	Attenuated replication-competent recombinant vesicular stomatitis virus (rVSV) vector including HIV-1 Gag protein	Profectus Biosciences/HIV Vaccine Trials Network (HVTN)	Phase I
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	South Africa AIDS Vaccine Initiative/ HVTN/Novartis	Phase I
SeV-G(NP), Ad35-GRIN	Sendai virus vector encoding HIV-1 Gag protein delivered intramuscularly or intranasally, adenovirus serotype 35 vector including HIV-1 clade A Gag, reverse transcriptase, integrase, and Nef genes	IAVI/DNAVEC	Phase I
LIPO-5, MVA HIV-B, GTU-MultiHIV	Five lipopeptides comprised of CTL epitopes from Gag, Pol, and Nef proteins MVA vector encoding Env, Gag, Pol, and Nef antigens from HIV clade B DNA vector encoding fusion protein of six different HIV genes Given in four different prime-boost combinations	French National Institute for Health and Medical Research-French National Agency for Research on AIDS and Viral Hepatitis (Inserm-ANRS)	Phase I Phase II

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
Ad4-mgag, Ad4-EnvC150	Live, replication-competent recombinant adenovirus serotype 4 vectors encoding HIV-1 clade C Env and HIV-1 mosaic Gag. Formulated either as enteric-coated capsules for oral administration of as an aqueous formulation for tonsillar administration.	NIAID/PaxVax, Inc.	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 antigen Boost: NYVAC vectors encoding Nat-B, CON-S or mosaic Env antigen	HVTN/IPPOX/Center for HIV/AIDS Vaccine Immunology (CHAVI)	Phase I
CN54gp140 + GLA-AF	HIV-1 clade C gp140 protein and glucopyranosyl lipid adjuvant - aqueous formulation (GLA-AF), delivered intramuscularly	Imperial College London/ Wellcome Trust/National Institute for Health Research, UK	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
rAAV1-PG9DP	Recombinant AAV vector encoding the PG9 broadly neutralizing antibody	International AIDS Vaccine Initiative/NIAID/ Children's Hospital of Philadelphia (CHOP)	Phase I
GTU-MultiHIV	DNA vector encoding fusion protein of six different HIV genes, administered by intramuscular, intradermal, or transcutaneous routes	Imperial College London/ European Commission - CUT'HIVAC Consortium	Phase I
MVA-B	MVA vector encoding Env, Gag, Pol, and Nef antigens from HIV clade B	Hospital Clinic of Barcelona	Phase I

The 31 percent reduction in the risk of HIV infection associated with receipt of ALVAC+AIDSVAX in the RV144 trial[3] continues to provide the impetus for the next round of planned efficacy trials. A multi-stakeholder partnership, the Pox-Protein Public-Private Partnership (P5), is leading the research; current P5 members are the Bill & Melinda Gates Foundation, the HVTN, Novartis Vaccines and Diagnostics, Sanofi Pasteur, the South African Medical Research Council, the U.S. Military HIV Research Program, and NIAID/Division of AIDS. The main site of these activities is South Africa, where a two-pronged strategy to follow up on RV144 will unfold under the aegis of the HVTN. One part will involve an evaluation of a regimen closely modeled on the original trial:

an ALVAC vector adapted to encode antigens from HIV subtype C (ALVAC vCP2438) followed by a boost with a bivalent envelope protein containing antigens from two subtype C isolates, formulated with an MF59 adjuvant. These vaccines will initially be tested in a phase I trial, HVTN 100, involving around 240 participants, slated to begin next year. If all proceeds according to plan, a traditional phase III efficacy study, HVTN 702, will follow in 2016, aiming to recruit 5,400 volunteers at high risk for HIV infection and projected to take six years to complete.

The second prong of the strategy is designated the "correlates program" and features a more complex adaptive clinical trial design including combinations of DNA and NYVAC vectors with envelope protein boosts formulated in one of two different adjuvants. Part A of this study, HVTN 701, comprises a phase I evaluation of safety and immunogenicity, while part B will be a phase IIb test of safety, immunogenicity, and efficacy, with a particular focus on identifying immune correlates of protection against HIV infection. Current estimates indicate a 2015 start date for part A, and 2016 for part B.[68,69] In addition to the work in South Africa, the U.S. Military HIV Research Program, which sponsored RV144, plans to conduct a follow-up trial in Thai MSM at high risk of HIV infection, with 2017 as the possible start date.[69]

In parallel with efforts to launch new trials, researchers are sifting through the available samples from RV144 participants in the hope of gaining a better understanding of how the slight degree of protection against HIV acquisition was achieved. Although the analyses are only exploratory, they have identified an association with IgG antibody responses to the V1/V2 region of the HIV envelope, and suggested that IgA antibody responses may have played a detrimental role.[70,71] The IgG antibodies are not neutralizing, but studies published over the last year indicate that they belong to a subclass (IgG3) associated with the mediation of additional antiviral activities including antibody-dependent cellular cytotoxicity and antibody-dependent phagocytosis.[72,73] Furthermore, in a prior trial of AIDSVAX alone that did not show significant protection against HIV, this type of antibody response was not predominant.

A similar tale has emerged from the most recently conducted HIV vaccine efficacy trial, HVTN 505, which studied a prime-boost combination of a DNA and Ad5 vector that included HIV envelope antigens from multiple clades. The results, published in October 2013, showed that vaccination did not reduce the

risk of acquiring HIV.[74] Subsequent evaluation of samples from HVTN 505 has revealed that the regimen induced only low levels of IgG and IgG3 antibody responses to V1/V2 compared with RV144.[75] Other factors that have been suggested as potential contributors to success in RV144 are the specific innate immune profile associated with ALVAC immunization compared with other poxvirus vectors,[76] and an interaction between vaccination and a particular immune response gene, HLA-A*02.[77] Taken together, these findings may offer important clues about the type of immune responses vaccines will need to induce in order to replicate or improve upon the RV144 results.

Several new HIV vaccine candidates have entered clinical trials over the past year. The first assessments of mosaic HIV antigens, delivered by DNA and NYVAC vectors, are now under way. Mosaic antigens, as their name implies, represent amalgams of components from multiple different HIV isolates, optimized to induce immune responses capable of recognizing the diversity of viruses that are circulating globally. Mosaic antigens have shown some promise for reducing acquisition risk in the SIV/macaque model.[78] Vaccine candidates are also being explored in new combinations with the aim of improving immunogenicity; examples include DNA and MVA vectors plus gp140 protein at Imperial College London and DNA and MVA vectors plus lipopeptides under the sponsorship of the French ANRS.

A vaccine based on adenovirus serotype 4 joins a growing roster of replication-competent vectors under evaluation (the others are vesicular stomatitis virus and the Tiantan vaccinia strain). The rationale is that the capacity to replicate allows a vector to induce a more sustained immune response to the antigens it encodes.[79] However, uncertainty persists about the safety of the adenovirus platform due to evidence that a replication-incompetent serotype 5 (Ad5) vector enhanced the risk of acquiring HIV in two efficacy trials, Step[80] and Phambili.[81] A meta-analysis of the three efficacy trials involving Ad5-based HIV vaccines has confirmed a statistically significant, roughly one-third increase in acquisition risk, although this was entirely driven by results from Step and Phambili and was not seen in HVTN 505[82] (although this may be because the latter trial featured exclusion criteria intended to minimize risk and included only one immunization with an Ad5 vector as opposed to three). At a mini-summit sponsored by NIAID in September 2013, it was concluded that no further studies of Ad5 vectors in HIV should be conducted. During the discussions at the mini-summit, it was noted that adenovirus vectors derived from other serotypes may also have the potential to enhance HIV acquisition, by boosting numbers of adenovirus-

specific CD4 T cells that are subsequently drawn to mucosal sites when vaccine recipients are exposed to natural adenovirus infections (which are common in nature). Adenovirus-specific CD4 T cells cross-react to antigens from multiple serotypes.[83] A published report from the mini-summit urges vigilance about this possibility in future studies of adenovirus vectors, while stressing that it remains speculative.[84]

At the beginning of this year, the first human trial was launched of a novel approach that straddles territory between gene therapy and vaccination. The aim is to prevent HIV infection with bNAbs. But instead of attempting to induce bNAb production by the immune system, the approach uses an adeno-associated virus (AAV) vector to deliver them into the body. The AAV vector is injected into muscle tissue, where it then acts as a factory churning out a constant supply of bNAbs. The strategy has shown efficacy in both the macaque[85] and humanized mouse[86] models. The phase I trial, which is taking place in the United Kingdom, represents the culmination of extensive, long-term preclinical development by the research group of Philip Johnson at the Children's Hospital of Philadelphia in close collaboration with (and with sponsorship from) the International AIDS Vaccine Initiative. Results are eagerly anticipated.

Researchers have not given up on trying to solve the difficult problem of inducing the immune system to produce bNAbs with a traditional vaccine. A confluence of developments has renewed optimism that a bNAb-inducing HIV vaccine is achievable. Key among them is the development of a stable version of the three-pronged HIV envelope structure targeted by bNAbs.[87,88] The HIV envelope trimer, as it is called, proved enormously difficult to reproduce for biological studies due to inherent instability and the frustrating tendency for lab-created mimics to fall apart. The solution of this problem has allowed scientists to conduct structural analyses that reveal how different bNAbs interact with the HIV envelope in order to successfully neutralize diverse viral isolates, providing critical information to aid the design of vaccine immunogens.[89,90,91,92,93,94] Complementing this line of research are recent studies describing how bNAb responses are generated in the rare individuals who develop them, which offer insight into how the process might be duplicated with a vaccine.[95,96,97,98]

CONCLUSIONS

The pipeline of antiretrovirals for prevention—agents that can be administered orally, parenterally, vaginally, and rectally, for daily, long-acting, and as-needed use—is robust. Importantly, many of these drugs and formulations are being developed by sponsors who recognize that poor adherence has been a sizeable barrier in clinical trials and, hence, that efforts to improve the acceptability of the preventive methods is a priority.

Continued funding of demonstration projects and implementation research to evaluate facilitators and barriers to PrEP and comprehensive services intended to support adherence and behavioral risk reduction is also essential. Cost-effectiveness evaluations are also needed to drive advocacy in support of strong policies defining comprehensive and coordinated HIV prevention–service delivery under the Affordable Care Act in the United States and through payer programs in low-, middle-, and high-income countries.

On the preventive vaccine front, there are reasons to be optimistic about long-term prospects, but a licensed product is not on the immediate horizon. The question whether the RV144 results can be repeated and improved likely won't be answered until the end of this decade at the earliest. And even if research progresses fruitfully, it is difficult to envisage a bNAb-inducing vaccine being developed until late into the 2020s. There is one approach that might alter this timeline: the hybrid of gene therapy and vaccination that employs an AAV vector to produce a continuous supply of bNAbs in the body; encouragingly, the first human trial began earlier this year, so it should soon be apparent if this novel idea has the potential to progress into efficacy studies.

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Research Toward a Cure and Immune-Based and Gene Therapies

By Richard Jefferys

Introduction

Research working toward the goal of curing HIV infection has rapidly assumed a central, prioritized role within the overall scientific portfolio. Funding has not swelled at the same pace, but there have been signs of change over the past year: in December 2013, President Obama announced an additional $100 million in U.S. government support though the National Institutes of Health (NIH), reassigned from areas now considered redundant.[1] In February 2014 the independent funder amfAR launched the "Countdown to a Cure for HIV/AIDS" campaign, which aims to bolster its cure research program to the tune of US$100 million over six years.[2] The International AIDS Society's "Towards a Cure" initiative is tracking support for cure research in collaboration with AVAC and the HIV Vaccines and Microbicides Resource Tracking Working Group, reporting US$78.2 million in global investments in 2012[3] (the 2013 figures will be released in July 2014).

The number of clinical trials under way has increased substantially since 2013, as has the diversity of approaches being evaluated (see table 1). However, with two notable exceptions, there is no expectation that this early generation of studies will lead to cures; rather, the hope is that information can be generated that will help achieve that goal in the future. One exception comprises the attempts to repeat the outcome achieved in Timothy Ray Brown, the lone adult considered cured of HIV, in other HIV-positive people who have cancers requiring treatment with stem cell transplants. Two trials, one for adults and another for younger individuals (BMT CTN 0903 and IMPAACT P1107), will attempt to locate appropriate stem cell donors heterozygous for the CCR5-Δ32 mutation, as was done in Brown's case. This approach is suitable only for people with life-threatening cancers, due to the high mortality rate associated with stem cell transplantation. The dangers of the procedure were highlighted last year when a 12-year-old boy with HIV and cancer received cord blood stem cells heterozygous for the CCR5-Δ32 mutation, with the aim of curing both diseases, but died shortly afterward due to graft-versus-host disease (a condition that can occur if the transplanted cells are recognized as foreign and attacked by the immune system).[4]

The second instance where there may be reason for optimism about the possibility of achieving cures is a clinical trial based on the case of the "Mississippi baby." This case was first publicly reported at the Conference on Retroviruses and Opportunistic Infections (CROI) in March of 2013 and subsequently published in the *New England Journal of Medicine* last October.[5] An update at CROI 2014 revealed that the child is now over three years old and remains in remission, possibly cured, with no HIV activity detectable after nearly two years off antiretroviral therapy (ART).[6] The salutary outcome is believed to be a result of receiving approximately 18 months of ART that was started immediately after birth. The trial, IMPAACT P1115, to be conducted by the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), involves immediate treatment of babies infected with HIV because their mothers failed to receive appropriate prevention of mother-to-child transmission (PMTCT). While the possibility of sparing these newborns a lifelong burden of ART needs to be pursued, the goal of ensuring that no HIV-positive mother lacks access to PMTCT remains paramount.

The remaining cure research pipeline consists largely of early-phase studies, such as those testing agents that might have the potential to coax the latent HIV reservoir out of hiding. Strategies such as therapeutic vaccination and gene therapy, which were previously considered separately in this chapter of the *Pipeline Report*, are now included under the cure umbrella as they are generally viewed as part of the field. Definitions in this realm can be somewhat fuzzy, however, and some candidates may end up also being assessed to see if they can add benefit to ongoing ART.

As noted in previous *Pipeline Reports*, the number of candidate immune-based therapies being evaluated specifically for use as an adjunct to ART has dwindled. But there remains a potential need: a recent analysis of a large cohort of HIV-positive people receiving ART in Europe reported that 15 percent (835 out of 5,550), of those starting with low CD4 T-cell counts failed to surpass the threshold of 200 cells/mm^3 despite more than three years of HIV viral-load suppression.[7] These individuals faced a significantly increased risk of illness and death. Furthermore, elevated inflammation and immunologic perturbations characteristic of old age, particularly a low CD4/CD8 ratio, can persist among individuals on long-term ART and remain targets for immune-based interventions due to associations with non-AIDS-defining illnesses and mortality.[8,9]

Table 1. Research Toward a Cure 2014: Clinical Trials and Observational Studies

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase
ANTIBODIES				
3BNC117	Broadly neutralizing monoclonal antibody	NCT02018510	Rockefeller University	Phase I
BMS-936559	Anti-PD-L1 antibody	NCT02028403 (not yet open for enrollment)	National Institute of Allergy and Infectious Diseases (NIAID)	Phase I
VRC01	Broadly neutralizing monoclonal antibody	NCT01950325	NIAID	Phase I
CHERUB 001	Intravenous immunoglobulin in primary HIV infection	No clinicaltrials.gov entry yet	CHERUB (Collaborative HIV Eradication of viral Reservoirs: UK BRC)	N/A
ANTIFIBROTIC				
ACE inhibitors		NCT01535235	University of California, San Francisco/ amfAR	Phase IV
ANTIRETROVIRAL THERAPY IN HIV CONTROLLERS				
emtricitabine + rilpivirine + tenofovir		NCT01777997	AIDS Clinical Trials Group (ACTG)/NIAID	Phase IV
ASSEMBLY INHIBITOR				
BIT225	Inhibitor of HIV assembly in macrophages	ACTRN12612000696897 (completed)	Biotron Limited	Phase I
COMBINATIONS				
SB-728-T + cyclophosphamide	Autologous CD4 T cells gene-modified to inhibit CCR5 expression + transient chemotherapy	NCT01543152	Sangamo BioSciences	Phase I/II
romidepsin (trial part A), **Vacc-4x + romidepsin** (trial part B)	HDAC inhibitor + peptide-based therapeutic vaccine	NCT02092116	Bionor Immuno AS/ Celgene	Phase I/II
Vacc-4x + lenalidomide	Peptide-based therapeutic vaccine + immunomodulator	NCT01704781	Bionor Immuno AS	Phase I/II

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase
GENE THERAPIES				
CaI-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	Calimmune	Phase I/II
VRX496	Autologous CD4 T cells -modified with an antisense gene targeting the HIV envelope	NCT00295477 (closed to enrollment)	University of Pennsylvania	Phase I/II
MazF-T	Autologous CD4 T cells gene-modified with MazF endoribonuclease gene to inhibit HIV	NCT01787994	Takara Bio/University of Pennsylvania	Phase I
SB-728-T	Autologous CD4 T cells gene-modified to inhibit CCR5 expression	NCT01044654 (closed to enrollment)	Sangamo BioSciences	Phase I
GENE THERAPIES FOR HIV-POSITIVE PEOPLE WITH CANCERS				
High-dose chemotherapy with transplantation of gene-modified stem cells for high-risk AIDS-related lymphoma	Stem cells gene-modified to express an HIV entry inhibitor C46	NCT00858793	Universitätsklinikum Hamburg-Eppendorf	Phase I/II
Busulfan and gene therapy after frontline chemotherapy in patients with AIDS-related non-Hodgkin's lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-shI-TAR-CCR5RZ)	NCT01961063	City of Hope Medical Center	Not listed
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-shI-TAR-CCR5RZ)	NCT00569985	City of Hope Medical Center	Not listed
Genetically modified peripheral blood stem cell transplant in treating patients with HIV-associated non-Hodgkin's or Hodgkin's lymphoma	Stem cells gene-modified to express an HIV entry inhibitor C46	NCT01769911 (not yet open for enrollment)	Fred Hutchinson Cancer Research Center	Not listed

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase
LATENCY-REVERSING AGENTS				
vorinostat	HDAC inhibitor	NCT01365065 (closed to enrollment)	Bayside Health/Merck	Phase II
disulfiram	Acetaldehyde dehydrogenase inhibitor	NCT01944371	University of California, San Francisco/Monash University/amfAR	Phase I/II
panobinostat	HDAC inhibitor	NCT01680094 (completed)	University of Aarhus/ Massachusetts General Hospital/ Monash University/ Karolinska Institutet/ Novartis/amfAR	Phase I/II
Poly-ICLC	TLR-3 agonist	NCT02071095	Nina Bhardwaj, MD/ Campbell Foundation/ Oncovir, Inc.	Phase I/II
romidepsin	HDAC inhibitor	NCT01933594	ACTG/NIAID/Gilead	Phase I/II
vorinostat	HDAC inhibitor	NCT01319383	University of North Carolina at Chapel Hill/ NIAID/Merck	Phase I/II
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	ACTG	N/A
CHERUB 003	Prospective cohort study evaluating the effects of chemotherapy on the HIV reservoir	NCT01902693	Imperial College London/ CHERUB	N/A
CODEX (the "Extreme" cohort)	Long-term nonprogressors and HIV controllers	NCT01520844	French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	N/A

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase
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, Thailand/Thai Red Cross AIDS Research Centre	N/A
The use of leukapheresis to support HIV pathogenesis studies		NCT01161199	University of California, San Francisco	N/A
Tissue drug levels of HIV medications		NCT01490346	University of Minnesota – Clinical and Translational Science Institute/NIAID	N/A
ULTRASTOP/ERAMUNE-03 (Towards HIV Functional Cure)	Antiretroviral treatment interruption	NCT01876862 (not yet open for enrollment)	Objectif Recherche VACcin Sida (ORVACS)/Fondation Bettencourt Schueller	N/A
STEM CELL TRANSPLANTATION				
BMT CTN 0903	Allogeneic transplant in individuals with chemotherapy-sensitive hematologic malignancies and coincident HIV infection	NCT01410344	National Heart, Lung, and Blood Institute (NHLBI)/ National Cancer Institute (NCI)/Blood and Marrow Transplant Clinical Trials Network	Phase II
Immune response after stem cell transplant in HIV-positive patients with hematologic cancer		NCT00968630	Fred Hutchinson Cancer Research Center	Phase II
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				
DermaVir	Topically applied DNA vaccine	NCT00711230 (closed to enrollment)	Genetic Immunity	Phase II
AGS-004	Personalized therapeutic vaccine utilizing patient-derived dendritic cells and HIV antigens	NCT01069809 (closed to enrollment)	Argos Therapeutics	Phase II
GSK Biologicals HIV Vaccine 732462	p24-RT-Nef-p17 fusion protein vaccine	NCT01218113 (completed)	GlaxoSmithKline	Phase II

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase
GTU-multiHIV + LIPO-5	DNA + lipopeptide vaccines	NCT01492985	French National Institute for Health and Medical Research/French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	Phase II
Tat Protein Vaccine	Recombinant, biologically active HIV-1 Tat protein vaccine	NCT01513135	Barbara Ensoli, MD, Istituto Superiore di Sanità/Italian Ministry of Foreign Affairs – General Direction for Cooperation and Development	Phase II
VAC-3S	Peptide-based vaccine	NCT02041247	InnaVirVax	Phase II
AGS-004	Personalized therapeutic vaccine utilizing patient-derived dendritic cells and HIV antigens	NCT02042248	University of North Carolina at Chapel Hill/ Argos Therapeutics/U.S. National Institutes of Health (NIH)	Phase I/II
Dendritic cell vaccine	mRNA-transfected autologous dendritic cells	NCT00833781 (closed to enrollment)	Massachusetts General Hospital	Phase I/II
Dendritic cell vaccine (DCV-2)	Autologous myeloid dendritic cell vaccine	NCT00402142 (completed)	Hospital Clinic of Barcelona	Phase I/II
Tat Oyi	Tat protein-based vaccine	NCT01793818 (closed to enrollment)	Biosantech	Phase I/II
THV01	Lentiviral vector-based vaccine	NCT02054286	Theravectys S.A.	Phase I/II
Vacc-C5	Peptide-based vaccine with GM-CSF or Alhydrogel adjuvant	NCT01627678 (completed)	Bionor Immuno AS	Phase I/II
AFO-18	Peptide-based vaccine with CAF01 adjuvant	NCT01141205 (completed)	Statens Serum Institut/ Ministry of the Interior and Health, Denmark/ European and Developing Countries Clinical Trials Partnership (EDCTP)	Phase I
AFO-18	Peptide-based vaccine with CAF01 adjuvant	NCT01009762 (completed)	Statens Serum Institut/ Rigshospitalet/Hvidovre University Hospital/ Ministry of the Interior and Health, Denmark	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase
ChAdV63.HIVcons + MVA.HIVconsv	Chimpanzee adenovirus and modified vaccinia Ankara strain (MVA) viral vector vaccines	NCT01712425 (closed to enrollment)	IrsiCaixa/Fundació Lluita contra la SIDA/Hospital Clinic of Barcelona/ HIVACAT/University of Oxford	Phase I
Dendritic cells loaded with HIV-1 lipopeptides	Dendritic cell-based vaccine	NCT00796770 (completed)	Baylor Research Institute/ ANRS	Phase I
D-GPE DNA + M-GPE MVA	DNA and modified vaccinia Ankara strain viral vector vaccines	NCT01881581	Centers for Disease Control and Prevention, China	Phase I
HIVAX	Lentiviral vector-based vaccine	NCT01428596	GeneCure Biotechnologies	Phase I
HIV-v	Peptide-based therapeutic vaccine	NCT01071031 (completed)	SEEK	Phase I
JS7 DNA + MVA62B	DNA and modified vaccinia Ankara strain viral vector vaccines	NCT01378156 (closed to enrollment)	GeoVax, Inc.	Phase I
MAG-pDNA + rVSV$_{IN}$ HIV-1 Gag	DNA and vesicular stomatitis virus viral vector vaccines	NCT01859325	NIAID/Profectus Biosciences, Inc.	Phase I
MVA.HIVconsv	Modified vaccinia Ankara strain (MVA) viral vector vaccine	NCT01024842 (closed to enrollment)	University of Oxford/ Medical Research Council	Phase I
PENNVAX-B (Gag, Pol, Env) + electroporation	DNA vaccine + electroporation	NCT01082692 (completed)	Inovio Pharmaceuticals	Phase I
TREATMENT INTENSIFICATION				
AAHIV (for acute HIV infection)	Combination antiretroviral therapy	NCT00796263	South East Asia Research Collaboration with Hawaii	Phase III
New Era Study	Multi-drug class (MDC) Combination antiretroviral therapy	NCT00908544 (closed to enrollment)	MUC Research GmbH	Not listed
maraviroc	CCR5 inhibitor	NCT00795444 (closed to enrollment)	Fundación para la Investigación Biomédica del Hospital Universitario Ramón y Cajal/Pfizer	Phase II
peginterferon alfa-2b	Cytokine	NCT01935089	University of Pennsylvania/Wistar Institute	Phase II

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase
alpha interferon intensification	Cytokine	NCT01295515	NIAID	Phase I/II
IMPAACT P1115	Very early intensive treatment of HIV-infected infants to achieve HIV remission	NCT02140255	IMPAACT/NIAID/NICHD	Phase I/II
Intense acute infection study	Combination antiretroviral therapy	NCT01154673 (closed to enrollment)	University of Toronto	Phase II/III

Note: Some candidates likely to be the subject of further research are included, although they are not currently in an ongoing trial (entries where the trial is noted as completed). For a more extensive listing of completed trials related to cure research, with links to published and presented results where available, see http://www.treatmentactiongroup.org/cure/trials.

Stem Cell Transplants

Among the most significant news over the past year was an update on two HIV-positive individuals from the Boston area, who had shown indications of having been cured after receiving stem cell transplants to treat cancers. Unlike Timothy Brown, these individuals received transplants from donors wild-type for the CCR5-Δ32 mutation, meaning the cells expressed normal levels of the HIV coreceptor CCR5. An initial published paper describing the cases indicated that HIV reservoirs were significantly depleted, possibly even eradicated, but at that time ART was still being maintained.[10] In July 2013, the first data was reported from the period after both individuals interrupted ART, and the news appeared good; HIV remained undetectable.[11] But another update in December brought bad tidings: HIV replication had rebounded, after 12 weeks in one case and 32 weeks in the other.[12] Timothy Henrich presented details at CROI 2014, showing that viral load reached very high levels in both individuals, but was ultimately successfully re-suppressed by ART. Genetic sequencing confirmed that the source of the recrudescence in viral replication was the same HIV present prior to the stem cell transplants, and not a new infection.[13] The outcome is obviously disappointing, but also contributes important information to the cure research effort. Among the implications:

- Timothy Brown's receipt of a stem cell transplant from a donor heterozygous for the CCR5-Δ32 mutation may have been crucial to the cure achieved in his case (Brown continues to show no signs of HIV activity off ART).

- The significant diminution in the size of the latent HIV reservoir in the Boston patients (greater than three logs) was insufficient to result in a permanent cure, suggesting that the bar is set very high for approaches that aim to cure HIV infection by reducing the number of latently infected cells. This finding appears to be consistent with a mathematical model developed by Alison Hill and colleagues, which suggests that reservoir reductions of greater than five or six logs (100,000-fold or a million-fold) may be needed to cure the majority of patients.[14]

- Long-term monitoring of HIV viral load is essential in any case where it is suspected that a cure might have occurred, because late viral rebound is possible.

- The inability to detect HIV using the most sensitive current assays does not necessarily mean that no virus is present in the body.

In an attempt to circumvent the difficulty of identifying stem cell donors heterozygous for the CCR5-Δ32 mutation for people with HIV and cancers requiring transplants (as was done for Timothy Brown), several trials are testing whether stem cells can be genetically modified to create resistance to HIV. Earlier this year, the City of Hope National Medical Center in California opened enrollment for a study for HIV-positive people with non-Hodgkin's lymphoma that will modify stem cells with three different RNA-based HIV inhibitors, and administer the chemotherapy drug busulfan in an attempt to promote the engraftment of the gene-modified cells. The Fred Hutchinson Cancer Research Center has a trial pending that plans to alter stem cells with a gene encoding an HIV entry inhibitor, C46; it will be open to individuals with either non-Hodgkin's or Hodgkin's lymphoma.

Updates on SB-728-T

Sangamo BioSciences is attempting to turn the lessons from the Timothy Brown case into a more accessible gene therapy approach for HIV. Rather than involving stem cell transplants, SB-728-T aims to disable CCR5 genes in CD4 T cells extracted from HIV-positive individuals; the cells are then expanded and reinfused. The goal is to create a population of CD4 T cells that are resistant to HIV because they do not express the CCR5 coreceptor. Results from one of the first phase I trials of SB-728-T received high-profile publication in the *New England Journal of Medicine* in March 2014.[15] In the 12 HIV-positive participants, the treatment was safe, with transient infusion reactions the main

side effect. CD4 T-cell counts were increased significantly, and gene-modified CD4 T cells persisted at low levels (~1–2% of circulating CD4 T cells) during long-term follow-up. Six participants underwent a 12-week ART interruption, and an intriguing finding was that one of these individuals experienced a viral-load rebound followed by a decline to undetectable levels just before ART was reinitiated (three of the other participants showed viral-load set points similar to those pre-ART, while the remaining two had to restart ART quickly due to high viral loads).

Further analysis revealed that this last individual is heterozygous for the CCR5-Δ32 mutation, meaning that one copy of the CCR5 gene is already disabled in the person's CD4 T cells (each cell contains two CCR5 genes, one on each set of chromosomes). As a result, there was less work for SB-728-T to do: it had to disable only one CCR5 gene in each CD4 T cell in order to completely abrogate expression of the CCR5 receptor. The lesson Sangamo BioSciences has drawn from this fortuitous case is that maximizing the number of CD4 T cells modified to lack CCR5 may be able to lead to control of HIV in the absence of ART. The possibility is being explored further in two ongoing trials; one has recruited only CCR5-Δ32 heterozygotes, and the other is administering a chemotherapy drug, cyclophosphamide (Cytoxan), prior to the CD4 T-cell infusions. The rationale for the latter strategy is that Cytoxan should reduce the number of existing CD4 T cells, and thus create more immunologic space for the gene-modified cells to expand into.

At CROI 2014, Gary Blick presented some preliminary data from the trial involving Cytoxan.[16] The uptake of gene-modified cells appeared to be enhanced in the two recipients of the highest Cytoxan dose, and these individuals also experienced significant viral declines during an ART interruption, but it is not possible to draw conclusions based on the small number of participants involved. An additional cohort is now being recruited that will receive a slightly higher Cytoxan dose. Blick noted that there is an inverse correlation between the number of gene-modified CD4 T cells and viral-load levels during ART interruptions, suggesting better results are attainable if the numbers can be further boosted. Blick also highlighted that one participant in the trial for CCR5-Δ32 heterozygotes has maintained a viral load of less than 50 copies/mL for an extended period after ART interruption (31 weeks at the time of the report).

Latency-Reversing Agents

HDAC inhibitors, a class of anticancer drugs, continue to represent lead candidates for rousting latent HIV from dormancy. Results from a phase I trial of panobinostat in people on ART suggest the drug was successful in prompting at least some latently HIV-infected cells to begin making HIV RNA,[17] a possible first step toward targeting these cells for elimination. Similar findings have previously been reported from two phase I evaluations of the HDAC inhibitor vorinostat.[18,19] However, recent studies have raised questions about the effectiveness of HDAC inhibitors and other proposed latency-reversing agents (LRAs). The problem is that inducing latent HIV to generate viral RNA may not necessarily be sufficient to lead to the generation of viral proteins and the production of new viruses. Triggering these latter steps in the HIV life cycle is believed to be necessary in order for the latently infected cell to be destroyed, either by the immune system or viral cytopathic effects.

The laboratory of Robert Siliciano at the Johns Hopkins University tested the activity of several LRAs, including the HDAC inhibitors panobinostat, vorinostat, and romidepsin, using latently infected CD4 T cells isolated from HIV-positive individuals on ART. None of the LRAs significantly increased HIV production.[20] However, preliminary follow-up experiments presented at CROI 2014 offered hints that combinations of LRAs may perform better.[21] Additionally, an assessment of romidepsin by another laboratory has reported seemingly contradictory evidence that the drug induced latent HIV to produce new viruses.[22] It is hoped that greater clarity about the potential of HDAC inhibitors will be provided by two trials of romidepsin in people on ART that began this year—one being conducted by the AIDS Clinical Trials Group (ACTG) in the United States, the other by researchers at Aarhus University in Denmark.

The latter study is divided into two parts, A and B. Part A administers romidepsin, while part B combines romidepsin with the therapeutic vaccine Vacc-4x. The goal is to assess whether the combination can deliver a one-two punch to the HIV reservoir, with the vaccine intended to enhance the ability of the immune system to target and eliminate any latently infected cells that are induced to produce viruses by romidepsin. Vacc-4x consists of selected peptides from conserved regions of the HIV p24 protein, and has been associated with lower viral-load rebounds after ART interruption in a previous phase II clinical trial.[23]

Among the other news regarding LRAs was publication of the results of the first trial of the anti-alcoholism drug disulfiram.[24] Although not clear-cut, there was some indication of a stimulating effect on latent HIV occurring shortly after disulfiram administration, and this observation is now being followed up in another, larger study. Interest in toll-like receptor (TLR) agonists as possible LRAs was highlighted in TAG's *2013 Pipeline Report*, and Rockefeller University has since launched a trial of poly-ICLC, a TLR-3 agonist more commonly used as a vaccine adjuvant, in order to assess its effect on the latent HIV reservoir.

Targeting PD-1

PD-1 is a signaling molecule that can be expressed on the surface of CD4 T cells. Transient expression of PD-1 is associated with T-cell activation, while the persistent presence of the molecule is linked to a type of cellular dysfunction referred to as T-cell exhaustion. PD-1 delivers signals to the cell by interacting with molecules expressed by other cells, specifically the PD-1 ligands PD-L1 and PD-L2. PD-1 has emerged as a target in cure research for two reasons: because it is preferentially expressed by latently infected CD4 T cells,[25] and because antibodies against PD-1 may be able to restore the functions of HIV-specific CD4 and CD8 T cells that have become exhausted.[26]

In collaboration with Bristol-Myers Squibb, the ACTG has now launched the first clinical trial in HIV of an antibody that targets PD-1 signaling by blocking PD-L1. Encouraging results from preclinical experiments in SIV-infected macaques were presented at CROI 2014, indicating that the antibody has the potential to beneficially modulate viral replication.[27] However, safety will need to be carefully assessed, as the PD-1 pathway is also involved in the prevention of autoimmunity.[28]

The ACTG had also been planning to conduct a clinical trial of an antibody against PD-1 developed by Merck, but disappointingly the company recently withdrew support. The reasons for the decision are unknown, but may be due to Merck's seeking FDA approval of the antibody for the treatment of cancer (a condition for which it has shown great promise[29]).

Broadly Neutralizing Antibodies

The research effort to identify and characterize broadly neutralizing antibodies (bNAbs) has been driven primarily by the desire to develop an effective preventive HIV vaccine (see "Preventive Technologies," p. 55). But the past year

has seen a surge in interest in exploring the therapeutic potential of bNAbs due to promising results reported in both HIV-infected humanized mice[30] and SIV-infected macaques.[31,32] In particular, an experiment performed by the laboratory of Dan Barouch showed that, in some macaques with low-baseline SIV viral loads, short-term administration of a bNAb was associated with sustained control of SIV replication after therapy was stopped. Barouch found evidence of enhanced clearance of SIV-infected cells in the treated animals, suggesting that the bNAb had boosted antibody-mediated effector mechanisms capable of promoting the recognition and killing of these cells.[33] Two phase I human trials testing the effects of infusions of bNAbs are now under way.

Therapeutic Vaccines

In addition to the combination study involving Vacc-4x and romidepsin, new trials of therapeutic vaccines include an evaluation of AGS-004 being conducted by investigators associated with the Collaboratory of AIDS Researchers for Eradication (CARE), one of three cure research consortiums funded by the NIH under its Martin Delaney Collaboratory program. AGS-004 is being developed by Argos Therapeutics and represents a personalized approach to vaccination: dendritic cells are extracted from study participants, mixed with HIV antigens derived from the same individual's infecting virus, and then administered as a vaccine. The goal is to induce potent immune responses capable of targeting the HIV present in the recipient. Prior studies have produced some evidence that immune responses created by the vaccine are associated with a delayed HIV viral-load rebound during ART interruption,[34] but the CARE researchers will be looking at the impact of immunization on the HIV reservoir and residual viral replication in HIV-positive people on continuous ART.

VAC-3S is a novel candidate that induces antibody responses to a specific part of HIV's gp41 envelope protein: a motif named 3S. The rationale for the development of the vaccine derives from evidence that these antibodies might protect against some of HIV's pathogenic effects on the immune system, by interfering with a putative mechanism of CD4 T-cell depletion.[35] A phase I/IIa trial demonstrated safety and immunogenicity,[36] and a phase II study has been launched as a result. The vaccine provides an example of the overlap between immune-based therapy and cure research, as the investigators hypothesize that it might reduce both inflammation and the HIV reservoir.

Table 2. Immune-Based Therapy Pipeline 2014

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
sitagliptin	Anti-inflammatory	Washington University School of Medicine	Phase III
Low-dose methotrexate	Anti-inflammatory	NIAID	Phase II
Niacin	Vitamin B3	McGill University Health Center/CIHR Canadian HIV Trials Network	Phase II
Saccharomyces boulardii	Probiotics	Parc de Salut Mar	Phase II
losartan	Angiotensin II receptor antagonist, anti-inflammatory	Minneapolis Medical Research Foundation	Phase II
chloroquine phosphate	Antimalarial, anti-inflammatory	NIAID/ACTG	Phase II
etoricoxib	Cox-2 inhibitor, anti-inflammatory	Oslo University Hospital	Phase II
Interleukin-7 (IL-7)	Cytokine	French National Agency for Research on AIDS and Viral Hepatitis (ANRS) and Cognate Biosciences	Phase II
lubiprostone	Apical lumen ClC-2 chloride channel activator	Ruth M. Rothstein CORE Center/Chicago Developmental Center for AIDS Research	Phase II
dipyridamole	Phosphodiesterase type 5 inhibitor, anti-inflammatory	Sharon Riddler, University of Pittsburgh/ NIAID	Phase I/II
Tripterygium wilfordii Hook F	Traditional Chinese medicine, anti-inflammatory	Beijing 302 Hospital Peking Union Medical College	Phase I/II
Umbilical cord mesenchymal stem cells (UC-MSC)	Adult stem cells originating from the mesenchymal and connective tissues	Beijing 302 Hospital	Phase I//II
HLA-B*57 cell transfer	Cell infusion	NIH Clinical Center	Phase I
hydroxychloroquine	Antimalarial, antirheumatic, anti-inflammatory	St Stephens AIDS Trust	Phase I

Interleukin-7 (IL-7)

Unfortunately, the fate of IL-7 illustrates the challenges associated with developing adjunctive immune-based therapies for people with poor immune reconstitution despite ART (immunologic nonresponders, or INRs). IL-7 has been shown to significantly increase CD4 T-cell counts,[37] and a recent small study uncovered evidence that it also diminishes levels of important inflammatory biomarkers.[38] The manufacturer, Cytheris, had ambitious plans to conduct a phase III clinical endpoint trial in INRs, but earlier this year the

news emerged that the company had gone out of business. The rights for pursuing IL-7 as a therapy for HIV-related immune impairment have reportedly been taken over by a collaboration involving the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) and Cognate Biosciences. At best, this will certainly delay evaluation of the ability of IL-7 to reduce morbidity and mortality in INRs. At this time, it appears to be the only candidate with sufficient data to justify such a trial, so INRs are likely to be left without therapeutic options beyond ART for some time.

Targeting the Gut to Reduce Immune Activation

Four recent trials analyzed whether treatments that target the gut might diminish immune activation and inflammation in HIV infection. The rationale is that reduction of microbial translocation—the leakage of normally friendly bacteria from the gut into the systemic circulation—should lessen stimulation of the immune system. While not necessarily immune-based, these approaches aim to work via an immunologic mechanism. However, they had little or no effect. Sevelamer is a treatment for reducing high blood levels of phosphorus in kidney disease that can also bind to bacterial endotoxin (lipopolysaccharide), a product of microbial translocation. An eight-week trial in HIV-positive people who had not yet started ART did not uncover any significant effects on markers of microbial translocation or inflammation, although there were significant reductions in LDL cholesterol and tissue factor, suggesting a possible beneficial impact on cardiovascular disease risk.[39] Concerns about potential interactions and overlapping toxicities with ART suggest it is unlikely that sevelamer will have a role as an adjunctive therapy.

Mesalamine is an FDA-approved, bowel-specific anti-inflammatory drug. In a study in HIV-positive people on ART, no changes in either systemic or gut immune activation levels were noted, and inflammatory biomarkers were also unaffected.[40] The antibiotic rifaximin was tested in INRs, but resulted in minimal changes in markers of immune activation and inflammation that did not lead to increases in CD4 T-cell counts.[41]

Some signs of success were seen with a probiotic supplement, Biola, administered to HIV-positive people on ART. Over eight weeks there was a significant decline in levels of D-dimer, an inflammatory biomarker associated with morbidity and mortality in HIV. IL-6 and CRP also fell, but to a less significant extent.[42] A new trial of a probiotic, *Saccharomyces boulardii*, is taking place in Barcelona, Spain (see table 2).

Panoply of Anti-Inflammatories

A variety of potential anti-inflammatory agents have entered clinical trials over the past year. With the exception of *Saccharomyces boulardii*, they all aim to work systemically rather than targeting the gut. Among them are sitagliptin, a diabetes drug that has been reported to reduce markers of inflammation in people who are HIV-negative;[43] low-dose methotrexate, an immune suppressant; losartan, an anti-hypertensive; and dipyridamole, indicated for the prevention of blood clots. The vitamin niacin is also being evaluated in a trial in Canada that will look at both immune activation and inflammatory biomarkers.

CONCLUSION

The opening of new trials and influx of additional funding—albeit still insufficient for the task at hand—demonstrate that momentum is continuing to build in HIV cure research. Although another year has passed without additional proven cases mirroring those of Timothy Brown and the "Mississippi baby" (now a child), there is hope that this situation may change in the not-too-distant future. But the development of widely accessible interventions capable of curing the majority of HIV-positive people remains a stern challenge with no solution imminent. For this reason, the bulk of the cure research that has entered the clinic represents tentative exploratory steps aiming to inform the next round of trials. Advocacy continues to be essential for spurring these efforts, ensuring that funding support grows, and enhancing understanding of the science among the HIV/AIDS community and broader public.

The immune-based therapy field, in contrast, lies disconcertingly fallow. Small studies of anti-inflammatory approaches are still opening, but it is difficult to envision any leading to licensure of adjunctive treatments capable of reducing the residual risk of morbidity and mortality that can persist among ART recipients, particularly INRs. Commercial interest in this area seems meager. A broader dialogue among activists, scientists, funders, pharmaceutical companies, and other interested parties may be needed in order to assess whether the problems in this area can be solved.

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Fit for Purpose: Treatment Optimization

By Polly Clayden

Since the *2013 Pipeline Report* treatment optimization has continued to gain traction. Results from one of the key dose optimization trials ENCORE1—showing a lower dose of efavirenz (EFV) is non-inferior to the currently approved one— were published,[1] and dolutegravir (DTG)—one of the most promising pipeline drugs for this purpose—was approved for use in rich countries.[2, 3]

The importance of making the necessary investment to generate data—that will not come out of trials required for approval in rich countries—to inform recommendations for low- and middle-income countries is being more widely discussed. Real life trial designs are being finessed, including in countries where the results will determine treatment strategies, and some are even being funded.[4]

If that wasn't enough, *Current Opinion in HIV and AIDS* devoted a whole issue to treatment optimization in November 2013.[5] In one opinion paper from this journal the authors note that an "entirely nontoxic combination of antiretroviral drugs for first-line and second-line use would be an important advance for this field" and suggest that lamivudine (3TC), emtricitabine (FTC) and raltegravir (RAL) each provide clinical proof-of-concept that regimens with long-term safety and minimal side effects are a possibility.[6]

World Health Organization (WHO) released a *March 2014 Supplement to the 2013 Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection*, which provides more detail on optimized treatment and the role of the evolving science.[7]

Sharp-eyed readers will notice a subtle title change from last year in this update, written with optimism that joined up research and guidance seems to be happening: more fit and less retro.

The Story so Far

Treatment 2.0—a strategic approach by WHO and UNAIDS to the achievement of universal access to antiretroviral therapy and to making the most of the role of antiretrovirals in preventing new infections—includes treatment optimization as one of its critical components.[8]

Discussions about optimization—particularly through appropriate dose reduction—of approved antiretrovirals have been ongoing now for over a decade,[9,10] the rationale being that when developing new drugs, the highest tolerated doses in phase II are often selected for phase III and, in turn, approval, where in some cases lower doses may have equivalent efficacy. Efficiencies can also be achieved by reducing the amount of active pharmaceutical ingredient (API) with improved bioavailability through reformulation, or by tweaking the process chemistry.

The Conference on Dose Optimization (CADO)—a collaborative project of the Clinton Health Access Initiative (CHAI), the Johns Hopkins University School of Medicine, and the Bill & Melinda Gates Foundation, held in 2010 and attended by process chemists, clinical pharmacologists, infectious disease specialists and experts in regulatory and ethical issues—led to a consensus statement on optimizing the manufacturing, formulation, and dosage of antiretroviral drugs for more cost-efficient delivery in resource-limited settings.[11,12]

As the statement explains, the API is the largest part of the product cost of generic drugs; a reduction in this would potentially decrease the total cost of the product. The cost of a marketed generic drug typically consists of: API (65% to 75% of the total market price), formulation (10% to 20%), and packaging and profits (5% to15%).

There are several ways through dose optimization that API reduction might be accomplished:

> **Dose reduction.** In order to achieve regulatory approval for a dose lower than that currently approved, fully powered non-inferiority studies (phase III)—similar to those conducted by industry for the approval of a new drug—need to be done. It would take about three to six years to generate sufficient data to file with regulatory agencies, plus time to approval (about three months to a year). The estimated cost would be US$15 to 22 million.

Reformulation. This strategy makes use of technologies and/or inactive ingredients to increase the bioavailability of a drug, which enables reduction of the approved dose. A reformulated compound will need bioequivalence studies with the approved formulation (phase I). The estimated time frame to regulatory filing is two to three years, at a cost of US$2 to 8 million.

Process chemistry. It may also be possible to alter the manufacturing process leading to more efficient and less expensive API production. For this strategy to be successful, regulatory authorities would need to see only equivalent stability and purity data. This would take about one to two years, at an estimated cost of US$1 to 2 million.

Other factors in price reduction:

- Sourcing less expensive raw materials. This price depends on the volume needed, an increase in demand can attract new suppliers and in turn competition.
- Improvements in the manufacturing process can mean raw materials are converted to API more efficiently.
- Shelf life extension. To extend a typical two-year shelf life, real-time stability testing would be required with clear regulatory pathways.

In 2011 WHO held a follow up meeting to the first CADO, to work out ways to incorporate treatment optimization into future guidelines and the Treatment 2.0 initiative.[13] This yielded a number of short-term research priorities and recommendations including increased harmonization of adult and pediatric regimens, through FDCs and other simplified formulations.

Subsequent discussions at meetings led by Médecins Sans Frontières (MSF) and WHO as well as the 2nd Conference on Dose Optimisation II (CADO2), have explored medium- and longer-term horizons for future treatment strategies.[14,15,16]

The plans, established at CADO 1 to increase cost-efficiencies, remain unchanged, and this research continues to gain momentum. In the four years since the original meeting, there has been an increasing emphasis on patient acceptability and preferences. Discussions have included a broader group of representatives from the community and caregivers with consensus that

improved efficiencies need, not only reduce costs, but also improve tolerability and outcomes for people with HIV. It is acknowledged that these factors will be increasingly critical as indications for treatment grow and more asymptomatic people with HIV are offered antiretroviral treatment. All potential treatment options must be measured against these factors.

The aforementioned meetings and publications have described the target product profile (TPP) of a "dream regimen" of antiretrovirals—summarized in table 1.

TABLE 1. Target Product Profile of a Dream ART Regimen

Safe and Effective	Superior or Equivalent to Currently Recommended Drugs
Simple	Possible to be given in decentralized facilities or the community. One pill once a day (less frequently might be possible in the future). No lead-in dosing. No dose adjustments when given with other common medicines. Heat-stable. Shelf life of two or more years.
Tolerable	Minimal toxicity. Reformulation and/or dose reduction might improve tolerability.
Durable	High genetic barrier to resistance. Low pharmacokinetic variability. Forgiving of missed doses. Tolerable for easier adherence.
Universal	Safe and effective across all CD4 strata; in people with high viral load; in men and women; during pregnancy; across age groups and with common coinfections such as tuberculosis (TB) or viral hepatitis.
Affordable	ARV coverage does not meet the estimated current need. Meanwhile, evidence is growing for earlier and wider use of treatment.

Current World Health Organization Recommendations

For adult first-line treatment, a one pill, once-a-day fixed dose combination (FDC) of EFV plus tenofovir disoproxil fumarate (TDF) plus 3TC is agreed—across all expert consultations as well as in the *2013 World Health Organization Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection*[17]—to be the current preferred option in the short- and medium-term.

The key messages from the guidelines are:

1. Use of once daily regimens is better than twice-daily regimens from both clinical and programmatic standpoints.
2. FDCs are preferred for simplification, convenience, adherence, more efficient procurement, lower risk of stock outs and resistance.
3. EFV is considered superior to nevirapine (NVP) in the long term, as studies showed less discontinuation. It is also associated with other clinical and programmatic advantages such as no need of lead in dose, use with TB treatment and safety/availability as a once daily FDC.
4. For sequencing, TDF use has advantages from both clinical and programmatic perspectives: once daily, better in terms of resistance, and limits the risk of interaction with PIs.

CHAI produces an annual list of ceiling prices available to countries participating in their procurement consortium.[18] These prices, alongside those published by MSF Access Campaign in their excellent *Untangling the Web of Antiretroviral Price Reductions* inform those quoted in this chapter.[19]

The 2013 CHAI ceiling price for the preferred first line FDC is now US$131 per patient per year (pppy), which is a 21% reduction since 2012. With successful optimization work, this regimen could be expected to be less than $100 pppy.[20] Future changes to this regimen must either offer efficiencies with its components (such as a reduced dose with the same durability and improved tolerability), or superiority with new compounds.

The WHO 2013 guidelines-recommended second-line regimen remains ritonavir (RTV)-boosted protease inhibitor-based and, unlike recommendations in rich countries, lopinavir/ritonavir (LPV/r) rather than darunavir/ritonavir (DRV/r) is included alongside atazanavir/ritonavir (ATV/r). An optimized ATV/r regimen could be expected to be less than $275 pppy.

TABLE 2. 2013 WHO Guidelines–Recommended ART Regimens

First-line	TDF + 3TC (or FTC) + EFV preferred (including pregnant women) AZT alternative to TDF NVP alternative to EFV
Second-line	ATV/r or LPV/r preferred + TDF + 3TC preferred backbone (if AZT or d4T first-line) + AZT + 3TC preferred (if TDF first-line)
Third-line	No specific recommendations: Integrase inhibitor (INI) or second-generation PI or NNRTI are mentioned

ATV/r, atazanavir/ritonavir; AZT, zidovudine; d4T,stavudine; EFV,efavirenz; FTC,emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

Treatment-limiting central nervous system (CNS) toxicities that are a concern with EFV could possibly be reduced with a lower dose. Fears about its use during pregnancy are steadily being assuaged, and more permissive recommendations—in line with the British HIV Association guidelines—are made in the WHO 2013 guidelines.[21, 22, 23, 24, 25]

Despite direct comparisons as monotherapy, 3TC and FTC are largely considered to be interchangeable in terms of efficacy and safety, and the WHO systematic review concluded this to be true.[26] Both are nucleoside reverse transcriptase inhibitors (NRTIs) and are structurally similar molecules with low toxicity, and both are effective against hepatitis B virus. Cost comparisons make 3TC the preferred option—using FTC instead in combination with EFV and TDF adds an annual patient cost of US$25 to a combined product. But this gap in price appears to be narrowing. Currently 3TC is available in more FDCs than FTC.

Updated systematic reviews looking at EFV in pregnancy and 3TC versus FTC are both included in the WHO March 2014 supplement to the guidelines.

Work on the bioavailability of TDF could bring down the price (currently US$54 pppy as a single agent), and further reductions still might be possible in the future with the pipeline pro-drug, tenofovir alafenamide (TAF).

LPV/r is still the most widely used protease inhibitor in second line regimens in low- and middle-income countries. But, the United States Food and Drug Administration (FDA) has tentatively approved a heat-stable formulation of ATV/r.[27, 28] This 300/100 mg one-pill once-daily formulation is now US$220

pppy and compares favourably to LPV/r costing US$300 pppy, with four pills a day and twice-daily dosing. Mylan Pharmaceuticals has developed a two pill once-a-day co-packaged regimen of this plus 3TC and TDF; the ceiling price is US$306 pppy.

Once-daily heat-stable DRV/r would offer a better option to LPV/r second line. At present a suitable formulation (and suitable price) remains elusive. More research is required to establish optimal dosing. With expected comparable price to LPV/r (there is potential to reduce the current cost of DRV/r at $900 to below $350 pppy, if it was used in similar volumes to that of LPV/r currently) and a better profile, DRV/r should be a second-line option and not just considered for third-line treatment.

WHO recommendations for third-line treatment were introduced for the first time in 2010 and they remain much the same in 2013, suggesting, as well DRV/r, RAL, and second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), etravirine (ETR) in nucleos(t)ide (NRTI)-sparing regimens. None of these yet have generic versions, and the costs are considerable.

CADO2 Recommendations

It was agreed at CADO-2 that although first line standard of care is hard to beat, CNS side effects associated with EFV; and renal and bone toxicities associated with TDF (as well as its high milligram dose of 300 mg) might be improved upon. Issues of tolerability might be increasingly unacceptable as the eligibility criteria for antiretroviral therapy continues to broaden and more asymptomatic people start treatment.

The CADO-2 participants concluded that an FDC of TAF/3TC/DTG first line could be a possible future option (or one with a lower dose of EFV), with DRV/r and two NRTIs second line. People currently receiving EFV based first-line regimens might receive an FDC of DTG/DRV/r second-line.

In the Meantime Can we Do Better With What we Have?

Optimization with some of the approved antiretrovirals might offer several advantages over the current doses and/or formulations, and work is underway or under discussion with several compounds. [29] See table 3.

TABLE 3. Approved Antiretroviral Compounds with Potential for Dose Optimization

Compound/approved dose	Class	Sponsor/approach	Outcomes	Status
Tenofovir disoproxil fumarate (TDF) 300 mg once daily	NtRTI	CHAI in partnership with Scynexis, Corealis and Aurobindo Reformulation	Approx 33% reduction anticipated Target 200 mg TDF-containing FDC tablet Cost reduction $50 to $35 pppy	TDF (hx) Underway
Zidovudine (AZT) 300 mg twice daily	NRTI	Geneva University Hospital Dose optimization RCT	Dose reduced to 200mg twice daily Cost reduction $89 to $60 pppy	MiniZID Phase III Completed January 2014 Results to be announced this year
Stavudine (d4T) 30 mg twice daily	NRTI	Wits Reproductive Health Institute Dose optimization and comparison with TDF, RCT	Dose reduced to 20mg twice daily Cost reduction $25 to $20 pppy	WHCS-001 Phase III To be completed end 2015/ early 2016
Efavirenz (EFV) 600 mg once daily	NNRTI	Kirby Institute Dose optimization RCT CHAI Reformulation	Dose reduced to 400 mg once daily Potential additional 33% reduction by reformulation Cost reduction $63 to $31 pppy	ENCORE 1 400 mg non-inferior to 600 mg at 48 weeks
Atazanavir/ritonavir (ATV/r) 300/100 mg once daily	PI	HIVNAT/Kirby Institute Dose optimization RCT CHAI Process chemistry	Dose reduced to 200/100 Cost reduction $355 to $200 pppy Additional potential price reduction by process chemistry	LASA III Phase III to be completed 2014
Darunavir/ritonavir (DRV/r) 800/100 mg once daily or 600/100 mg twice daily	PI	Under discussion Process chemistry, dose optimization and reformulation	API reduced from above $2000 to below $1000. Dose reduced from 800/100 to 400/100 mg once daily. Cost reduction $835 to below $350 pppy	Under discussion
Ritonavir (RTV) 100 mg	Booster	Dose optimization	Boosting dose of atazanavir and darunavir reduced to 50 mg	Under discussion

Tenofovir

TDF is preferred as part of first-line treatment everywhere. It is considered to be the best NRTI on the market, and this is likely to continue for several years.

The price of TDF has dropped considerably since its introduction into the generic market. This is largely due to efficiencies in raw material sourcing and improved processing, which led to a 57 % drop in price between 2006 and 2010.[30,31] It is now available for about US$50 pppy, a 74 % drop since 2006: a TDF-based FDC regimen is now available for about US$125 pppy.

There are limits to the lowest possible price of TDF due to its high milligram dose (300 mg) with the current formulation.

CHAI is developing a dosage form of TDF called TDF (hx) in partnership with companies performing the preclinical work (Scynexis), formulation screening and GMP work (Corealis) and a generic manufacturer (Aurobindo).

Through reformulation of the excipients, they aim to increase bioavailability and, in turn, lower the dose to an anticipated 200 mg, while maintaining equivalent exposure.

Bioequivalence studies will compare TDF (hx) to the 300 mg originator formulation of TDF (Viread) to provide evidence for tentative FDA approval of TDF (hx)-containing FDCs.

CHAI's goal is to reach the market with a TDF (hx)-containing FDC in late 2017.

As well as TAF, being developed by Gilead, Merck is developing CMX-157, another prodrug of tenofovir.[32,33,34]

A TAF-containing FDC is not expected to reach the market in low- and middle-income countries before 2020 and would take a while to completely replace TDF. There has been little news of CMX-157.

AZT

If TDF remains the preferred first-line NRTI, AZT is likely to be used second-line in the short term.

The dose of AZT was reduced considerably from the initial 300 mg every four

hours to 250 to 300 mg twice daily, after similar efficacy and increased safety was demonstrated.[35]

Although AZT is generally better tolerated than d4T over a long-term period, its hematologic toxicities (anemia/neutropenia) remain a concern in many low- and middle-income countries.

The MINIZID study looks at 200 mg versus 300 mg AZT twice daily (as part of a regimen with 3TC plus an NNRTI), with reduction of anemia as the primary endpoint.

This is a 48-week phase II study in 136 treatment-naive patients, sponsored by the University of Geneva and being conducted at the Hôpital de la Caisse Nationale de Prévoyance Sociale, Yaoundé, Cameroon. Recruitment began in August 2011 and it was completed in January 2014.[36]

If this strategy is successful, the study will not generate sufficient data for regulatory approval of the lower dose, but will provide proof of principle. Results will be announced in July this year.

Some Asian countries such as Thailand and India already use the AZT 250 mg tablet twice daily, and Thailand is currently using 200 mg twice daily in patients weighing less than 50 kg.

d4T

Of all the dose optimization strategies proposed or ongoing, the decision to use d4T is the most controversial. Unlike the other antiretrovirals for which these strategies are being suggested or conducted, d4T is no longer a preferred option in any guideline, anywhere, due to its toxicity profile. For several years, WHO has issued guidance for phasing out d4T.

The Wits Reproductive Health Institute in South Africa is leading a phase IIIb trial comparing 20 mg d4T twice daily to 300 mg TDF once daily in approximately 1,000 patients in South Africa, India and Uganda. The trial is supported by the Bill & Melinda Gates Foundation.

The primary objective is to demonstrate the non-inferiority of 20 d4T to 300 mg TDF (both in a regimen with 3TC plus EFV) in treatment-naive patients. The proportion of patients receiving each regimen with undetectable viral load (less than 200 copies/mL) at 48 weeks, will determine this. The secondary endpoints

are to evaluate the tolerability, overall safety, and efficacy of 20 mg d4T compared to 300 mg TDF.

The trial is concerning, as it will not answer d4T's long-term toxicity question. The 20 mg d4T dose might be acceptable in a short-term 48- or even 96-week virological endpoint study. But, because mitochondrial toxicity is both dose- and time-dependent, many of d4T's most serious side effects (such as peripheral neuropathy and lipoatrophy) would not necessarily emerge until after such a study was completed. Although it looks at lipoatrophy, this study does not include monitoring of surrogate markers for mitochondrial toxicity, so it cannot shed light on the incidence of this serious adverse event.

The d4T parallel track program, which randomized over 10,000 patients to receive 40 (30) mg or 20 (15) mg (between October 1992 and February 1994), showed a higher incidence of neuropathy in the high-dose arm (21%). Nonetheless, the incidence of neuropathy observed in the lower dose arm was also unacceptably high (15%).[37]

In addition to concerns about cumulative toxicities, d4T-related cost savings might become irrelevant by the trial's end. Through other dose optimization strategies and perhaps promising newly approved and pipeline compounds, alternatives are likely to become available that could drive regimen costs down with less risk to patient safety.

Activists from all over the world have opposed this trial.[38,39,40,41,42,43,44]

Since the trial was designed the price of TDF has come down more than was originally anticipated—TDF (hx) could reduce this even further—and uptake of TDF-containing FDCs has increased.

The most useful data from this trial will be on the safety of TDF in a resource limited setting.

Efavirenz

EFV fulfils many of the desirable characteristics for the TPP. But it is associated with CNS side effects, which can lead to drug discontinuation, reported in as much as half the people receiving it in settings with access to alternatives.[45]

The ENCORE 1 study, showing 400 mg EFV to be non-inferior to 600 mg, was completed in July 2013. The 48-week results were published in *The Lancet* in April this year.[46,]

The study found a reduced dose of 400 mg EFV non-inferior to the 600 mg standard dose (both plus TDF/FTC) in 636 treatment-naive patients at 48 weeks.

The study was conducted in Europe, Australasia, Latin America, Asia, and Africa.

Significantly fewer patients (approximately 3%) discontinued treatment due to EFV-related side effects (rash, CNS, gastrointestinal, but not psychiatric) from the 400 mg arm compared to the 600 mg arm and 10% fewer participants reported these side effects.

A very high proportion (approximately 90%) of participants had an undetectable viral load in this study.

Results from a pharmacokinetic sub-study of ENCORE 1 suggest that the current targets for EFV might be too high.[47,48]

That comparable efficacy was achieved at reduced dose of EFV in ENCORE 1 (and potentially reduced cost) is an important finding.

The ENCORE 1 investigators suggest, "Lower dose efavirenz should be recommended as part of routine care". WHO and the Adults ART Working Group question whether the lower dose would be robust in the presence of rifampicin (which reduces concentrations of EFV due to a drug-drug interaction) in treatment of TB/HIV coinfection and in the third trimester of pregnancy.

It seems that to recommend 400 mg EFV widely pharmacokinetic studies with rifampicin and in pregnant women will have to be conducted. One question will be, what pharmacokinetic targets are appropriate for treatment success?

The high API of EFV is due in part to its poor water solubility. CHAI is looking at reformulation, targeting the inactive ingredients, to improve this.

Nanosuspensions of EFV, using freeze-drying technology are also in development, which could result in improved bioavailability and possibly greater antiviral activity.[49,50]

The research group at the University of Liverpool is developing a nanosuspension of EFV.[51]

Atazanavir

Dose reduction may also be possible with ATV/r, and the HIV Netherlands Australia Thailand Research Collaboration, with some support from the Kirby Institute, is conducting a trial that might provide some evidence for this strategy.[52]

The low-dose ATV/r versus standard-dose ATV/r (LASA) study is comparing the efficacy and safety of ATV/r at either 200/100 mg or 300/100 mg once-daily in 560 Thai patients in combination with two NRTIs. This non-inferiority, phase IV study with about 600 patients began recruiting in March 2011 and results should be announced this year.

This study enrolled patients who were already virologically suppressed to switch to the lower or standard dose of ATV/r. This research is important for Thailand as patients tend to have a lower body weight, and hyperbilirubinemia occurs quite frequently. It will be difficult to generalize the results from this research beyond the study population, but positive results would provide good reason to conduct a study in treatment-naive patients from a broader population.

CHAI is also working on optimizing the process chemistry.

Darunavir

DRV/r is generally considered to be the most durable protease inhibitor, but there is no generic formulation, and cost has been a barrier to its wide use. As it is not yet recommended for second-line treatment by WHO there has been limited work on its optimization.

This drug has different approved doses for treatment-naive (including treatment- experienced but with no DRV-associated mutations) and protease inhibitor-experienced patients. Treatment-naive patients receive DRV/r at an 8:1 (800/100 mg) ratio once daily, and experienced patients at a 6:1 ratio (600/100 mg) twice daily. The original dose ranging studies of DRV/r were conducted in highly protease inhibitor-experienced patients[53, 54] for protease inhibitor-naive people there might be potential for dose reduction to 400/100 mg.

The ratios also vary for children depending on their weight band and treatment experience.

The establishment of single ratios for adults and children (as well as

recommendations for when best to use it) would make simpler DRV/r-based regimens and formulations more feasible.

CHAI is working on optimizing the process chemistry.

Ritonavir

It might be possible to give ATV and DRV with a lower boosting dose of RTV.

Lower doses could be better tolerated, cheaper, and easier to coformulate with protease inhibitors than the current dose.

If a 50 mg heat-stable tablet of ritonavir could be manufactured or 50 mg co-formulated with either PI, new bioequivalence trials would be needed to ensure that boosting effects were similar to those that have been achieved previously in small pharmacokinetic trials with the liquid formulation.

A 50 mg RTV tablet would also be very useful for pediatric dosing, as the liquid is expensive, impractical (particularly for resource-limited settings) and tastes dreadful.[55]

Research Gaps and Planned Trials to Address Them

For the recommendations from CADO 2 and the Adults ART Working Group to be realized, new trials are needed to address gaps in information on how new optimized doses, recently approved or pipeline drugs will perform in public health programs in low- and middle-income counties. Table 4 summarises research gaps and what is needed and Table 7 describes trials in the planning stage or about to start.

Table 4: Action Needed for Antiretroviral Treatment Optimization

Optimised strategy	Tolerability	Resistance	Convenience	PW, TB, children	Cost reduction	Action needed	Estimated timeline (years)
Low dose EFV	√	?	√	?	√	PK studies (PW and TB)	1-2
Low dose DRV/r	√	?	√	?	√	PK studies (titration of best DRV:RTV ratio) RCT (comparative studies standard vs. low dose)	2-5
Use of DTG	√	√	√	?	√	Studies in PW, TB and children Comparative trials (TDF/TAF) first line RCT (DRV/r+DTG second line)	2-5
Use of TAF	√	?	√	?	√	Comparative trials using DTG Studies in PW, TB and children	2-5
Long-acting formulations	√	?	√	?	√	Phase II/III studies (treatment and preventative)	>5

PW, pregnant women; PK, pharmacokinetic; RCT, randomized controlled trial.
Source: Adapted from Marco Vitoria. Global Access to New HIV Therapies. WHO 2014. 2014 June.

First-line studies are needed to determine FDC regimens that are equally or more potent and more durable, tolerable and affordable than TDF/ XTC (refers to either 3TC or FTC)/EFV 600mg, including TAF/ XTC/DTG and TAF/XTC/EFV 400mg.

For second-line, studies are needed to identify improved regimens, particularly looking at the role of DRV/r in replacing LPV/r or ATV/r. Studies of reduced dose DRV/r, in combination with recycled NRTIs or DTG are important.

A one pill, once a day option is desirable for second-line.

Several trials are either at the planning stage or a bit further along the pipeline.

Low Dose Efavirenz

Pharmacokinetic-pharmacodynamic modelling of the data from ENCORE1 is currently ongoing to help better understand predictors of EFV pharmacokinetics and response in a heterogeneous population.

Since the announcement of the trial results last year, there has been a lot of discussion about recommending the reduced dose, particularly in low-income countries where the resulting cost savings would be considerable.

Questions about whether or not 400 mg will be robust enough in the third trimester of pregnancy and in the presence of concomitant treatment for TB have delayed recommendations from WHO and national guidelines.

There are five studies that include 235 women treated with 600 mg EFV in pregnancy in which drug concentrations were not significantly affected and there were high rates of viral load suppression in the mothers at the time of delivery.[56] The results suggest that pregnancy has slight if any clinically important effects on EFV pharmacokinetics.

For rifampicin, there have been a number of short-term pharmacokinetic studies with 600 mg EFV showing reduction in plasma concentrations. It is unclear how useful these results are when EFV has not reached steady state. Longer-term studies in HIV-positive people have shown increased Cmin or no effect.[57] In order to determine whether the pharmacokinetic interaction between rifampicin and EFV is different using the 400mg dose (there may be different induction effects) a new study is considered necessary.

It seems that to recommend 400 mg EFV widely pharmacokinetic studies with rifampicin and in pregnant women will have to be conducted and these are in the planning stage.

It is also important to remember that in the early DMP-266 005 trial of EFV there was no difference in viral suppression between people receiving 200 mg, 400 mg and 600 mg at 16 weeks.[58] There is talk of exploring the 200 mg dose compared to 400mg and 600 mg.

Dolutegravir

With a low 50 mg once-daily dose that does not require boosting, very good efficacy, minimal toxicity, pregnancy category B, and the potential to be low cost and coformulated, DTG might be an option for use in low- and middle-income countries. It could replace EFV first-line or be used second-line. It is also predicted to cost US$30 pppy to manufacture: 90% cheaper than RAL.

DTG was superior to EFV at 48 weeks in antiretroviral naive patients in phase III trials.[59] Data from this comparison and from studies comparing DTG to RAL

and in people with resistance to other integrase inhibitors[60,61] were used to gain approval for a broad indication in adults and adolescents aged 12 and above.[62] The indication for 12 to18 year olds is based on a 24-week open-label label study in integrase inhibitor-naive patients.

Some of the registrational trials were open label and included people that received a TDF/FTC backbone (as opposed to ABC/3TC from the originator company) so there are some preliminary data on this potential preferred regimen. See table 5.

Table 5: Numbers of people receiving TDF/3TC in DTG arms of phase III clinical trials

Trial	Number and percentage on TDF/FTC
SPRING-2	242 (59%)
SINGLE	All received ABC/3TC (regimen comparison study)
FLAMINGO	163 (67%)
SAILING	Not in publication. Numbers will be small as most people has a boosted PI in their background regimen plus one other antiretroviral

Although some of the registrational trials now have two years data, how DTG is likely to perform in a real world, low- or middle-income setting still poses questions. Populations in these settings include significantly larger proportions of women of childbearing age, children, and people with TB, malaria, and other coinfections, but research is conducted in order to provide information to register drugs for rich countries.[63]

DTG has been studied in several treatment scenarios and regimens, but so far this has not included key populations who would be treated with DTG in low-and middle-income countries. The registrational trials for DTG were about 80% men, few non-white participants and hardly anyone co-infected with other diseases (a few hepatitis B and none with TB or malaria). People with baseline NRTI resistance were excluded. Table 6 shows the number of women in phase III DTG trials.

Table 6. Numbers of women in DTG arms of phase III clinical trials

Trial	Number and percentage of women
SPRING-2	63 (15%)
SINGLE	67 (16%)
FLAMINGO	31 (13%)
SAILING	107 (30%)
VIKING-3	42 (23%)

Information about treating HIV/TB coinfection with a DTG-based regimen is limited. So far a phase I study has been conducted in healthy volunteers of DTG given with rifampicin and with rifabutin.[64] This suggested that 50 mg twice daily dosing is likely to be required when it is co-administered with rifampicin to overcome UGT1A/CYP3A induction by this drug, which is used in standard first line TB treatment. A study of 50 mg DTG twice daily during TB treatment is in the final planning stages.

As yet there is no information about DTG in pregnant women, although animal reproduction studies are not always predictive of human response, no safety issues were revealed in preclinical studies.

The originator company is sponsoring a number of trials to address some of these gaps and several investigator-led trials are also planned.

Low Dose Darunavir/ritonavir

The FDA approved dose for DRV/r is 600/100 mg twice daily for people pretreated with protease inhibitors and 800/100 mg for protease inhibitor naive people. It might be possible to reduce the dose of DRV/r for protease inhibitor-naive patients from 800/100 mg to 400/100 mg once-daily (or even 50 mg RTV).

No dose finding studies have ever been conducted with DRV/r in naive patients.

One-Pill, Two-Pill, Red-Pill, Blue-Pill

For people failing EFV-based first line treatment—greater access to viral load monitoring is expected to swell this population—discussions about a one-pill once-daily second-line regimen with DRV/r are underway.

A regimen of DRV/r plus DTG has the potential to be a once-daily coformulated second-line option, with no cross-resistance to the current recommended first line. The potential strategy using the once daily first-line followed by coformulated DRV/r plus DTG is known as Pill A, Pill B (Pill 1, Pill 2 or Red Pill, Blue Pill). Planned studies will compare two doses of DRV/r (800 and 400 mg) in regimens with either DTG or two NRTIs.

TABLE 7: Planned Treatment Optimization Trials

Trial	Implementer/Sponsor	Design	Status/Comments
Low dose EFV studies			
EFV 400 mg TB	SSAT/BMGF	PK EFV 400 mg with isoniazid and rifampicin	Protocol in final stages
EFV 400 mg pregnancy	SSAT/BMGF	PK EFV 400 mg in third trimester pregnancy and post partum	Protocol in final stages
ULTRA-HAART EFV 200 vs 400 vs 600 mg	UK MRC	EFV 200 vs 400 vs. 600 mg once daily, non-inferiority plus superior tolerability with reduced doses 96 weeks Multinational	Funding approval phase
Dolutegravir			
NAMSAL DTG vs 400 mg EFV	ANRS	400 mg EFV plus 3TC/TDF vs DTG plus 3TC/TDF in 550 antiretroviral naive participants 48 weeks Sites in several African countries	First line, phase III investigator-led study Few exclusion criteria, includes people with TB co-infection and aims to be as close as possible to real life Cofunding under discussion
DOLphin (dolutegravir in pregnant HIV mothers and neonates)	University of Liverpool/ Makerere University/ ViiV	DTG PK in pregnant women in third trimester and post partum during breastfeeding 60 late presenting women (after 28 weeks gestation) Women randomized 1:1 to receive DTG (50 mg once daily) or standard of care (EFV) plus two NRTIs. Sites in Uganda	Phase II investigator-led study Protocol in final stages

Trial	Implementer/Sponsor	Design	Status/Comments
TB	ViiV	DTG vs EFV, 50 mg DTG twice daily during TB treatment with rifampicin in 125 treatment naïve participants 48 weeks	Phase IIIb Protocol approved
Malaria	University of Liverpool/ Makerere University	PK DTG and artemisinin-based combination therapies for in 46 healthy volunteers	Phase I investigator-led study
Second line	ViiV	DTG vs LPV/r in approximately 600 1st line treatment experienced participants with virological failure in LMIC Multinational	Phase IIIb
ARIA	ViiV	DTG/ABC/3TC vs. ATV/r+TDF/FTC in 470 treatment naive women Pregnancy is an exclusion criterion Multinational, sites in South Africa	Phase IIIb study Underway
Pregnancy	ViiV	DTG 50 mg PK and safety third trimester and post partum in women who become pregnant in DTG/ABC/3TC FDC study	Not yet recruiting
SL2 pilot	BMGF	DTG+DRV/r 400/100mg once-daily * vs DTG+DRV/r 800/100 once daily vs. TDF/FTC+DRV/r once daily in 120 treatment naïve participants 48 weeks	Funding approval phase
SL2 registration	BMGF	DTG+DRV/r 400/100 vs. TDF/FTC+DRV/r 800/100 once daily in 600 1st line experienced participants Powered for non-inferiority 96 weeks Africa/SE Asia	Funding approval phase Data for FDA, PEPFAR and WHO approval
Darunavir/ritonavir			
DRV/r once daily trial (South Africa)	WRHI	200 2nd line participants stable on LPV/r+2 NRTI twice daily to stay or switch to DRV/r 400/100mg once daily 48 weeks	Funding approval stage
DRV/r once daily (France)	ANRS	Single arm 100 stable participants switch to DRV 400/100 once daily plus 2 NRTI	Starting later 2014

ANRS, National Agency for AIDS Research, France; BMGF, Bill & Melinda Gates Foundation; SSAT, St Stephen's AIDS Trust, UK; UK MRC, UK Medicines Research Council; WRHI, Wits Reproductive Health and HIV Institute, South Africa.
*Arm conditional on favourable results from DRV/r 400/100 mg

Tenofovir alafenamide

TAF is not yet approved and in phase III—it could also be a useful new drug (the development plans are discussed in the adult antiretroviral chapter of this report). With doses 10 times or more lower than that of TDF, the cost of TAF is predicted to be appropriately lower, and could come in at an annual patient cost of as little as US$20.[65]

Gilead are hopeful that this compound will have a better safety profile at a much lower dose than TDF. It is critical that Gilead recognizes the potential for this compound as a future component of generic FDCs.

At present the Gilead is prioritising the development of TAF in potential FDCs with elvitegravir (EVG, its own integrase inhibitor that needs to be boosted), the boosting agent cobicistat (COBI) and FTC. It is also developing an FDC with boosted DRV/r.

Due to a drug-drug interaction with COBI that increases the levels of tenofovir 2.5-fold, a dose of 10 mg is being used in regimens with boosted agents.

The information generated by the development program might not be sufficient inform the production of a generic FDC of TAF/DTG/3TC, as prioritised by CADO-2.

Close to 300 activist organisations and individuals signed letter to Gilead demanding that the company conducts investigations into dosing of TAF in unboosted regimens.[66]

Recent discussions have been more promising and the company is developing a 10mg and/or 25mg TAF plus 200mg FTC coformulated tablet(s). The TAF dose will depend on the results of pharmacokinetic evaluations. From the original dose ranging studies where 8 mg monotherapy was non-inferior to 300 mg TDF, 10mg might be sufficient for unboosted regimens.

This drug-drug interaction work is currently ongoing.

In future the long term it will be important to include TAF in real life trials, in place of TDF.

Long Acting Formulations

There is a lot of excitement about the possibility of long acting formulations for resource limited settings—also discussed in the adult antiretroviral chapter of this report—and their potential to vastly change standard of care.

As yet there is not clarity on the target product profile—both for the molecules and for patient acceptability—for these formulations. Nor is it clear if the right combination of compounds required to construct a suitable regimen are available or even in development.

What Needs to Be Done?

1. **Treatment optimization must best serve people with HIV**

   This is repeated once again but deserves emphasis. The d4T trial remains an example of a widely unpopular strategy. Acceptability for HIV-positive people and activists is always important. This will become increasingly so as indications for starting become broader and more asymptomatic people with HIV are offered treatment.

   There is some concern that DTG might only be prioritized for second-line treatment. If DTG is as good a drug as it appears (and a better and more tolerable one than EFV) it should also be recommended first-line. There will be sufficient numbers of people who fail first-line treatment with the currently recommended EFV-based regimen to justify the DRV/r plus DTG second-line strategy. Research and formulation work needed to make first-line DTG regimens an option must be conducted.

2. **Plan phase III and subsequent trials to generate necessary data**

   As far as possible when trials are being planned for registration, these should be designed with broader populations—that will eventually use the drug—in mind.

   Where information is not going to be forthcoming from these, the originator companies and independent investigators need to fill the gaps in a timely fashion.

3. Investments must be made

In order to generate data to provide evidence to make it possible to use new drugs and strategies that will not come from registrational trials additional research will be needed. Funding and support for complementary studies for resource limited settings is critical.

4. Speed up the time between approvals

There are still big gaps between full FDA/EMA approval and WHO prequalification, FDA tentative approval, and approval by local regulatory agencies.

Delays with the registration process, in addition to production by generic manufacturers and recommendations in national guidelines, means that it takes years from promising results in trials and initial approval to wide availability for the majority of people in need of antiretroviral treatment.

5. Joined up planning and thinking

This is happening more and more. It is unfortunate that after ENCORE1 results were announced additional information is still needed before the lower dose EFV can be recommended. For future optimization work, additional research needs to be done simultaneously with the main trials and not considered afterwards.

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The Pediatric Antiretroviral Pipeline

By Polly Clayden

Since last year's *Pipeline Report* dolutegravir (DTG) was approved for children aged 12 years and older in the United States and Europe.[1,2] The approvals for this age group were granted at the same time as that for adults—a good precedent for older children.

At the other end of the age band spectrum, in the United States, raltegravir (RAL) was approved for infants aged four weeks and older[3] and atazanavir (ATV) for three months and older.[4]

The *World Health Organization (WHO) 2014 Supplement to the 2013 Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection* includes a useful pediatric chapter, *Optimizing Antiretroviral Drugs for Children: Medium- and Long-Term Priorities*.[5] The chapter considers both priority formulations needed to treat children according to the guidelines and research priorities for pipeline drugs at advanced stages of development.

The list of pediatric formulations recommended by WHO and currently available was updated, and shows that what we have on offer now is still far from optimal.[6]

UNITAID, Drugs for Neglected Diseases Initiative (DNDi) and the Medicines Patent Pool (MPP) launched the Paediatric HIV Treatment Initiative (PHTI) that should help to move along the development and delivery of specific formulations and regimens appropriate to children. Despite considerable strides in the last few years, innovation and access in antiretrovirals for children still lags behind that for adults.[7]

WHO Recommendations

One of the goals of treatment optimization is to align pediatric antiretroviral regimens with recommendations for adults. With current options, the youngest children need to be considered differently, and there is some room for interpretation in the guidelines as to what age this harmonization should begin.

In order to implement the revised guidelines, child-sized solid dosing forms of recommended antiretrovirals, in appropriate strengths, are needed to facilitate dosages according to WHO simplified dosing tables.

Where possible these should be fixed-dose combination (FDC) dispersible tablets. For compounds that cannot be formulated in this way (large and/or insoluble molecules) granules are preferable to liquids. Liquid formulations are expensive, have short shelf lives, and often require a cold chain, making them hard to store and transport.

WHO recommendations for children are shown in table 1.

Table 1: WHO recommendations for children

First line	<3 years old	LPV/r-based regimens regardless of previous NNRTI exposure. If LPV/r is not feasible, NVP-based Consider substituting LPV/r with an NNRTI after sustained virological suppression (defined as viral load less than 400 copies/mL at six months, confirmed at 12 months from starting treatment) Children who develop active TB while on LPV/r- or NVP-based regimens should be switched to ABC + 3TC + AZT during TB treatment. They should switch back to the original regimen when their treatment for TB is completed The NRTI backbone should be one of the following (in order of preference): ABC or AZT + 3TC; d4T + 3TC
	> 3 years	EFV preferred and NVP alternative < 12 years or weighing less than 35 kg, backbone (in order of preference): ABC+3TC; AZT or TDF + 3TC or FTC
	>12 years	Adolescents 12 years (weighing more than 35 kg) should align with adults, the backbone: TDF+ 3TC or FTC; ABC or AZT + 3TC.
Second line		After first-line NNRTI failure, a LPV/r regimen is preferred After LPV/r failure, children <3 should remain on the regimen with improved adherence support After failure of first-line regimen containing ABC or TDF + 3TC or FTC, the preferred backbone is AZT + 3TC After failure of first-line regimen containing AZT or d4T + 3TC or FTC, the preferred backbone is ABC or TDF + 3TC or FTC

ABC, abacavir; AZT, zidovudine; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; TB, tuberculosis

Missing Formulations

In contrast to adults—who have two preferred first line regimens and a couple of alternatives—WHO recommendations for children are not very simple and somewhat aspirational. Only one regimen, zidovudine (AZT) plus lamivudine (3TC) plus nevirapine (NVP) is currently available as an FDC. Many gaps remain in available products for children

According to recommendations from the Paediatric Antiretroviral Drug Optimization (PADO) conference—that informed the WHO 2014 supplement—and the Paediatric Antiretroviral Working Group (PAWG) of the WHO, the following formulations must be given priority in the medium term (five years):

Zidovudine (AZT) or abacavir (ABC) plus 3TC plus lopinavir/ritonavir (LPV/r) These formulations are in development and urgently needed to make it possible to give FDCs to children younger than three. Solid forms could overcome palatability issues with the currently available LPV/r liquid formulation that tastes dreadful (although taste making is a lot harder than it sounds). Many barriers with supply chain—transport, storage and distribution—would also be addressed.

ABC plus 3TC plus efavirenz (EFV) Currently this regimen can only be given by using ABC/3TC co-formulated tablets with EFV tablets. A one-pill once-daily regimen for children aged three to 10 years would be useful. There is some discussion as to what dosing ratios for the FDC best facilitate recommendations for the individual agents across weight bands. Optimal doses need to avoid under and overdosing of children at either end of each weight band, as far as possible, and be most suitable from a regulatory standpoint.

Darunavir/ritonavir (DRV/r) This boosted protease inhibitor could offer an alternative to LPV/r second-line. Children who fail on LPV/r-based first-line regimens particularly need a robust option second-line. Dosing recommendations (approved by regulators in the United States and Europe) for DRV/r for children in low- and middle-income countries need to be simplified to reduce the number of different formulations and minimize pill burden. A 240/40 mg DRV/r tablet for twice-daily dosing is a priority for children in weight bands 10 kg and above. There is a waiver for children less than three years old.

Ritonavir (RTV) granules An alternative to the liquid formulation is needed to make double boosting—adding extra RTV to overcome pharmacokinetic interactions with tuberculosis (TB) drugs during cotreatment—easier with LPV/r.

Beyond five years, the participants of the PADO conference recommended that an FDC containing raltegravir (RAL) with 3TC and ABC or AZT should be encouraged. This regimen would provide a second line option, particularly to the children who fail on LPV/r first-line before they are three years old.

Three of the new drugs, currently under investigation or in phase III for adults or children, were recommended to be given priority:

Dolutegravir This integrase inhibitor has recently been approved for adults and children aged 12 years and above. It is currently under study for use in all age groups from birth. DTG has shown good safety, efficacy and tolerability so far, does not require boosting and has a low milligram dose. There is a lot of interest in this drug as an option for adults and children for first- and second-line regimens.

Tenofovir alafenamide fumarate (TAF) A potentially safer alternative to tenofovir disoproxil fumarate (TDF)—which is associated with renal and bone toxicity—is a priority for children. Early data in adults suggests that TAF might have a better safety profile than TDF but this has yet to be confirmed in children. It also has a low milligram dose. It might also be an alternative to ABC, and contribute to harmonizing children's regimens with adults, particularly if it could be coformulated with DTG and 3TC.

Cobicistat (COBI) COBI might be a useful booster for children. RTV-boosted pediatric versions of atazanavir (ATV) and DRV are unavailable and COBI-boosted pediatric formulations are under investigation.

THE PIPELINE

This list is not exhaustive—pediatric investigation plans will be in place or under discussion for the agents in early phases of development described in the adult antiretroviral chapter—but includes those where studies have started in children.

For approval by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) antiretrovirals are studied in children in deescalated age bands: 12 to 18 years; six to 12 years; two to six years; six months to two years and less than six months. Data are required in the youngest age groups—down to newborns—unless a regulatory waiver is obtained.

The majority of formulations currently in development are solid rather than liquid ones—a vast improvement on earlier pediatric antiretrovirals.

NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITOR

Tenofovir alafenamide fumarate

TAF is not being developed as a single agent for adults or children but it is considered to be of high priority for future optimized generic FDCs.

The originator company, Gilead is investigating a coformulation with FTC, which hopefully will provide data to inform the dose of TAF as a component of future unboosted generic regimens.

Development of a TAF-containing FDC (see below) is priority for the company.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Etravirine

A scored 25 mg etravirine (ETR) tablet, and dosing recommendations for treatment-experienced children and adolescents ages six to less than18 years of age and weighing at least 16 kg, are currently approved.[8] The recommended dose is based on 5.2 mg/kg twice daily.

IMPAACT P1090 is evaluating the drug in treatment-naive and -experienced children ages two months to six years.[9] Phase I/II studies in the younger age groups are currently enrolling treatment-experienced children. There is a waiver for infants less than two months.

Rilpivirine

Rilpivirine (RPV) is approved for adults with viral load less than 100,000 copies/mL. PAINT (Pediatric study in Adolescents Investigating a New NNRTI TMC278), is an ongoing, open label, 48-week phase II trial looking at RPV pharmacokinetics, safety and efficacy in treatment naive adolescents aged 12 to 18 years, weighing more than 32 kg.[10]

RPV steady-state pharmacokinetics plus preliminary four-week safety and efficacy data from PAINT (with a 25 mg once daily dose) showed comparable RPV pharmacokinetic parameters between adults and adolescents.[11]

Participants (n=23) of a median age of 15 years were enrolled from sites in India, Thailand, Uganda and South Africa. All were treated with RPV in combination with two nucleos(t)ide reverse transcriptase inhibitors (NRTIs), taken with a meal.

There was no apparent relationship between pharmacokinetic parameters and weight, age or between sexes. PAINT is ongoing.

IMPAACT P1111 is planned in children from neonates (two weeks) to less than 12 years.[12]

A granule formulation is in development.

PROTEASE INHIBITORS

Atazanavir

FDA recently approved ATV oral powder for use in treatment naive or experienced infants over three months of age who weigh more than 10 kg or less than 25 kg.[13]

The oral powder must be mixed with food or drink for administration and RTV must be given immediately afterwards. It comes in packets containing 50 mg ATV.

Table 3 shows the recommended dosage of ATV oral powder and RTV.

Table 3: Recommended dosage of ATV oral powder and RTV oral solution for infants at least three months of age and weighing at least 10 kg and less than 25 kg

Body weight	ATV	RTV
>10 to <15 kg	200 mg (4 packets)	80 mg
>15 to <25 kg	250 mg (5 packets)	80 mg

The safety, pharmacokinetic profile, and virologic response of ATV in infants were established in three open-label, multicenter clinical trials: PACTG 1020A, AI424-451 (PRINCE 2), and AI424-397 (PRINCE 1).[14,15,16,17,18]

This approval for the youngest age group has taken its time—adult ATV approval was in 2003 and for older children in 2008.

Lopinavir/ritonavir

There is currently an 80/20 mg/mL liquid formulation of LPV/r, but it is unsuitable for most settings. It tastes appalling. There are also scaled down 100/25 mg heat stable tablets available for children, but these are only suitable for those weighing 10 kg or more. The tablets are formulated with the active ingredient embedded in a matrix of insoluble substances, so cannot be split or crushed as they lose bioavailability.

Cipla has developed a more acceptable solid formulation of LPV/r, which has been submitted to the FDA for approval.

This formulation (40/10 mg LPV/r) consists of a finite number of pellets in a capsule, which is opened and sprinkled on soft food. The development of this formulation of LPV/r has involved complex nomenclature: first called sprinkles, then briefly mini-tabs these are now referred to as pellets.

Data from a randomized crossover pharmacokinetic study in HIV-negative adults comparing a single dose of pellets from 10 capsules of LPV/r with a single dose of 5 mL Kaletra oral solution found most pharmacokinetic parameters fell within the conventional bioequivalence range of 80% to125 %. Where they fell outside, the differences were not large.[19] Both formulations were administered with about 150 g porridge and 240 mL water.

Initial data from CHAPAS-2[20]—which compared twice-daily pellets to tablets in children ages four to 13 years, and pellets with syrup in infants ages three to 12 months in a randomized cross-over pharmacokinetics study—found high variability in the younger cohort with both pellets and syrup, with no significant differences in sub-therapeutic concentrations between formulations. In the older children, LPV/r concentrations were lower in children receiving the pellets than in those who got the tablets.

The caregivers found the pellets were more acceptable for infants but not for older children, mainly due to the taste. Storage, transport, and conspicuousness of treatment were less problematic for pellets compared with syrups, but for older children, several caregivers commented about the number of capsules needing to be used.

At week eight, when they could chose which formulation to continue with, the majority of caregivers chose to continue pellets rather than syrups for the infants, but only a quarter of the older children chose pellets over tablets, and taste was particularly to blame.

When the investigators performed the same comparison in one to four year olds, LPV exposure with pellets was higher than with syrup and historical data for children aged six months to12 years.[21] There was moderately high variability in with both formulations but neither gave subtherapeutic levels.

Poor taste was reported most frequently as a problem with both formulations, followed by swallowing difficulty. Although the majority of caregivers rated both formulations unpleasant, they reported easier storage and transportation with pellets compared to syrup.

The LPV/r pellets have been submitted to the FDA for approval.

DNDi and Cipla are now developing a more palatable version of LPV/r for infants and young children: combined 4-in-1 granule formulation (finer than the 0.8mm pellets and more sand-like in texture) FDCs with two NRTIs, ABC or AZT, plus 3TC.

In recognition of the urgency of suitable options for the youngest age group DNDi was awarded a substantial grant by UNITAID to expedite the development and delivery of the 4-in-1 formulations.[22] The partnership is now working on further PK and acceptability investigations of improved granules with better taste masking.

The plan is to have the optimized 4-in-1 formulations by 2015.

INTEGRASE INHIBITORS

Dolutegravir

The FDA and EMA recently approved DTG for children and adolescents aged 12 and above. Since FDA approval DTG has also been approved in a further nine countries.

It is being evaluated for children in IMPAACT P1093 – an ongoing, phase I/II, open label pharmacokinetic, safety and efficacy study in children and adolescents.[23] Preliminary 24-week data from the 12 to 18 years cohort of the study were included with the adult regulatory submissions and led to the recent approvals.

Twenty-four week data have been shown for children aged six to 12 years and 48-week data for children and adolescents aged 12 to 18 years.[24]

Treatment experienced but integrase inhibitor naive children (n=11) with viral load > 1000 copies/mL were enrolled in an intensive PK evaluation. Participants received DTG tablets (10, 25, 50mg) dosed at 1 mg/kg once daily (based on weight bands) added to a stable, failing regimen, with optimized background therapy added after the pharmacokinetic evaluation, which was performed between days five and 10.

Children were a median age of 10 years and had received prior antiretroviral treatment for a median duration of about nine years and just over half were triple class experienced. The dose of 1 mg/kg once a day achieved adequate DTG exposure. Adolescents, aged 12 to 18, had also previously achieved pharmacokinetic parameters comparable to those in adults with the pediatric weight band dose.[25] Both age groups showed good short-term safety and tolerability.

And in a safety and efficacy evaluation of the older age group, at 48 weeks, 74% of adolescents (n=23), a median of 15 years achieved virologic suppression <400 copies/mL and 61% <50 copies/mL. There were no serious adverse events.[26]

Two reduced-strength 10 mg and 25 mg tablets have been developed for children.

A granule formulation is in development, and results from a phase I pharmacokinetic study in HIV-negative adults has been shown.[27] The granules were given with and without 30 mL of various liquids and compared to the current tablet formulation given with 240 mL of tap water.

Participants received a single dose of DTG as a 50 mg tablet (adult formulation) and as 10 g of granules given: with no liquid; with purified water; mineral water; or infant-formula milk.

DTG exposures of the granule formulation were all moderately higher than those of the tablet formulation, with or without liquids. Exposure was highest when the granule formulation was given with formula milk.

The granule formulation is currently being evaluated in the six to 12 age group of IMPAACT P1093.

A possible treatment strategy trial ODYSSEY (PENTA 20) of DTG in all age groups of children is also under discussion.

Development of a pediatric formulation of the FDC of DTG plus ABC plus 3TC, (572-Trii)—currently under investigation for adults—is also planned. Following the results from the ARROW trial,[28] which found once-daily dosing of ABC and 3TC non-inferior to twice-daily in children, ViiV is submitting data for this indication, which will inform the development of the once-daily pediatric formulation. The development of this formulation will depend on the DTG dosages across the age groups and the dosing ratios of the regimen components.

Further along the adult pipeline, the follow-up integrase inhibitor S/GSK-1265744, under investigation as a long-acting formulation, has provoked interest as a potential treatment of adolescents (as has the long-acting formulation of RPV).

The company is working in partnership with Clinton Health Access Initiative (CHAI) and Mylan on a dispersible tablet FDC of ABC plus 3TC. They will transfer the technology and resources to the generic company for production, registration, and distribution of this at the lowest possible cost for low-income countries.[29] Any lessons learned with the collaboration should be used to ensure that DTG—assuming it fulfills its early promise—is available, including in appropriate FDCs, for children in poor countries without delay.

Raltegravir

In December 2013 the FDA approved a new oral suspension formulation of RAL for use in infants aged four weeks and older, weighing at least 3 kg to less than 20 kg.[30]

Each single-use packet for oral suspension contains 100 mg of RAL, which is suspended in 5 mL of water giving a final concentration of 20 mg/mL.

The updated label now includes detailed information about dosing of both this suspension and the pediatric chewable formulation. Because the formulations are not bioequivalent, chewable tablets and the oral suspension are not interchangeable and have specific guidance.

The oral suspension is expected to be commercially available by the third quarter of 2014.

The adult 400 mg film-coated RAL tablet is approved in the United States for use in children ages six to less than 18 years, weighing above 10 kg, and 100 mg and 25 mg chewable tablets are approved for children above two to less than 12 years at a maximum dose of 300 mg.[31] The 100 mg tablet is scored so it can be divided in half.

The pediatric program is ongoing in IMPAACT P1066.[32]

RAL also has the potential for use as prophylaxis to prevent vertical transmission to infants, and for treatment of HIV-infected infants. IMPAACT P1097 is an ongoing phase IV washout (passive) pharmacokinetic and safety study of infants, born to women who received at least two weeks of RAL (400 mg twice daily) in pregnancy and through labor.[33,34,35]

This is the first clinical trial of an investigational antiretroviral to look at neonatal pharmacokinetics. RAL crosses the placenta well. It is metabolized primarily by a liver enzyme (UGT-1A1), which is immature in neonates. UGT pathways increase in activity hugely in the first weeks of life, reaching adult levels within three to six months.

Early results from this study show good placental transfer with cord blood to maternal plasma concentration ratio of approximately 1.5. Transplacental half-life is long—24 to 36 hours—in neonates. Neonatal RAL elimination is highly variable.

IMPAACT P1110 is an open label pharmacokinetic and safety single and multiple dose study of RAL granules in high-risk HIV-exposed neonates.[36] Multiple dosing will be from birth to six weeks and HIV-infected infants will continue after six weeks.

Elvitegravir

Elvitegravir (EVG) is an integrase inhibitor, given with a booster and mostly used for adults in the FDC containing EVG/COBI/FTC/TDF (E/C/F/TDF).

A phase Ib open-label non-randomized trial, conducted in treatment-experienced adolescents 12 to 18 years receiving 150 mg once daily EVG plus a RTV-boosted protease inhibitor-optimized background regimen, showed comparable exposures to that seen in adults.[37]

Two pediatric formulations are in development—a 50 mg tablet and a 5 mg/mL suspension. Single dose pharmacokinetics evaluations compared two formulations to the 150 mg adult formulation (all boosted by RTV) in a crossover study in HIV-negative adults.[38]

All formulations of EVG were given with 100 mg RTV within five minutes of a standard meal.

In this study, both pediatric formulations were bioequivalent to the adult formulation.

These RTV-boosted formulations will be evaluated in children in an ongoing phase II/III study in children aged 4 weeks to less than 18 years of age.[39]

EVG is also being studied in treatment naive adolescents aged 12 to 18 years as a component of the adult FDC, E/C/F/TDF containing EVG 150 mg, COBI150 mg, FTC 200 mg and TDF 300 mg.[40,41] Early data has shown similar exposures of all the individual agents to adults and good virologic suppression. Study of E/C/F/TDF in adolescents and children continues.

PENTA 17 will evaluate EVG with DRV/r in stable, virologically suppressed children.

An adolescent study of the FDC containing EVG/COBI/FTC/ TAF (E/C/F/TAF) in treatment naive adolescents is also ongoing.[42] Gilead plan to submit regulatory applications that include approval requests for adolescents ages 12 to less than18 years for this FDC.

PHARMACOKINETIC BOOSTER

Cobicistat

COBI is a CYP3A inhibitor with no antiretroviral activity that is approved for adults as a booster of ATV 300 mg or DRV 800 mg. It is also under investigation for children and adolescents six years and above as a component of the FDCs E/C/F/TDF and E/C/F/TAF.

A 50 mg pediatric immediate release tablet and a 20 mg pediatric dispersible tablet are in development. Both were compared to the 150 mg adult tablet formulation in a crossover study in HIV negative adults.[43] Both formulations were bioequivalent to the adult one.

COBI is being studied in treatment experienced children ages three months to 18 years, who are suppressed and on a RTV boosted ATV- or DRV-containing regimen.[44] The study will switch children from the RTV to COBI booster and look at steady state pharmacokinetics and confirm the dose. It will also evaluate the safety, tolerability, and efficacy of ATV/COBI or DRV/COBI.

There is a lot of interest in the potential role for COBI, not least because the RTV patent has not allowed coformulation with protease inhibitors other than the originator company Abbvie's LPV.

CCR5 RECEPTOR ANTAGONIST

Maraviroc

The A4001031 maraviroc (MVC) study is ongoing in children aged two to less than18 years old who are infected with the CCR5-tropic virus (virus variants that use the CCR5 receptor for entry). This drug will not work for people with the CXCR4-tropic virus or in dual- or mixed-virus (CCR5/CXCR4) populations.[45]

Preliminary data in 29 children showed body surface area (BSA)–based doses of MVC provided adequate exposures when administered with a protease inhibitor as part of their background regimen. Children who were not receiving a boosting agent in their background regimen required at least doubling of the initial dose.[46]

A BSA–scaled twice-daily tablet dose of MVC in treatment-experienced children

six years and above concomitantly receiving boosted protease inhibitors (DRV/r and LPV/r) achieved concentrations similar to those in adults receiving 150 mg MVC twice daily with a boosted protease inhibitor.[47]

Data from 94 participants in the A4001031 study continued to show that dosing is complex and determined by BSA and concomitant medications.[48]

BSA-based dosing with boosters scaled from the 300 mg adult dose provides MVC exposures achieving the target Cavg >100 ng/mL in all cohorts.[49]

Non-boosted regimens are still under evaluation and pharmacokinetic data suggests that doses are likely to be higher than the initial adult BSA scaled dose.

Enrollment in A4001031 will continue out to five years.

Table 2. The Pediatric Antiretroviral Pipeline

Compound	Sponsor	Formulation/s and dose	Status and comments
Nucleotide reverse transcriptase inhibitor			
Tenofovir alafenamide (TAF)	Gilead	Dose to be determined for children Under investigation in adolescents with adult dose as a component of E/C/F/TAF (see below)	Phase II/III E/C/F/TAF treatment-naive adolescents 12 to <18 years enrolling Co-formulation with FTC under discussion
Non-nucleoside reverse transcriptase inhibitors			
Etravirine (ETR)	Janssen	Dispersible tablets 25 (scored), 100 mg	Approved for 6 to18 years Phase I /II treatment experienced 2 months to <6 years and treatment-naive ≥2 months to <2 years enrolling
Rilpivirine (RPV)	Janssen	Tablet 25mg Granules 2.5 mg /g	Phase II 12 to <18 years >32kg enrolling Phase I/II, >2 to <12 years, planned
Protease inhibitors and combinations			
Atazanavir (ATV)	Bristol-Myers Squibb (BMS)	Powder 50mg sachet under development Capsules 100, 150, 200, 300mg	Approved for 3 months and above by FDA Phase III/IIIb ongoing, RTV boosted-ATV for 3 months to <6 years treatment-naive and experienced Other studies up to 11 years ongoing
Atazanavir/cobicistat ATV/COBI	Gilead/BMS	Co-formulated boosted PIs in development	Phase II/III treatment experienced 3months to <18 years
Darunavir/cobicistat DRV/COBI	Gilead/Janssen		
Lopinavir/ritonavir LPV/r	Cipla	40/10 mg pellets in capsules	Submitted to FDA
Lopinavir/ritonavir/ lamivudine/abacavir or zidovudine LPV/r/3TC/ABC or AZT	DNDi/Cipla	4-in-1 FDC granules	Formulation work ongoing
Booster			
Cobicistat (COBI)	Gilead	75 mg tablets 20 mg dispersible tablets for oral suspension	As booster with ATV and DRV Under development as component of E/C/F/TDF and E/C/F/TAF

Compound	Sponsor	Formulation/s and dose	Status and comments
Integrase inhibitors and combinations			
Raltegravir (RAL)	Merck	Granules for suspension 6mg/kg (100 mg sachet)	FDA-approval for use in children 4 weeks of age and older Neonate passive PK study ongoing (neonates born to women who received RAL in pregnancy and during labour) Neonates PK and safety study for prophylaxis ongoing in high-risk HIV-exposed neonates from birth to six weeks
Elvitegravir	Gilead	EVG reduced-strength tablets and suspension in development	EVG PK completed, RTV boosted 12 to <18 years RTV- boosted EVG to be studied in all age groups
E/C/F/TDF (Stribild)	Gilead	Reduced strength tablets in development	Studies underway in treatment naive 12 to <18 years 6 to <12 years planned (waiver <6 years)
E/C/F/TAF	Gilead	Reduced strength tablets in development	Studies underway in treatment naïve 12 to <18 years. 6 to <12 years planned (waiver <6 years)
Dolutegravir (DTG)	ViiV Healthcare	Granule formulation in development Reduced-strength 10 mg and 25 mg tablets	Approved for adolescents 12 to <18 years weighing ≥40kg in US and Europe Phase I/II study, 6 weeks to <18 years treatment-naive and -experienced children, ongoing Exposures from granules were moderately higher than with tablets and highest with formula milk in HIV-negative adults
DTG/ABC/3TC (572-Trii)	ViiV	Pediatric formulation development planned Dosing to be determined	Dependent on ongoing studies confirming DTG dose in children and ability to establish appropriate dosing ratios for components
CCR5 Receptor Antagonist			
Maraviroc (MVC)	ViiV	Suspension 20 mg/mL	Phase IV Treatment-experienced CCR5 tropic 2 to <18 years

What Needs to Be Done?

Despite progress scaling up antiretrovirals, the gap in coverage between adults and children is growing. The latest estimates suggest that only 34% of children less than 15 years old, eligible by WHO 2013 guidelines, were receiving treatment compared with 61% coverage for adults.

Partly due to the lack of suitable formulations, children's treatment remains much more centralized than adults. Task shifting and integration of services have not been adopted so widely for children compared to adults. We know how important it is to bring care and treatment closer to the people: every extra kilometer means loss to follow up.

The solid forms of LPV/r in the pipeline—the first awaiting approval any time soon—will do away with the need for a cold chain and other aspects of storage, transport, distribution and administration.

Their arrival will be good news: new formulations will not only enable countries to adopt WHO 2013 guidelines but will make task shifting and decentralization more possible.

Other good news is that there have been concerted efforts in the last year or so to define actions needed to increase access to drugs and formulations for children. It is encouraging that the recommendations from the PADO Conference, published in the WHO 2014, supplement as well as the roundtable, organized by DNDi that followed it,[50] differ little from those made in the *Pipeline Report* in this and previous years.

1. **Implement WHO Recommendations**

   As simpler formulations identified to implement the guidelines become available, countries must ensure that they are swiftly approved and distributed, with appropriate training for health workers.

2. **Support New Models of Research and Development**

   More innovative models of research and development, as well as agreements between originator companies and generic ones to produce child-adapted formulations in a timely fashion must be made. UNITAID, DNDi and the MPP recently announced the PHTI to expedite development and delivery of new antiretroviral formulations.[51]

The initiative will work on the priority formulations with a focus on research and development, intellectual property, and market shaping. DNDi will coordinate the research and development component of the PHTI, working with pharmaceutical companies, academic institutions, WHO expert groups, and other stakeholders.

3. Ensure that Patents are Not an Obstacle

The MPP is putting a lot of emphasis on pediatric antiretrovirals and for the PHTI it will build on patent sharing agreements that have already been negotiated.

ViiV Healthcare (DTG, ABC), Gilead Sciences (TDF, FTC), and Bristol-Myers Squibb (ATV), have licensed to the MPP. Merck/MSD and Abbvie are in negotiations to license pediatric formulations of RAL and LPV/r.

Licenses for the drugs in development need to make it easy to transfer patent agreements from one age group to another as approval is gained.

4. Speed Up Approval

The gap needs to be narrowed between approval of new drugs for adults, children and neonates.

Harmonization of regulatory requirements (including age categories and weight bands) between stringent authorities, WHO prequalification, and national authorities is urgently needed to help speed up approval.

5. Coordinate Procurement

Guidance on optimal formulations needs to be easily available to countries and updated as better ones become available.

Companies need to be informed of the priority formulations.

Donors need to ensure the availability of low volume products in a diminishing market.

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Hepatitis C Pipeline

By Tracy Swan

BONANZA! The Gold Rush Is Under Way

The direct-acting antiviral (DAA) era officially began in late 2013, with approval of the first all-oral treatment for hepatitis C virus (HCV) genotypes 2 and 3. A hefty pipeline will increase HCV treatment options, especially for people with genotype 1, by mid-to-late 2014. Cure rates above 95 percent—after only 12 weeks of treatment—have become commonplace in HCV clinical trials.* DAAs have been miraculous for people with cirrhosis, HIV/HCV coinfection, and before and after liver transplantation.

But the outrage about sky-high DAA prices is quickly overtaking excitement about these wonder drugs. Advocates and clinicians are forced to fight for access to outrageously expensive drugs for people who cannot wait for affordable options—or watch people die from a curable infection.

Gilead's nucleotide polymerase inhibitor, sofosbuvir—the backbone of most DAA regimens—is US$1,000 per tablet. Such a price limits access to this lifesaving drug, even in high-income countries, where the market for DAAs is projected to reach over US$100 billion by 2023.[1]

Gold Fever!

Analysts at Evaluate Pharma have deemed sofosbuvir "the most valuable research and development product [to date]."[2] At 21 weeks after launch, sofosbuvir sales have reached almost US$3 billion dollars, and analysts predict sales of up to US$9 billion dollars in 2014.[3]

If only 500,000 people in the U.S.—less than a quarter of those with chronic HCV—were treated with sofosbuvir, sales would reach US$45 billion dollars.

*A sustained virologic response (SVR)—meaning that hepatitis C virus becomes undetectable during treatment and remains undetectable for at least 12 weeks after treatment is finished—is equivalent to a cure.

DAAs Offer a Tantalizing Possibility: Global HCV Eradication

At least 185 million people have been infected with hepatitis C virus.[4] HCV is most prevalent in low- and middle-income countries (LMICs).[4] Egypt has the highest hepatitis C prevalence (14%) followed by Cameroon (13.8%), Uganda (6.6%), Uzbekistan (6.5%), the Democratic Republic of Congo (6.4%), and Pakistan (5.9%).[5,6,7] In populous LMICs such as China and India, HCV prevalence is lower, but the sheer number of people with HCV—almost 30 million in China and over 18 million in India—is staggering.[5,6,7]

Less toxic, more effective, and more convenient HCV treatment is a global boon for individual and public health. In April of 2014, the World Health Organization (WHO) issued *Guidelines for the Screening, Care and Treatment of Persons with Hepatitis C*.[8] The *Guidelines* are essential for informing decision makers and health care workers, but high-priced diagnostics and drugs will impede their implementation. "I hope these guidelines will help to promote a reduction in price and thereby an increase in access," said Stefan Wiktor, Team Lead of the WHO Global Hepatitis Programme.[9]

Global eradication of HCV is possible, if pharmaceutical companies will allow generic DAA production in LMICs. "Competition and generic production really are the keys to reductions in prices," says Dr. Wiktor.[10] DAAs can be produced inexpensively, according to an analysis from the University of Liverpool (using molecular weight, chemical structure, complexity, dose, and cost of comparable HIV antiretroviral agents). The actual production cost for 12 weeks of a single DAA ranges from US$10 to US$270, assuming an annual volume of 1–5 million treatment courses (see table 1).[5]

The Médecins Sans Frontières (MSF) Access Campaign has set a target price for the complete package of HCV diagnostics, care, and DAA treatment in LMICs: less than US$500.[11]

Table 1. DAA Regimens: Production Costs and Characteristics[5,12,13,14,15,16,17,18]

Regimen ($/gram)	Cost/Duration	Characteristics
Daclatasvir ($2–6/gram) + **sofosbuvir** ($2-4/gram)	$78–166/12-week	Pangenotypic SVR-24: 89–100% in phase II Ongoing phase III trials in HIV coinfection or cirrhosis/posttransplant May be possible to shorten treatment to 8 weeks in some populations
Daclatasvir + **ribavirin*** ($0.25–0.75/gram) + **sofosbuvir**	$112–224/12-week	Pangenotypic, RBV use may be unnecessary Ongoing phase III trial in cirrhosis/posttransplant

Regimen ($/gram)	Cost/Duration	Characteristics
ribavirin* + sofosbuvir	$102–194/12-week $204–388/24-week	Tx duration varies by HCV genotype; SVR-12, in treatment-naive: Genotype 1 (24 weeks of treatment) : 70% Genotype 2 (12 weeks of treatment): 93% Genotypes 3 and 4 (24 weeks of treatment): >90–100% Less effective in cirrhosis; may be possible to shorten treatment to 8 weeks in some populations
Simeprevir ($10–21/gram) **+ sofosbuvir**	$198–406/12-week	Effective against genotypes 1 and 4 (studied only in genotype 1); SVR-12 in null responders with mild-fibrosis, precirrhosis, and Child–Pugh class A cirrhosis: 93% SVR-12 in treatment-naive, precirrhosis, or Child–Pugh class A cirrhosis: 93%
Ribavirin* + simeprevir + sofosbuvir	$232–600/12-week	Adding RBV did not increase SVR in a phase II trial; ongoing phase III trials do not include RBV

* Weight-based dosing

HCV Diagnostics

Lack of access to HCV viral-load testing has been cited as a barrier to treatment scale-up, since it is essential—viral load is used to diagnose hepatitis C infection and to monitor response to, and outcome of, HCV treatment. Although DAA regimens require less monitoring than PEG-IFN-based treatment, the high price of, and technology required for, HCV viral-load testing curtails the opportunity to diagnose and treat hepatitis C.

AIDS activists—who are fighting to reduce the price of HIV viral-load testing in LMICs—may come to the rescue. Since the same technology can be used for both viruses, affordable HIV viral-load testing offers the potential to increase access to HCV viral-load testing. Other barriers will remain, even with affordable testing: the need for cold-chain transportation, expensive machinery, laboratory space, trained personnel, and stable electricity.

Lack of innovation in diagnostics is hindering global efforts to screen, diagnose, and treat HCV. Development of reliable, less complicated rapid and point-of-care testing is long overdue. The WHO has developed criteria for evaluating HIV point-of-care devices, known as ASSURED (affordable, sensitive, specific, user-friendly, rapid, and robust, equipment-free, and deliverable to end users).[19]

Choosing the Best First-Line DAA Regimen

I have the simplest tastes. I am always satisfied with the best.
—Oscar Wilde

Global progress against HCV has been hobbled by complex diagnostics and monitoring requirements, and suboptimal, expensive, and difficult-to-tolerate treatment. DAAs can radically simplify HCV treatment and reduce diagnostic and monitoring requirements. In the United States, the demand for HCV treatment is likely to outstrip the capacity of specialists to deliver it. Simple DAA regimens will make it easier for nonspecialist providers to begin treating HCV in people with less advanced liver disease.

The characteristics of optimal HCV regimens for resource-limited settings—simplicity, convenience, and manageability—are also relevant for high-income countries. Desirable characteristics for DAA regimens (assuming affordability, safety, and tolerability) include:

- Highly effective—cure rate of >80%—regardless of host and viral factors, especially in populations most likely to be prioritized for treatment (e.g., people with cirrhosis or HIV/HCV);
- Pangenotypic, potent regimens with a high barrier to drug resistance;
- Simple regimens that obviate a battery of pretreatment testing (IL-28B genotyping, viral subtyping, and drug resistance), and do not require extensive monitoring for safety, efficacy, and treatment outcome;
- Manageable drug-drug interactions, allowing coadministration with commonly used medications (treatment for HIV and tuberculosis, methadone, buprenorphine, statins, hormonal contraception, and psychotropic medications);
- Safety during pregnancy and nursing;
- Safety and efficacy in pediatrics;
- Fixed treatment duration (preferably ≤12 weeks);
- No food requirement;
- No cold storage needed;
- Once-daily dosing; and
- Low pill burden.

Table 2. DAA Regimens: Desirable Characteristics

Regimen/ Sponsor(s)	Status	Pangenotypic	Safe, effective in advanced liver disease	Acceptable tolerability (data may be limited)	Manageable drug-drug interactions	Duration ≤12 weeks	QD	Studied in HIV/HCV	SVR ≥90%
Fixed-dose combination (FDC): ABT-267/ABT-333/ ABT-450/r + RBV AbbVie	2014 Expected approval		X	X	?	X		X	X
Asunaprevir + BMS-791325 + daclatasvir BMS	2015 Expected approval		?	X	?	X			X
Daclatasvir + sofosbuvir BMS	2014 Expected approval	G1-3; ongoing trials in all genotypes	X	X	X	X	X	X	X
FDC: sofosbuvir/ ledipasvir Gilead	2014 Expected approval		X	X	?	X	X	X	X
FDC: sofosbuvir/ GS-5816 Gilead	2015 Possible approval	X	?	X	?	X	X	X	X
Sofosbuvir + RBV Gilead	Approved 2013	X	X	X	X			X	Only in G2
Sofosbuvir + PEG/IFN/RBV Gilead/Roche/ Merck; generics	Approved 2013	X	?	?	X	X		X	X
Sofosbuvir + simeprevir (off-label) Gilead/Janssen	Approved 2013		X*	X	X	X	X	X	X
MK-5172 + MK-8742 Merck	2015 Expected approval	Studies in G4–6 planned; also being studied with sofosbuvir in G3	?	X	?	?	X	X	X

*Child–Pugh class A cirrhosis only

There are no data on these regimens in people who inject drugs, during pregnancy and nursing, or in pediatrics (ribavirin is contraindicated in pregnancy, during nursing and in children under three years old). There are virtually no data on DAA safety, efficacy, and tolerability in people with common comorbidities.

Sofosbuvir, simeprevir, and ribavirin can be stored at room temperature (below 84°F or 28°C); sofosbuvir can be taken with or without food; ribavirin and simeprevir should be taken with food. Data on food and storage requirements for experimental DAAs are not available. All regimens have a low pill burden and require limited monitoring during treatment.

From the Graveyard to the Gravy Train: Nucleoside/tide Polymerase Inhibitors

Sofosbuvir—the only approved nucleoside/tide polymerase inhibitor—is pangenotypic, potent, has a high resistance barrier, few drug-drug interactions, and has proven to be safe and tolerable.

Developing HCV nucleoside/tide polymerase inhibitors is tricky, despite their potential. DAAs from this class (particularly guanosine-based nucleotides) have been discontinued because they were too toxic (BMS-986094 [renal and cardiac toxicity]; NM283 [gastrointestinal toxicity]; R1626 [lymphopenia and neutropenia]; PSI-983 [liver toxicity]).[20,21] Mericitabine is the only other nucleotide to have advanced into phase III, but further development seems to be stalled, possibly permanently. VX-135, a once promising candidate, has entered pharmaceutical limbo since Vertex announced plans to license it out.

But there may be more nucleotides: after setbacks with NM283, IDX184, and IDX19368—all discontinued—Idenix forged ahead with development of two uridine nucleotide polymerase inhibitors (IDX21437 and IDX21459). In June of 2014, Merck purchased Idenix. Achillion has a uridine nucleotide, ACH-3422, in a phase I trial.

HCV TREATMENT LANDSCAPE

Note: Comprehensive information on DAA regimens is available online, at http://www.pipelinereport.org/2014/hcv/update.

Genotype 1: There Is No Balm in Gilead

Despite the remarkably rapid progress against HCV, patients with genotype 1 and cirrhosis—who urgently need treatment to avert transplantation, liver cancer, and death—are still waiting for DAAs, since peginterferon may be too dangerous, too toxic, or ineffective. Yet there is an effective DAA regimen for genotype 1—even in null responders with compensated cirrhosis.

In COSMOS, a phase II trial, Janssen's simeprevir and Gilead's sofosbuvir were highly effective and safe for people with HCV genotype 1 and compensated cirrhosis, regardless of treatment history; cure rates over 90 percent were reported after 12 weeks of treatment.[22,23] Despite the need for, and promise, of this regimen, Gilead declined to continue codevelopment with Janssen.

Simeprevir and sofosbuvir have been approved separately. The combination was not approved by regulatory agencies, but treatment guidelines in the United States and the European Union recommend off-label use for people with HCV genotype 1 who are ineligible for interferon-based treatment.[24,25] Gilead's monopolistic approach has limited awareness of off-label HCV treatment options among physicians; according to a Decision Resources report, "a notable share" of gastroenterologists and infectious disease specialists continue to prescribe suboptimal boceprevir- and telaprevir-based treatment to genotype 1 patients (these regimens are no longer recommended by the American Association for the Study of Liver Diseases, the Infectious Diseases Society of America, or the European Association for the Study of the Liver).[26]

Collaboration between sponsors facilitates development of potentially lifesaving regimens. Unfortunately, commercial interests have trumped medical need—it is unacceptable that Gilead's desire to dominate the HCV market has delayed or complicated access to the best possible treatment.

Climb Every Mountain: Curing Genotype 3

Despite a gushing pipeline, there are still critical gaps in HCV treatment—especially in genotype 3, which has global distribution. An interferon-free cure-all for genotype 3—especially for people with cirrhosis—remains elusive, although there are DAA regimens in clinical trials. BMS is sponsoring ALLY-3, a 150-person phase III trial of daclatasvir and sofosbuvir in genotype 3 (treatment-naive and treatment-experienced). Merck is launching a phase IIb trial of sofosbuvir with a fixed-dose combination of MK-5172 (protease inhibitor) and MK-8742 (NS5A inhibitor) for 8 or 12 weeks.

There are three strategies for increasing efficacy of sofosbuvir-based treatment in genotype 3: adding peginterferon to a 12-week regimen of sofosbuvir and ribavirin; combining sofosbuvir with another DAA (daclatasvir, ledipasvir, or GS-5816); or extending the duration of treatment with sofosbuvir and ribavirin to 16 or 24 weeks. Each strategy has limitations. Peginterferon is unappealing to, or contraindicated for, many people; daclatasvir, ledipasvir, and GS-5816 are not yet approved (limiting access to people who are eligible for clinical trials, or early access and named-patient programs), and the cost of a 24-week regimen (US$168,000 for sofosbuvir) is likely to make payers balk.

High drug prices—not the basic human right to health care—are the bedrock of cost per cure.* Other factors, such as a country's disease burden, and the resources it has for hepatitis C are not considered. Cost per cure attempts to transform unaffordable medicines into bargains, by reducing health care costs in the future (for example, HCV cost per cure is less expensive than liver transplantation).

* "Cost per cure" is calculated by dividing a standard cost reference by the sustained virologic response (or cure) rate in a specific population, then multiplying it by 100.

Table 3. Genotype 3: Regimen, SVR-12, Relapse, and Cost[15,16,18,27,28,29,30,31,32]

Regimen/Duration	Population	SVR-12	Relapse	Estimated cost (U.S.-only; RBV 1,000 mg/day)*	Cost per cure (drugs only)
PEG-IFN/RBV, 24 weeks	Tx-naive	63% (110/176)	9% (16/176)	$20,478	$32,504
SOF + PEG-IFN/RBV, 12 weeks	Tx-naive	100% (18/18)	0%	$94,239	$94,239
	Tx-experienced	83% (20/24)	8% (2/24)		$113,540
SOF + RBV, 12 weeks	Tx-naive	56% (102/183)	40% (72/179)	$84,449	$150,801
	Tx- naive, HIV-positive	67% (28/42)	26% (11/42)		$126,043
	Tx-experienced	30% (19/64)	68% (44/64)		$281,496
SOF + RBV, 16 weeks	Tx-experienced	62% (39/63)	38% (24/63)	$112,598	$181,610
SOF + RBV, 24 weeks	Tx-naive	93% (98/105)	5% (5/105)	$168, 898	$181,610
	Tx-experienced	77% (112/145)	20% (29/144)		$219,348
SOF + DCV 3 RBV, 24 weeks	Tx-naive	89% (16/18)	<1% (1/18)	$211,974/$212,872**	$238,173/$239,182
SOF/LDV 3 RBV, 12 weeks	Tx-naive	64% (16/25)	32% (8/24)	?	?
	Tx-naive (+ RBV)	100% (26/26)			
SOF + GS-5816 (25 mg or 100 mg), 12 weeks	Tx-naive, 25 mg dose	93% (25/27)	<1% (1/27)	?	?
	Tx-naive, 100 mg dose	93% (25/27)	<1% (1/27)		

*Data from www.goodrx.com (Accessed on May 2, 2014).

**Daclatasvir price is based on the cost to France's ATU program, which is €35,000 (US$47,974.52) per patient, regardless of dose (Source: www.seronet.info/article/traiter-lhepatite-c-sans-interferon-des-atu-pour-le-simeprevir-et-le-daclatasvir-66334; accessed on May 3, 2014).

HIV: Not Special, Anymore

People with HIV and hepatitis C (especially genotype 1) are less likely to be cured by peginterferon and ribavirin treatment. In the DAA era, HIV is no longer a poor prognostic factor for response to HCV treatment. Adding a protease inhibitor to PEG-IFN and RBV has produced similar SVR rates, regardless of HIV status.[33,34,35,36]

Now, proof of concept has been established for efficacy of peginterferon-free regimens in people with HIV and HCV (see table 4). In fact, cure rates from some of the clinical trials in HIV/HCV have been higher than those in HCV monoinfection, probably due to experience with, and support for, adherence to antiretroviral therapy.

Table 4. SVR from Interferon-Free Trials in HIV/HCV[15,37,38]

Trial (N, regimen, population, phase, sponsor)	Treatment arm	SVR	Comments	ARVs allowed
PHOTON-1 Sofosbuvir + RBV N = 182 HCV genotype 1 ,2, & 3, Tx-naive, cirrhosis: 6% (12/182) Phase II Gilead	24 weeks, 2 drugs (G1)	SVR-12: 76% (87/114)	Less effective in IL28B non-CC genotypes, Black (vs. non-Black) participants, people with cirrhosis, males, and G1b	atazanavir/r, efavirenz, emtricitabine, darunavir/r, raltegravir, rilpivirine, tenofovir
	12 weeks, 2 drugs (G2)	SVR-12: 88% (23/26)		
	12 weeks, 2 drugs (G3)	SVR-12: 67% (28/42)		
C-WORTHY MK-5172 + MK-8742 ± RBV N = 59 HCV genotype 1, Tx-naive, noncirrhotic Phase II Merck	12 weeks, 2 drugs	SVR-12: 90% (26/29)	1 relapse in RBV arm; 2 virologic breakthrough in no-RBV arm; all were in G1a	abacavir, emtricitabine, raltegravir, tenofovir
	12 weeks, 3 drugs	SVR-12: 97% (28/29)		
ERADICATE FDC: Sofosbuvir/ ledipasvir N = 50 HCV genotype 1, Tx-naive, noncirrhotic Phase II Interim Data	12 weeks, 2 drugs ARV-treated, on current regimen for ≥8 weeks, CD4 >100/mm^3; HIV RNA <40 copies/mL	SVR-4: 100% (22/22)		efavirenz, emtricitabine, raltegravir, rilpivirine, tenofovir
	12 weeks, 2 drugs no ARVs, stable CD4 with HIV RNA <500 copies/mL or CD4 >500/mm^3	SVR-4: 100% (10/10)		

The only consideration for treating people coinfected with HIV and HCV is avoiding—or managing—drug-drug interactions between DAAs and antiretrovirals (ARVs). To date, the only pangenotypic DAA-based regimen that can be used without restrictions with ARVs (except AZT and ddI which are contraindicated with ribavirin) is 12 weeks of sofosbuvir, peginterferon, and ribavirin.

As of mid-2014, several trials are open or planned in people with HIV/HCV.

Table 5. Ongoing and Planned Trials in HIV/HCV Coinfection

Regimen, sponsor, phase	Population
TURQUOISE-I ABT-450/r/ABT-267 + ABT-333 + RBV AbbVie Phase III	Genotype 1, treatment-naive and treatment-experienced (+ PEG-IFN/RBV)
SWIFT-C Sofosbuvir + RBV AIDS Clinical Trials Group Phase I	Acute HCV infection (or reinfection); genotype not specified
Asunaprevir + daclatasvir BMS Phase II	Genotype 1b, treatment-naive and treatment-experienced (+ PEG-IFN/RBV); no ARV or raltegravir + tenofovir/emtricitabine or abacavir/lamivudine
ALLY-2 Daclatasvir + sofosbuvir BMS Phase III	Genotypes 1–6: treatment-naive and treatment-experienced
FDC: Sofosbuvir/ledipasvir Gilead Phase II	Genotype 1, treatment-naive
FDC: Sofosbuvir/ledipasvir or sofosbuvir + RBV Gilead Phase II	Genotypes 1, 4 (FDC) and genotypes 2, 3 (sofosbuvir + RBV); treatment-naive or treatment experienced (+ PEG-IFN/RBV); inherited bleeding disorder
FDC: Sofosbuvir/ledipasvir Gilead Phase II	Genotype 1, treatment-experienced (PEG-IFN/RBV + HCV protease inhibitor)
Sofosbuvir + RBV Gilead Phase III	Genotype 1-4 treatment-naive Genotype 2 and 3, treatment-experienced
FDC: Sofosbuvir/ledipasvir Gilead Phase III	Genotype 1 and 4, treatment-naive and treatment-experienced (+ RBV)
C-EDGE COINFECTION MK-5123 + MK-8742 Merck Phase III	Genotype 1, 4, 5, and 6; treatment-naive

Source: www.clinicaltrials.gov.

Hepatitis C Trials: Not Just for Middle-Aged, Non-Cirrhotic White Males?

A majority of the participants in HCV clinical trials are middle-aged white males. Enrollment of people from other racial and ethnic groups is shamefully inadequate. There are no data on participation in, or outcomes from, HCV clinical trials among Native Americans and Alaska Natives, although they share the highest incidence of, and mortality from, HCV in the United States.[39]

African Americans

Information about how DAAs perform in the people most likely to use them is critical, yet it often is unavailable until postmarketing studies have been completed. African Americans are underrepresented in clinical trials, despite high HCV prevalence (22% of cases in the U.S.).[40] Enrollment of African Americans hovers below 20 percent in all but one industry-sponsored trial, Gilead's PHOTON.

Hepatitis C infection is more likely to become chronic, and peginterferon-based treatment is less effective for people with the IL28B TT genotype and other genetic polymorphisms found more frequently among African Americans than people of other races and ethnicities.[41] African Americans with HCV have poor posttransplant survival rates, and significantly higher incidence of, and mortality from liver cancer than their white counterparts.[42,43]

Hispanics

Hispanics are twice as likely to die from viral hepatitis than non-Hispanic Whites.[44] HCV progresses more rapidly in Hispanics than African Americans or Whites, and they are more likely to develop cirrhosis.[45] Type 2 diabetes (which is associated with poor response to peginterferon) is prevalent among Hispanics, underscoring the need for more effective HCV treatment, yet they are often underrepresented in clinical trials.

Women

Although HCV trials enroll a substantial proportion of women, sponsors fail to break out race and ethnicity data by gender, obscuring possible differences in efficacy. Sex- and age-specific side effects are not well characterized in HCV clinical trials, leaving women without adequate information to inform their HCV treatment decisions.

Table 6. Participation in HCV Clinical Trials by Gender, Race, and Ethnicity; Genotype 1[13,15,16,33,34,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64]

Trial: N, Population, and Phase	Women	African American/ Black	Hispanic/ Latino/Latina	Asian	Other
Sponsor: ABBVIE					
PEARL-II (N = 186) G1b only; Tx-experienced, noncirrhotic Phase III	45% (84/186)	91% (170/186) white; no other race/ethnicity reported			
PEARL-III (N = 419) G1b only; Tx-naive, noncirrhotic Phase III	56.5% (237/419)	5% (20/419)	1.5% (7/419)	6.5% (28/419)	
PEARL-IV (N = 305) G1a only; Tx-naive, noncirrhotic Phase III	35%(106/305)	12% (36/305)	9% (28/305)		4% (12/305)
SAPPHIRE-I (N = 631) Tx-naive, noncirrhotic Phase III	45.5% (287/631)	5.5% (34/631)	5% (32/631)		
SAPPHIRE-II (N = 394) Tx-experienced, noncirrhotic Phase III	42% (167/394)	8% (32/394)	6% (25/394)	1.5% (6/394)	
TURQUOISE-II (N = 380) Tx-naive and Tx-experienced; compensated cirrhosis Phase III	30% (113/380)	3% (12/380)	12% (45/380)	2% (8/380)	
Sponsor: BMS					
AI444040 (N = 167) G1a only; Tx-naive and Tx-experienced, noncirrhotic Phase II	47% (78/167)	14% (24/167)			4% (6/167)
A1443-014 (N = 166) Tx-naive; 9%; cirrhosis Phase II	33% (54/166)	16% (27/166)		1% (2/166)	
HALLMARK DUAL (N = 745) G1b only; Tx-naive and Tx-experienced; 30% cirrhosis Phase III	55% (411/745)	6% (42/745)		25% (186/745)	

Trial: N, Population, and Phase	Women	African American/ Black	Hispanic/ Latino/Latina	Asian	Other
Sponsor: BOEHRINGER INGELHEIM					
STARTVerso 1 and 2 (N = 1,309) Tx-naive; 9% cirrhosis Phase III	44% (578/1309)	7% (94/1309)			
STARTVerso 3 (N = 678) Tx-experienced; 21% cirrhosis Phase III	42% (275/678)	<4% (24/678)		18% (124/678)	
STARTVerso 4 (N = 308) HIV-positive, Tx-naive or relapse; 17% cirrhosis Phase III	19% (60/308)	14% (42/308)		2% (7/308)	1% (3/308)
Sponsor: GILEAD					
NEUTRINO (N = 327) G1 (N = 292); Tx-naive; 17% cirrhosis Phase III	36% (118/327)	17% (54/327)	14% (46/327)	2% (7/327)	3% (9/327)
ION-1 (N = 865) Tx-naive; 16% cirrhosis Phase III	40.5% (352/865)	12.5% (108/865)	12% (101/865)	<2% (11/865)	<2% (11/865)
ION-2 (N = 440) Tx- experienced; 20% cirrhosis Phase III	35% (153/440)	17% (77/440)	9% (41/440)	<0.5% (1/440)	<1% (2 other, one Hawaiian/ Asian Pacific Islander)
ION-3 (N = 647) Tx-naive; noncirrhotic Phase III	42% (272/647)	19% (123/647)	6% (39/647)		2.5% (17/647)
PHOTON-1 (N = 114) HIV-positive, Tx-naive; 4% cirrhosis Phase III	18% (21/114)	33% (37/114)	22% (25/114)		
Sponsor: JANSSEN					
C0212 (N = 106) HIV-positive; Tx naive and tx-experienced; 10% cirrhosis Phase II	15% (16/106)	14% (14/106)			
COSMOS (N = 167) Tx-naive and Tx-experienced; 40% cirrhosis Phase II	36% (60/167)	19% (31/167)	21% (35/167)		

Trial: N, Population, and Phase	Women	African American/ Black	Hispanic/ Latino/Latina	Asian	Other
PROMISE (N = 393) Relapsers; 15% cirrhosis Phase III	34% (133/393)	3% (13/393)	6% (24/393)	3% (11/393)	1% (1 Asian Pacific Islander; 1 mixed-race)
QUEST-1 (N = 394) Tx-naive; 12% cirrhosis Phase III	43.5%(172/394)	8% (30/393)		2% (7/393)	
QUEST-2 (N = 391) Tx-naive; 8% cirrhosis Phase III	44% (171/391)	91.5% (329/ 360) white; no other race/ethnicity reported			
Sponsor: MERCK					
C-WORTHY (N = 159) Tx-naive; noncirrhotic Phase II	50% (78/159)	7% (11/159)	10% (15/159)	<3% (4/159)	
C-WORTHY (N = 253) Tx-naive and null responders; 40% cirrhosis Phase II	41% (105/253)	6% (15/253)	5% (12/253)		2% (5/253)
Sponsor: NIAID					
SPARE (N = 60) Tx-naive; 22% precirrhosis or cirrhosis Phase II	38% (23/60)	83% (50/60)	4% (2/60)		
SYNERGY (N = 60) Tx-naive; 5% cirrhosis Phase II	29% (17/60)	89% (53/60)			

ADVERSE EVENTS

The expression "generally well tolerated" is used to describe virtually any adverse event (AE) that doesn't kill participants in HCV clinical trials. AE reports from DAA trials tend to be overshadowed by the astonishing cure rates and ever-shorter treatment durations. Years of looking at long, long lists of AEs and high discontinuation rates from trials of peginterferon and ribavirin-based regimens have numbed conference attendees (who are also not the ones experiencing them). But these adverse events are likely to be worse in the real

world, given that people in clinical trials are usually healthier, monitored more closely, and cared for by more experienced clinicians.

In phase II and phase III trials of DAAs, at least five percent of study participants experienced an adverse event (see table 7). Adverse events are not always reported in terms of severity and duration, and it is unclear how many people are bedeviled by multiple AEs.

Ribavirin the Terrible

Although peginterferon is quickly becoming a therapeutic relic, ribavirin is still in the mix. It may be more toxic than anyone realized. Some of the AEs associated with peginterferon (irritability, anxiety, depression, insomnia, nausea, muscle and joint pain) have now been reported in ribavirin-containing arms of peginterferon-free trials.

Even without ribavirin, it is difficult to identify which drug or drugs are the culprits, since DAAs are not used alone.

Table 7. Adverse Events in ≥5 Percent of Participants, from a Sampling of Phase II and Phase III DAA Trials (Alphabetical Order)[15,18,27,28,30,49,50,57,63,65,66,67]

	Treatment-Naive	Treatment-Experienced
RBV-free	Abdominal distention, abdominal pain, anxiety, asthenia, back pain, common cold, constipation, cough, diarrhea, dizziness, dysmenorrhea, dyspepsia, nasopharyngitis, night sweats, fatigue, headache, insomnia, irritability, nausea, oropharyngeal pain, pain, pruritus, rash, shoulder pain, upper abdominal pain, vomiting	Abdominal distention, anxiety, arthralgia, back pain, constipation, cough, diarrhea, dizziness, dry skin, dysmenorrhea, dyspepsia, fatigue, headache, insomnia, irritability, nasopharyngitis, nausea, oropharyngeal pain, pain, pruritus, rash, upper abdominal pain, vomiting
RBV-containing	Anemia, arthralgia, asthenia, back pain, decreased appetite, diarrhea, dizziness, dyspepsia, fatigue, headache, insomnia, irritability, myalgia, nausea, pruritus, pyrexia, rash, upper respiratory tract infection	Anemia, arthralgia, asthenia, cough, depression, diarrhea, dizziness, fatigue, headache, insomnia, irritability, nausea, pain, pruritus, rash, upper respiratory tract infection

People Who Inject Drugs

In the developed world, 80 percent of new HCV infections occur in people who inject drugs (PWID), due to lack of access to sterile injection equipment.[68] Worldwide, 10 to 15 million PWID have been infected with hepatitis C virus.[69] Yet only two to four percent of PWID have been treated, due to a range of structural, socioeconomic, cultural, legal, and other barriers.[70] Concerns about poor adherence lead some physicians to withhold treatment from PWID, regardless of evidence that adherence and HCV treatment outcomes among people who inject drugs are similar to those among people who are not injecting drugs.[71]

From TasP to CasP

> ***I don't want to be called a transmitter—that's electricity.***
> —Jude Byrne, Senior Project Officer, National Hepatitis C and Other BBVs/STIs Program, Australian Injecting & Illicit Drug Users League (AIVL)

Research on HIV treatment as prevention (TasP) has inspired modelers to look at the impact of HCV treatment on prevalence among people who inject drugs. Unlike HIV, hepatitis C can be cured; only a few months of oral drugs are needed to accomplish this. Mathematical models indicate that treating a small proportion of PWID will significantly reduce HCV prevalence, given the high SVR rates seen in DAA clinical trials.[72]

HCV cure as prevention (CasP) is an advocacy platform for ramping up access to both HCV prevention and treatment for PWID. But barriers such as criminalization and discrimination will stymie efforts to implement CasP among PWID. It is critical that people who inject drugs be involved in the design, implementation, and oversight of CasP programs, and that these programs be linked to larger social justice movements.

Pregnancy and Pediatrics

Each year, 60,000 infants are born with HCV infection. In HCV-monoinfected women, the rate of vertical transmission is three to five percent; HIV coinfection doubles the risk.[73,74] It may be possible to prevent vertical transmission with ribavirin-free DAA regimens, but there have not been any trials so far.

The standard of care for children from 3 to 17 years of age is peginterferon and ribavirin, which has many side effects and may inhibit growth.[75] Earlier HCV regimens were not ideal for use in pediatrics (or adults). Newer DAA regimens should be studied in pediatrics.

CONCLUSION

Although the HIV experience is valuable for tackling HCV, there are significant differences between these viruses and responses to them. HIV activists have mobilized worldwide using a human rights–based framework, wielding evidence from global research networks to fight for programs that prevent, diagnose, and treat HIV. In contrast, the dialogue about HCV has been primarily focused on cost-effectiveness, due to high prices and flaccid responses from governments and donors.

The hard work—transforming the HCV treatment cascade from scarcely a dribble into a waterfall—is just beginning. Access to affordable HCV viral-load testing and treatment can become a reality, so long as people are willing to fight for them.

The lessons learned from AIDS treatment activism and scale-up are relevant to hepatitis C: drugs cannot stop an epidemic by themselves, no matter how good they are. Activists, donors, governments, implementers, and clinicians must work together to make sure that HCV treatment reaches all who need it.

RECOMMENDATIONS

Research

1. Support public-private research partnerships for HCV diagnostics and treatment; leaving drug development solely to the pharmaceutical industry does not serve public health, and may be hazardous.
2. Focus on development of HCV diagnostics for resource-limited settings, using the WHO ASSURED criteria; pilot HCV treatment projects are opportunities to simultaneously validate innovative HCV diagnostics.
3. Identify and study the best DAAs for preventing vertical transmission.
4. Launch pediatric trials in HCV and HIV/HCV coinfection (with the most suitable candidates).
5. Study DAA regimens in people with HCV genotypes 5 and 6.
6. Develop DAAs in different formulations (long-acting, single-injection) to facilitate HCV treatment scale-up.
7. Enroll representative populations in HCV clinical trials, especially people with advanced liver disease from high-prevalence populations.

Policy and Implementation

1. Governments must not continue to ignore HCV; it is time for national plans to address the epidemic. People with HCV and their allies, people who inject drugs, epidemiologists, medical providers, researchers, and policy makers need to participate in development and implementation of their national plans.
2. Donors need to support and coordinate efforts to increase global access to HCV prevention, diagnostics, care, and treatment in LMICs.
3. Pharmaceutical companies must allow generic competition, since they have ample opportunity to recoup investment in, and amply profit from their DAAs.
4. Implementers must gear up; it is time to initiate widespread capacity building so that nonspecialist providers, community health care workers, and peers can deliver HCV education, screening, care, and treatment.
5. People who inject drugs must have the opportunity to participate in the design, implementation, and oversight of HCV prevention, testing, and treatment programs intended for them.

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Global Update: Hepatitis C Treatment Activism

By Karyn Kaplan and Tracy Swan

> *How can governments and donors effectively address HCV if pharma refuses to drop drug prices?*
> —Paata Sabelashvili, Activist, Georgian Harm Reduction Network

Keeping up with the rapid pace of hepatitis C drug development, activists across the world are educating communities, working with national governments, and pressuring the United Nations and global funding agencies to give hepatitis C virus (HCV) the attention it deserves, and to bring an end to the global epidemic. Their work includes:

- raising awareness about HCV, especially among people who inject drugs, people coinfected with HIV and HCV, key decision makers, and donors;
- pushing for affordable HCV drugs and diagnostics, monitoring access to HCV treatment; and
- helping to develop, implement, and increase funding for local and national HCV programs.

While keeping the pressure on locally and nationally, activists are also collaborating on regional and international advocacy strategies and campaigns. They are pressuring drug companies to cut prices, opening pathways for generic production through patent opposition, and ensuring that global health authorities can no longer ignore hepatitis C.

The "Missing Campaign"

In June 2013, ACT UP–Basel, the Asia Pacific Network of People Living with HIV/AIDS, the International Network of People who Use Drugs, Médecins du Monde, and Treatment Action Group launched the "Missing" campaign.

The campaign was directed at the World Health Organization's (WHO's) Director–General, Dr. Margaret Chan. The campaign highlighted the lack of WHO resources and leadership to fight hepatitis C, and demanded a response from Chan. In response, campaign sponsors were invited to meet with leaders from the WHO's HIV and global hepatitis programs.

In March 2014, the WHO convened a Strategic and Technical Advisory Committee on Viral Hepatitis, and a Global Partners' Meeting on Hepatitis, where stakeholders from around the world (including the "Missing" campaigners) discussed the epidemics, shared country-specific responses, and outlined steps to address viral hepatitis on a global level. Participants issued a "call to action" to pressure the international community to act.

Sofosbuvir Patent Opposition

In November 2013, lawyers at Initiatives for Medicines, Access & Knowledge filed the first of two patent oppositions to sofosbuvir, based on India's criteria for novelty and innovation.

If Gilead is not granted the patent for sofosbuvir in India, generic drug makers can produce it there and—following the pattern of HIV antiretrovirals—competition will dramatically lower the price, making sofosbuvir affordable for millions of people who would otherwise lack access to it.

First HCV World Community Advisory Board (CAB) Meeting

In February 2013, 38 activists from 22 countries gathered in Bangkok to share information and strategize before meetings with six pharmaceutical companies producing direct-acting antivirals (DAAs) or pegylated interferon. They discussed plans for registering, licensing, pricing, and marketing HCV treatment in low- and middle-income countries. A complete report from the HCV World CAB meeting is available at http://www.treatmentactiongroup.org/hcv/publications/wcab-report-2014.

Hepatitis C Treatment Guidelines

In April 2014, the WHO released its first HCV treatment guidelines; activists participated in their development and review. The guidelines were created for low- and middle-income countries to support development and implementation of evidence-based HCV screening, care, and treatment programs.

"Sovaldi, So Expensive" Campaign

In April 2014, activists organized the first-ever protest at the European Association for the Study of the Liver meeting, to protest against the high price of Gilead's HCV drug, Sovaldi (sofosbuvir). Sovaldi is inexpensive to produce (see "Hepatitis C Pipeline," p. 153), yet Gilead has priced it at $1,000 per day in the United States. Although the company has announced agreements to discount Sovaldi in certain countries, the price is still too high. Many other countries—some home to millions of people with HCV—are not included in these agreements and cannot gain access to Sovaldi.

During the protest, demonstrators chanted, "pills cost pennies, greed costs lives," and "let doctors cure people."

World Health Assembly Resolution

In May 2014, activists and their allies joined forces to pass a resolution on viral hepatitis sponsored by the Brazilian government. The resolution—which was passed unanimously—calls on the Director–General of the World Health Organization, member states, and other stakeholders to take aggressive steps to end viral hepatitis.

UNITAID Support

In 2013, UNITAID—a global health organization that funds HIV/AIDS, tuberculosis, and malaria projects, primarily in low-income countries—signaled interest in hepatitis C coinfection by including it in its *Strategy 2013–2016* report and soliciting letters of intent. In response, activists generated a sign-on letter—endorsed by 135 organizations around the world—urging UNITAID to facilitate access to affordable HCV diagnostics and treatment.

In May 2014, UNITAID's executive board awarded up to US$20 million dollars to nongovernmental organizations to advance the ultimate goal: access to high-quality, affordable HCV diagnostics and treatment for people coinfected with HIV and hepatitis C.

The Tuberculosis Diagnostics Pipeline

By Colleen Daniels

Accurate diagnosis of tuberculosis (TB) is the gateway to treatment and—it is hoped—cure for people with latent TB infection (LTBI) or active TB disease. According to the Stop TB Partnership and the World Health Organization (WHO), 3 million of the 9 million people who develop TB disease every year are not recorded as diagnosed or treated.[1]

Sputum smear microscopy is still the most widely used TB diagnostic test, despite its lack of sensitivity, most notably among children and people living with HIV. There is still no simple, instrument-free, point-of-care diagnostic test for active TB. Products moving forward are listed in table 1.

Table 1. 2014 Tuberculosis Diagnostics Pipeline

Test	Developer(s), Country	Type/Sample	Status*
Molecular-based technologies			
Genedrive MTB/RIF ID	Epistem, United Kingdom	Real-time PCR for TB and rifampin (RIF) resistance	Sponsor claims field trials under way[2]
Line probe assay (LiPA)	Nipro Corporation, Japan	LiPA kit to detect pncA mutations associated with pyrazinamide-resistant TB	Evaluated at two centralized labs by FIND[3,4]
FluoroType MTB	Hain Lifescience, Germany	Semi-automated NAAT for detection of Mycobacterium tuberculosis complex in clinical specimens	Study results published.[5] The assay is marketed in Europe and will be made available globally in 2014
FluoroType MTB RNA	Hain Lifescience, Germany	Molecular therapy monitoring of people with Mycobacterium tuberculosis (MTB) who are on treatment	First clinical data will become available in 2014[6]
LATE-PCR with Lights-On/Lights-Off Probes and PrimeSafe technology[7]	Stellenbosch University, South Africa; Brandeis University, United States; Hain Lifescience, Germany	PCR test for simultaneous detection of MTB and resistance to isoniazid, rifampin, ethambutol, and injectables. Technology licensed from Brandeis University for development by Hain Lifescience to detect MDR- and XDR-TB in a single-tube PCR assay	The technology will be presented at validation sites throughout Q3 of 2014. Due to be CE-marked (European Union accreditation for medical devices) by Q2 of 2015[8,9]
Pure LAMP	Eiken Chemical Company, Japan	Manual TB detection based on loop-mediated isothermal amplification (LAMP) using a nucleic acid amplification method	Published study[10] from microscopy centers in China. Now on path for WHO review[11]

Test	Developer(s), Country	Type/Sample	Status*
Nonmolecular technologies			
Alere Determine TB-LAM Ag lipoarabinomannan (LAM) lateral flow test	Alere, United States	Lateral flow urine test detects TB LAM in adults with HIV and advanced immunosuppression	On the market; independent field studies completed; additional studies under way[12,13]
TB Scope[14]	CellScope Mobile Microscopy/Fletcher Lab, University of California, Berkeley, United States	Automated imaging using sensitive fluorescence method	Currently being tested in Hanoi, Vietnam, as part of a WHO study to provide TB diagnosis at peripheral levels of the health care system[15]
Culture-based technologies			
TREK Sensititre MYCOTB MIC plate	Trek Diagnostic Systems/ Thermo Fisher Scientific, United States	A dry microdilution plate containing lyophilized antibiotics for determination of minimum inhibitory concentrations of first- and second-line TB drugs (except pyrazinamide)	In field studies[16]

*Unlike with the phase designations for drug development (i.e., phase I, IIa, IIb, III), there are no global standard definitions for the stages or definitions for diagnostics development. The European Union (E.U.), the U.S. Food and Drug Administration (FDA),[17,18] and the WHO[19] each uses different definitions and terminology.

Only technologies with documented progress—data published in peer-reviewed journals —since the *2013 Pipeline Report* are shown in table 1. Several sponsors claim that they have additional tests in development, but these have made no visible progress since 2012. After the approval of Xpert MTB/RIF by the WHO in 2010, the diagnostics pipeline for molecular technologies expanded. TB experts spoke hopefully of "fast followers," hoping that these tests might be cheaper, faster, or easier to use than Xpert MTB/RIF. No such test has yet been validated by the WHO or a stringent regulatory authority.

Xpert MTB/RIF Implementation Science Moves Forward

Cepheid's GeneXpert system was recommended by the WHO in 2010. It uses a rapid, automated, cartridge-based nucleic acid amplification test (NAAT) platform that detects the TB organism and some common rifampin-resistance mutations. The Xpert MTB/RIF assay is more accurate than smear microscopy and much faster than TB culture. Data from the implementation of Xpert MTB/RIF may have helped persuade more countries to use it.[20]

A 2013 *Cochrane Review*[21] analysis focusing on 18 studies reported a "pooled sensitivity of 88% and specificity of 98%" when Xpert MTB/RIF replaced smear microscopy as an initial test, and pooled sensitivity of "67% and specificity of 98%" when used as a follow-up test after a smear-negative culture result. The authors concluded that Xpert MTB/RIF can be used as an "initial diagnostic test for TB detection and [rifampin] resistance" and would be "valuable" as an add-on test.[22] In 2014, the *Cochrane Review* published an updated analysis of Xpert (27 studies), with highly consistent results.[23]

The WHO updated its policy guidance on Xpert MTB/RIF in October 2013, recommending that the assay be used for initial diagnosis in individuals suspected of having MDR-TB or HIV-associated TB. It added conditional recommendations regarding the assay's use as a follow-up to microscopy, in "adults who are suspected of having TB but not at risk of MDR-TB or HIV-associated TB."[24] The update provided recommendations on using Xpert MTB/RIF to detect TB in children.[25]

A systematic review and meta-analysis[26] determined that Xpert MTB/RIF performed well compared with culture and a composite reference standard in the detection of certain types of extrapulmonary TB. The WHO recommends using Xpert MTB/RIF rather than conventional tests for "diagnosis of TB in lymph nodes and other tissues, and as the preferred initial test for diagnosis of TB meningitis [tuberculous meningitis]."[27]

One of the many studies published in the past year and a half on Xpert MTB/RIF showed that nurses can administer the assay effectively in primary health care settings.[28] Rapid diagnosis allows more patients to start treatment the same day. Hanrahan and colleagues found that those who received an Xpert MTB/RIF–positive test at a primary health clinic had a median time of zero days time to treatment initiation.[29] In a study done in South Korea, the median turnaround time for the Xpert MTB/RIF assay was 0 and 6 days; the median time to treatment was 7 days compared with 21 days in those who did not have a diagnosis with Xpert MTB/RIF.[30]

In some of these studies, Xpert MTB/RIF was used to diagnose tuberculous meningitis; one in Vietnam showed that diagnosis was possible: Xpert MTB/RIF had a sensitivity of 59.3% when compared with microscopy (78.6%) and the Mycobacterial Growth Indicator Tube (MGIT) liquid culture system (66.5%).[31] Several studies also tried using samples other than sputum to detect TB using Xpert MTB/RIF.[32,33] Among people with HIV, exhaled breath condensate, urine,

saliva, and blood samples did not allow TB detection using Xpert MTB/RIF.[34] Another study found that Xpert MTB/RIF can be used as the initial diagnostic for HIV-associated lymph node tuberculosis. A single Xpert test had a 88.2% and a sensitivity of 93.3%, though this improved with decreasing CD4 cell count. All patients who had a positive Xpert MTB/RIF result initiated treatment within one day compared with those without an Xpert MTB/RIF result.[35] A study with Xpert using stool as a specimen for the diagnosis of pulmonary TB in HIV-positive children found that Xpert detected "8/17 (47%) culture-confirmed tuberculosis cases, including 4/5 (80%) HIV-infected and 4/12 (33%) HIV-uninfected children."[36]

Many studies showed that Xpert MTB/RIF increased detection of TB, both drug-resistant and drug-susceptible. An active case-finding study in Phnom Penh, Cambodia, increased detection of drug-susceptible and drug-resistant TB by using a symptom screening followed by smear microscopy and targeted use of Xpert MTB/RIF.[37] At health centers in Adama Town and the Oromia region of Ethiopia, Xpert MTB/RIF was found to increase the TB detection rate by 47.4% (64 cases) compared with smear microscopy, especially in patients with advanced immunosuppression.[38] Results from the implementation of Xpert MTB/RIF in nine TB REACH projects show that Xpert MTB/RIF detected TB in a large number of people with TB that routine services failed to detect. In Kenya, Malawi, the Democratic Republic of Congo, and Nepal, diagnostic interventions that included Xpert MTB/RIF to test people who were sputum smear–negative found 2,833 people that would previously have been unidentified.[39]

Some published data suggest that Xpert MTB/RIF has not demonstrated a clear effect in improving patient outcomes.[40,41] The TB NEAT[42] and TB Extend[43] studies concluded that Xpert MTB/RIF does not necessarily increase the number of people treated, but does increase the number of people diagnosed with microbiologically confirmed TB. In many countries, including South Africa, Xpert MTB/RIF testing is done through a laboratory service rather than in community clinics. If Xpert MTB/RIF was implemented at more peripheral levels of the health system, it would be possible for people to have a single visit to a health facility and start treatment the same day, thereby reducing loss to follow-up, morbidity, and mortality.

Current operational research studies on Xpert MTB/RIF listed on ClinicalTrials.gov focus on achieving the best clinical outcomes and reducing TB in HIV-

positive adults and children, using Xpert MTB/RIF in mobile units, assessing Xpert MTB/RIF diagnosis at the point of treatment, and intensifying case finding with a package of diagnostic tools including Xpert MTB/RIF.

Xpert MTB/RIF is a major advance in TB diagnostics. Among the short-term priorities should be understanding how best to implement Xpert MTB/RIF in order to improve individual and public health, increasing the ruggedness of the instrument in order to ensure that it operates reliably in a variety of climates and settings, determining specimen processing and testing procedures that optimize yield from Xpert MTB/RIF testing of nonrespiratory specimens, and increasing the assay's sensitivity to enable it to detect a greater proportion of paucibacillary TB.

Alere Determine LAM – A Useful Test in Advanced Immunosuppression

An important advance in assays over the past year is the Alere Determine TB LAM (lipoarabinomannan) lateral flow test. Several studies are assessing its ability to detect TB in severely immunosuppressed people with HIV, who are among the hardest to diagnose.

One of the key findings, presented at the Conference for Retroviruses and Opportunistic Infections in Boston, Massachusetts, in February 2014, is the importance of the Determine LAM urinary test as an add-on rather than a stand-alone test. Steven Lawn presented data showing an increase in detection from 26.6% to 80.6%, when the Determine LAM test was added to an Xpert MTB/RIF test. When combined, Determine TB LAM and Xpert MTB/RIF detected 69.1% of culture-confirmed cases, enabling them to find MTB infection in 85% of people with CD4 cell counts below 100/mm^3.[44] In Uganda, a study showed that the sensitivity of Xpert MTB/RIF and Determine LAM, used together, is superior to that of either test alone.[45]

A study conducted in Ethiopia in people with HIV found that the Determine TB LAM assay worked best in those who had a CD4 cell count ≤100/mm^3 and that it could be used with sputum microscopy in this group.[46] A study conducted in hospital and outpatient settings in Uganda and South Africa found that in HIV-positive adults with symptoms of TB who had a CD4 cell count ≤100/mm^3, the assay detected over half of culture-positive tuberculosis samples in less than 30 minutes.[47] Getting sputum samples from children is difficult, so for them a urinary LAM test would be best for TB detection; however, a study in South

Africa showed that the test has insufficient sensitivity and specificity to diagnose TB in children, whether they have HIV or not.[48]

Determine TB LAM tests can also be used to rule in TB in patients with advanced HIV-induced immunosuppression and lead to early treatment initiation.[49] The test is cheap, produces results in less than 30 minutes, and can be used at the point of care. The WHO must review available evidence on Determine TB LAM, and provide guidance so that this test, if appropriate, can be used widely in people with HIV and low CD4 counts, and possible TB.

Other Diagnostics Progressing

New additions to the 2014 table are the LiPA (Nipro), the FluoroType MTB (Hain Lifescience), the FluoroType MTB RNA (Hain Lifescience), and the Pure LAMP (Eiken Chemical). The LiPA is a drug susceptibility test (DST). A recent study found no difference between conventional DST and LiPA for rifampin, pyrazinamide, and levofloxacin, but it did find a difference in isoniazid susceptibility.[50] FIND is evaluating LiPA at two centralized laboratories.
The FluoroType MTB is a semi-automated nucleic acid amplification test to detect MTB. A study evaluated the test in a laboratory in Germany and found it had a sensitivity of 99.2% (smear-positive 100%; smear-negative 56.3%) and a specificity of 98.9%. The authors concluded that the test results were comparable to non-nucleic acid amplification tests on the market.
The FluoroType MTB RNA is a molecular platform that monitors therapy of people with TB. The assay is in development, and Hain Lifescience intends to publish its first clinical data this year.[51] There is a need for additional well-designed, quality-monitored studies to ensure the reproducibility of these results. The Pure LAMP is a manual TB detection tool based on loop-mediated isothermal amplification (LAMP) using a nucleic acid amplification method.
A study at county-level TB laboratories in China found 92.12% sensitivity in smear-positive, culture-positive TB patients and 53.81% in smear-negative, culture-positive patients. Specificity was 98.32%. The study found that there was a lower contamination rate than in solid culture.[52]

The linear-after-the-exponential PCR (LATE-PCR) with Lights-On/Lights-Off probes is a test that can detect MTB and resistance to isoniazid, rifampin, ethambutol, fluoroquinolones, amikacin, kanamycin, and capreomycin in less than three hours.[53] Brandeis University licensed this technology to Hain Lifescience. Hain will work to develop assay versions to detect MDR and XDR-TB in one single-tube PCR assay.

The TREK Sensititre MYCOTB MIC plate is a culture-based technology for DST. A study conducted in the Republic of Korea and Uganda assessed the performance and feasibility compared to the agar proportion method (APM). Results between the MYCOTB and APM showed ≥92% for 7 of 12 drugs with respect to susceptible or resistant TB isolates when assessed with a strict definition.[54] Minimum inhibitory concentration (MIC) results are used to optimize therapy in a number of infectious diseases other than TB. The availability of a simple, commercially produced MIC plate for MTB testing that shows what drugs the person's strain of TB is resistant to could facilitate individualized approaches to the management of highly drug-resistant TB.

Other studies currently under way are assessing the use of interferon gamma release assays (IGRAs), primarily Quantiferon TB Gold (QFT), for diagnosis of latent TB infection in health care workers in high- and middle-income countries and in children. Two studies (NCT00982969 and NCT00962676) are assessing the clinical use of QFT in the diagnosis of active TB in immunosuppressed and immunocompetent patients. The WHO recommends against the use of IGRAs for the detection of active TB in any setting.[55]

Three studies (NCT01301144, NCT01748357, NCT01379066) are looking at the efficacy of volatile organic compounds (VOC), with one study assessing the Siemens VOC breath analyzer. No published data on these studies were available in 2013.

Diagnostics from the 2013 Pipeline with No Reported Progress

The following tests from the *2013 Pipeline Report* are not included in this year's table, as no new data have been published: the Alere Q, B-Smart GeneXpert XDR cartridge, GenoType MTBDR*sl*, iCubate, Infiniti MTB, Loopamp TB detection, GenoType MTBDR*plus* 2.0, NATeasy, TruArray, Truenat, TB rapid screen, TBDx, BNP Middlebrook, MDR/XDR-TB Color Test, BreathLink, and the breathalyzer prototype. Of these, the GenoType MTBDR*plus* 2.0, iCubate System, EasyNAT TB Diagnostic Kit, and the Truenat MTB test are now available on the market. The GenoType MTBDR*plus* 2.0 and the Truenat had data published in 2007–2012 and 2012, respectively. The Truenat is currently included in a study (NCT01589289) on predictors of tropical diseases in neurological disorders in the Democratic Republic of the Congo. FIND and Applied Visual Life Sciences (Leesburg, Virginia) recently announced a collaboration to evaluate the TBDx automated platform.

The developer of Truenat, Bigtec Laboratories, states that it has tested the assay's performance against Xpert MTB/RIF, is now evaluating the test in the public sector in India to inform national TB policy, is attempting to validate the Truenat MTB test for detection of TB in extrapulmonary samples, and is developing a resistance assay for detection of MDR-TB. Truenat said that it is developing a multicenter trial in collaboration with FIND.[56]

Basic Science and Biomarkers

Current limits on our understanding of the biology of TB infection and disease limit scientific approaches to developing better diagnostic tests. There is simply not enough research being funded and conducted in basic science and biomarker discovery for TB. A ClinicalTrials.gov search found only three studies (NCT01269268, NCT00023439, and NCT00212498) investigating potential TB biomarkers.[57]

Funding

Funding for TB diagnostic R&D remains grossly insufficient; there was a 23.4% decline in spending between 2011 and 2012 according to our most recent report on TB R&D resource tracking.[58] In 2012, US$42,429,160 was spent globally when the *Global Plan to Stop TB 2011–2015* called for annual spending of US$340 million.[59] This serious inadequacy of funding is one of the main reasons for the lack of movement in the diagnostics pipeline.

Whole-Genome Sequencing: The Final Frontier?

Whole-genome sequencing is becoming cheaper and more widely used for a variety of scientific investigations, including disease diagnosis, staging, and response to therapy.[60] Current technologies available from Illumina, Oxford Nanopore Technologies, Life Technologies, and Integrated Nano-Technologies can be used for whole-genome sequencing for TB. South Africa uses whole-genome sequencing as part of its TB drug-resistance surveillance, and the United Kingdom uses it for management of patients with very difficult XDR-TB cases. If the technology can be developed,[61] there is potential to use whole-genome sequencing to manage patients with MDR- and XDR-TB. Whole-genome sequencing has the potential to help guide clinicians in the selection of

regimens to which a patient's TB organism is susceptible. However, additional basic-science research is needed to more fully delineate the mechanisms of resistance and the spectrum of genetic determinants of resistance for certain drugs.

Identifying High-Priority Target Product Profiles and Market Size Estimation

While much of the current activity is centered around scale-up of Xpert MTB/RIF and evaluation of newer molecular tests, there are many other gaps in TB diagnostics, including a simple, low-cost triage test to identify patients who need further testing; a simple, biomarker-based TB test for nonsputum samples; a molecular or nonmolecular smear replacement test at the microscopy-center level; and tests for systematic screening.

Kik and colleagues published a study[62] in which the greatest needs were identified using several criteria, with the engagement of stakeholder groups. A rapid, sputum-based, molecular test for microscopy centers (with the option of an add-on DST cartridge) ranked highest, followed by a rapid biomarker-based, instrument-free test for nonsputum samples (which also detects childhood and extrapulmonary TB).

Parallel efforts to estimate potential markets for new TB tests are ongoing. This information will be most helpful to product developers and could catalyze new investments. Kik and colleagues estimated that the potential market size for a smear replacement molecular test (costing US$5) to be 30.8 million tests annually, with a potential market value of US$154 million per year in 22 high-burden countries.[63]

An expert consensus group convened by the WHO, the Global Laboratory Initiative, the Stop TB Partnership, and FIND met in Geneva, Switzerland, in May 2014 to develop, review, and agree on the minimum requirements for products most urgently needed; a report is expected in late 2014.

CONCLUSION

The TB diagnostics pipeline is at a standstill. Several potentially promising technologies are stuck in early development with little funding and no cohesive strategy to develop and evaluate them faster and more effectively. The TB diagnostics pipeline needs to be coordinated, prioritized, and funded by the TB and research communities together.

RECOMMENDATIONS

1. Public- and private-sector R&D funders and research institutes must include more clinicians as researchers in the development process to ensure that basic science and biomarker research prioritizes needs based product development.

2. Public- and private-sector R&D funders, investigators, and civil-society must prioritize and fully fund the development of an accurate, fast, cheap, point-of-care diagnostic for TB.

3. Public- and private-sector R&D funders and investigators must prioritize and fully fund basic science, biomarker research, in order to gain a better understanding of TB disease.

4. Public- and private-sector R&D funders and policy makers setting the agenda for R&D must create new opportunities for investigators and developers to be able to translate findings from biomarker research into technologies.

5. Public- and private-sector R&D funders must fully fund specimen- and strain banks to increase their capacity and investigators' access to them, and to facilitate technology development and early testing. They must develop standard operating procedures across initiatives so that samples and information can be shared.

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Tuberculosis Drug Development Hobbles Forward

By Erica Lessem

Introduction

After forty years without new approved drug classes, tuberculosis (TB) treatment has recently advanced with the approval of two new compounds to treat multidrug-resistant TB (MDR-TB): delamanid and bedaquiline.[1,2,3] Yet with limited access to these drugs, and with no data on how they can be used to shorten or otherwise optimize MDR-TB treatment regimens, this is more an incremental step than a leap forward. Progress toward identifying shorter and better regimens for treating drug-sensitive TB is similarly slow, and there are no validated options for treating TB infection in contacts of people with MDR-TB. The TB drug pipeline features only six compounds from four different classes. The few new drugs in phase II studies have been stalled there for years; of them, only bedaquiline is likely to move to a phase III trial in the next five years. There are no TB drugs in phase I trials (see table 1).

Investments in TB drug research are paltry, totaling just US$238 million in 2012, or less than one-third of the estimated amount needed.[4] With Pfizer and AstraZeneca's departures from TB drug research and development (R&D) in the past year, and with Janssen's delays in starting the pediatric and phase III trials required by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as part of bedaquiline's accelerated approval, pharmaceutical investments in TB R&D—which fell by 22 percent in 2012—are likely to drop further.[5] Increased investment in TB drug R&D is urgently needed to expand the pipeline and accelerate the progression of not just new compounds, but optimized regimens, through it. On the program side, improvements to patient-centered service delivery, more flexible guidelines to aid the uptake of new treatments, and better supply management are needed to ensure that people with TB receive the best possible care or, in some cases, experimental therapies.

Table 1. New Drugs in Clinical Trials for Tuberculosis

Drug	Sponsor(s)	Phase	Class
AZD5847	AstraZeneca	IIa	oxazolidinone
bedaquiline	Janssen	IIb/III	diarylquinoline
delamanid	Otsuka	III	nitroimidazole
PA-824	TB Alliance	III	nitroimidazole
SQ109	Sequella/Infectex	IIb/III	ethylenediamine
sutezolid	Sequella	IIa	oxazolidinone

Spotlight: Problems with drug purchasing and supply management

Better TB therapies will have an impact only if they are accessible to patients and doctors who need them. Commitments to affordable drug pricing, and increased funding of infrastructure and program capacity, must therefore accompany investments in TB R&D. TB programs face many serious access problems: Novartis refuses to engage meaningfully to make clofazimine available for TB patients; Pfizer's exorbitant pricing of linezolid makes it unaffordable for most programs; and even the old, largely cheap drugs—including isoniazid, essential for preventing and treating TB—that have been on the market for decades are often subject to shortages due to poor demand forecasting and disruptions on the limited manufacturing side. With the added costs of new drugs bedaquiline and delamanid, and as more programs try to buy companion drugs such as linezolid, TB programs need additional funding from national budgets and donors to ensure that their patients can benefit from innovations in treatment. To end supply shortages, TB programs and regulatory authorities—including those in the United States—must find more resourceful ways to get the drugs and to encourage manufacturers to develop reliable supplies of cheap, quality-assured products. The Global Drug Facility (GDF) offers one mechanism for doing this globally, yet for the United States to benefit from lower prices and more stable supply, the FDA would need to welcome and ease the registration of global generic products domestically, perhaps through technical support for manufacturers, and incentives such as faster reviews and waivers or discounts for registration fees. Countries need more support and expertise in estimating demand and in managing supply chains.

LATENT TB INFECTION

Table 2. Latent Tuberculosis Infection Studies

Study/Regimen	Status	Population	Sponsor(s)
A5279 Self-administered daily rifapentine + INH for 1 month (vs. INH daily for 9 months) NCT01404312*	Enrolling	People with HIV with positive skin test/IGRA or living in high–TB prevalence regions	ACTG
A5300/TB-CHAMP Levofloxacin-based regimen to be determined (vs. placebo or INH)	Protocol in development	Household contacts (including children) of individuals with MDR-TB	ACTG, IMPAACT
iAdhere (S33) Self-administered once-weekly rifapentine + INH for 12 weeks (with and without electronic reminders) NCT01582711*	Fully enrolled	Adults with LTBI	TBTC
PREVENT TB (TBTC S26, A5259) Once-weekly rifapentine + INH for 12 weeks (directly observed) NCT00023452*	Completed	Persons with LTBI and high risk of progression, including children and people with HIV	TBTC, ACTG
4R vs. 9H 4 months daily rifampin (self-administered) NCT00931736*	Enrolling	Adults with positive skin test or QFT, including people with HIV not on ARVs whose efficacy is reduced by rifampin	McGill University, CIHR

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

ACTG: AIDS Clinical Trials Group, U.S. National Institute of Allergy and Infectious Diseases (NIAID)
ARVs: antiretrovirals
CIHR: Canadian Institutes of Health Research
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
INH: isoniazid
LTBI: latent tuberculosis infection
TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention

As an effective TB vaccine remains elusive (see the "Tuberculosis Vaccines Pipeline," p. 233), treating latent TB infection (LTBI) is one of the most effective ways to prevent active TB disease and is particularly important in people with HIV and children. Yet investment in better strategies to treat LTBI has been

minimal, despite the huge potential market: up to one-third of the world's population is infected with TB. A rare advance came when the SOWETO and PREVENT TB studies demonstrated that LTBI treatment could be shortened to just 12, once-weekly doses of rifapentine and isoniazid.[6,7]

An extension of the PREVENT TB randomized, open-label noninferiority study to 400 people with HIV showed this regimen to be as safe (3% vs. 4% discontinuation due to adverse drug reaction; $P = .79$) and effective (1.01% vs. 3.5% cumulative TB rate; 95% CI: −5.6% to +0.6%) as nine months of daily isoniazid, and with higher completion rates (89% vs. 64%; $P < .001$).[8] Rifapentine and efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla) were tolerated well when coadministered, with no clinically significant impact on CD4 counts or HIV viral load. A single administration of rifapentine increased the maximum concentration of tenofovir by 23 percent, while repeated weekly dosing of rifapentine modestly reduced (by 15%) tenofovir and efavirenz minimum concentrations.[9] Rifapentine's sponsor, Sanofi, announced in December 2013 that it was reducing the drug's cost in the United States by 57 percent, finally facilitating access after a year-and-a-half-long advocacy campaign.[10] AIDS Clinical Trials Group Study (ACTG) A5279 is now examining a daily one-month rifapentine-based regimen in people with HIV; a substudy indicated that this regimen does not significantly affect efavirenz clearance.[11]

Despite these advances in shortening treatment for latent, drug-susceptible TB infection, millions of people with LTBI due to exposure to MDR-TB (which, by definition, is resistant to isoniazid and rifamycins) still lack validated options for treating their infection. Observational studies, despite their limitations, suggest that preventive therapy for people thought to be latently infected with MDR-TB may be feasible, tolerable, and potentially effective. For example, during a 2008 MDR-TB outbreak in the Federated States of Micronesia, contacts with LTBI were offered treatment with one year of a fluoroquinolone with or without ethambutol or ethionamide, and followed up for two years afterwards.[12] Of the 104 who initiated treatment, none developed active disease and 89 percent completed therapy, though half reported side effects.[13] Of 15 who refused preventive therapy, three developed MDR-TB. The ACTG (funded by the U.S. National Institutes of Health [NIH]) and International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) networks are working jointly on a planned study of levofloxacin-based MDR-TB preventive therapy.

TB DISEASE

Table 3. Active Tuberculosis Disease Studies

Study	Phase	Includes new drug(s)	May shorten DS-TB treatment	May shorten DR-TB treatment	May make DR-TB treatment more effective	For DR-TB, may reduce pill burden or improve tolerability	May have price, registration, or other access barriers
C213	III	delamanid		X	X		X
STREAM	III	bedaquiline		X	X		X
REMox NCT00864383*	III		X				X
STAND NC-006, ACTGPR682	III	PA-824	X	X	X	X	X
TBTC 31	III		X				X
NExT	III	bedaquiline		X	X	X	X
MAMS-TB-01 NCT01785186*	II	(SQ109 stopped)	X				
MARVEL A5319	II	bedaquiline PA-824 delamanid (pending agreement with sponsor)		X	X	X	X
NiX-TB	II	bedaquiline PA-824		X	X	X	X
NC-005	II	bedaquiline PA-824	X	X	X	X	X
ACTG 5343	I	bedaquiline delamanid			X		X

*Clinicaltrials.gov identifier; for more details, see www.clinicaltrials.gov.

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

Bedaquiline (brand name Sirturo; formerly known as TMC207)

Bedaquiline, the first new TB drug from a new drug class to receive approval in over four decades, has advanced little since its FDA approval in 2012. On the accessibility front, its sponsor, Janssen, has done well with pre-approval access and rapid registration, but poorly with pricing. Janssen's inflexible tiered pricing system puts a course of bedaquiline at an outrageous US$26,000 in high income countries, and still unaffordable US$3,000 and US$900 for middle- and low- income countries, respectively (see table 4).[14] This tiered-pricing also challenges the Global Drug Facility's ability to pool demand to distribute the drug effectively. Bedaquiline recently obtained approval in Europe, Russia, and South Korea.[15,16,17] Guidance on the use of bedaquiline is now available from both the U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO), though the latter recommends informed consent—unusual as this requirement is not in place for other MDR-TB drugs, for which even fewer clinical trial data support their use.[18,19] Access to bedaquiline remains limited—primarily through Janssen's commendable compassionate use program and expanded access trial. Few patients have actually benefitted from the drug's being on the market. Despite probable approvals in more of the high-burden countries in which Janssen has filed, TB programs' conservatism and tight budgets, coupled with the drug's steep pricing and lack of inclusion on the WHO's Essential Medicines List, may prove to be continuing barriers to access (see table 4).

Janssen has completely stalled on the research side. Its long-delayed study in children has been postponed yet again (see "Playing Catch-Up: The Pediatric Tuberculosis Treatment Pipeline," p. 217). A drug-drug interaction study with delamanid has yet to start. The study is needed to determine whether the two drugs are safe to give together, given that each has cardiac side effects (QT prolongation, or a disturbance in the heart's electrical activity). Over two years after advocates began calling for this study, the ACTG is now rapidly developing A5343, which is urgently necessary as both drugs are now on the market. A phase III trial—a requirement of FDA approval, and particularly important given unexplained long-term excess mortality noted in one phase IIb trial—has still not begun.[20,21] Janssen's phase III plans for bedaquiline now center around adding two bedaquiline-containing arms in a second stage of the ongoing STREAM MDR-TB treatment trial (see table 3). One arm will explore bedaquiline's ability to contribute to a nine-month, all-oral regimen; the other will test whether bedaquiline can shorten treatment to six months.

Each of the two bedaquiline-containing arms, however, will be compared not with the current standard of care, but with the STREAM trial's original experimental arm. This original experimental arm consists of a modified "Bangladesh" regimen (named after a similar regimen first introduced in Bangladesh in a poorly conceived sequential observational cohort study), which includes clofazimine, ethambutol, moxifloxacin, and pyrazinamide given for nine months, supplemented by isoniazid, kanamycin, and prothionamide in the first four months only. This design bases the whole evaluation of bedaquiline in the second stage on the risky assumption that the experimental modified Bangladesh arm will succeed in the first stage of the trial.[22]

Delamanid (brand name Deltyba; formerly known as OPC67683)

Delamanid became the second new drug to receive regulatory approval to treat MDR-TB in Europe in 2014.[23] In contrast to bedaquiline, delamanid is zipping through pediatric and phase III clinical trials. (Note that European approval requires an additional phase IV study to determine whether the current dosing schedule—100 mg twice daily for two months, then 200 mg daily for four months—or 400 mg daily as a single dose for six months is optimal.) These investments in research have made Otsuka the leading private-sector funder of TB R&D for seven years in a row.[24]

Yet Otsuka's access strategy is disappointing. The company refused to start compassionate use until its phase III trial was nearly complete and regulatory approval was ensured, defying principles of pre-approval access and denying many people with otherwise untreatable cases of MDR-TB a chance for cure. Its limited compassionate use program precludes patients from getting delamanid in conjunction with other new drugs (including bedaquiline), even though compassionate use by definition operates in a realm with incomplete safety and efficacy data, and patients are willing to accept greater risk given a lack of validated treatment alternatives. Like Janssen, Otsuka plans for a tiered-pricing approach, though details are unknown as delamanid has yet to receive marketing approval from a low- or middle- income country—a result of Otsuka's egregious delay in submitting regulatory filings outside of rich countries; it has not filed in any of the countries where it conducted clinical trials, or in a single high–TB burden country.

No data exist on whether bedaquiline and delamanid can be used together safely to improve TB treatment regimens. Both drugs have been developed individually as additions to existing treatment schemes (though the STREAM trial

and TB Alliance are exploring bedaquiline in combinations). Thus, while each may improve the efficacy of a regimen, its ability alone or in combination to shorten treatment, replace other drugs, permit all-oral regimens, or reduce pill burdens or side effects for patients remains undemonstrated. New research to inform optimal combinations—including the NIH-funded ACTG A5343 drug-drug interaction study mentioned above—needs to start soon. While A5343 is incomplete, conservative Otsuka has been slow to collaborate with researchers designing combination trials, though it may participate in the ACTG's A5319 MARVEL trial and allow delamanid to be studied as part of regimens that include multiple new drugs if the results of A5343 are promising. However, the South African Medicine Control Council's NExT study for people with extensively drug-resistant TB (XDR-TB), which planned to conduct a safety study of bedaquiline and delamanid before moving into a nine-month phase III study of the two drugs plus linezolid and p-aminosalicylic acid, has had to completely redesign its protocol due to unavailability of delamanid. Pivotal trials to inform better treatment for MDR- and XDR-TB must have access to both drugs together to determine their role in optimizing treatment for drug-resistant TB.

Table 4. Bedaquiline and Delamanid: Research and Access

	Bedaquiline	Delamanid
RESEARCH		
Pediatrics (see "Playing Catch-Up" p. 217)	Trial not yet started	Trial started June 2013
Phase III trial	Trial not yet started (two arms to be added to STREAM trial early 2015)	Enrollment completed November 2013; results expected end of 2014
ACCESS		
Compassionate use	Started first quarter of 2011 342 patients enrolled (as of March 5, 2014)	Started first quarter of 2014 3 patients enrolled (as of March 24, 2014)
Expanded access trials	Started 2011 in China, Lithuania, Russia	none
Approvals	United States (2012), Russia (2013), Europe (2014), South Korea (2014)	Europe (2014)
Additional registrations (decision pending)	China, Colombia, India, Kazakhstan, South Africa, Thailand, Vietnam, Philippines	Japan
WHO Essential Medicines List inclusion	none	none
Pricing	Tiered pricing by country income level (per-pill price: high US$159.57; middle US$15.96; low US$4.79)	Tiered pricing by country income level (details unannounced)

Oxazolidinones

Remaining optimism for the TB drug pipeline centers around the oxazolidinone drug class. As additional drugs are urgently needed to accompany bedaquiline and delamanid, researchers and clinicians are increasingly interested in three drugs: linezolid—a drug approved for other bacterial infections and used off-label to treat difficult cases of drug-resistant TB—and its new chemical relatives, sutezolid and AZD5847. Yet data to support linezolid's clinical efficacy and safety remain limited. Follow-up data from a 2012 study analyzing posttreatment relapses are still pending, but earlier analyses showed potential efficacy, but high rates of adverse events.[25]

Sutezolid and AZD5847 are moving very slowly through the pipeline after their respective sponsors, Pfizer and AstraZeneca, withdrew from TB R&D. Pfizer sold its rights to sutezolid to the small company Sequella without providing adequate resources to develop the drug; Sequella lacks both the active pharmaceutical ingredient and the funds to process sutezolid into pill form for use in studies. After inexplicable delay, Pfizer finally published the results of a phase IIa study of sutezolid in a peer-reviewed journal.[26] In a two-week study of its early bactericidal activity in patients with smear-positive pulmonary TB, sutezolid was safe and well tolerated at either 600 mg twice daily or 1,200 mg once daily, and significantly reduced the number of TB bacteria in sputum (daily log change of −0.088 colony-forming units; 90% CI: −0.112 to −0.065, $P < .0001$ for the 600 mg twice-daily dose; and daily log change of −0.068 colony-forming units; 90% CI: −0.090 to −0.045, $P < .0001$ for the 1,200 mg once-daily dose), demonstrating that the drug is active in humans.[27] The NIH recently completed a phase IIa trial of AZD5847; results are pending.

New combinations

The TB Alliance's development of new drugs in combination is a good model for the field. The TB Alliance has been developing PA-824 (in the same drug class—nitroimidazoles—as delamanid) in various combinations of new and existing drugs. Study NC-003 compared the bactericidal activity and safety of several combinations of new and existing drugs given for two weeks to people with drug-sensitive TB. It found that a combination of bedaquiline, PA-824, and pyrazinamide (PZA) was the best at reducing the amount of TB bacteria in sputum (0.167 colony-forming units; 95% CI: 0.078–0.256), similar to standard first-line treatment (0.151 colony-forming units; 95% CI: 0.070–0.231), but moderately prolonged cardiac conduction. Clofazimine

alone had no early bactericidal activity and did not add to that of the studied combinations.[28] The TB Alliance now plans to bring bedaquiline, PA-824, and PZA (with the addition of moxifloxacin for patients with MDR-TB) into a two-month study (NC-005). Some consider the inclusion of bedaquiline in studies of people with DS-TB controversial, given concerns about the drug's safety. Community groups have offered guidance on what additional information is needed for developers to ethically study bedaquiline in DS-TB.[29] The TB Alliance is also planning the NiX-TB study of bedaquiline, PA-824, and linezolid for people with XDR-TB. The ACTG A5319 MARVEL study currently plans to study bedaquiline, PA-824, and PZA given with either linezolid or levofloxacin in people with MDR-TB.

The TB Alliance NC-002 study evaluated PA-824 at doses of 100 and 200 mg daily with moxifloxacin and PZA for two months in people with both drug-susceptible and multidrug-resistant TB; both new combinations of PA-824, moxifloxacin, and PZA resulted in significantly higher rates of sputum culture conversion at eight weeks than did the standard of care. The TB Alliance will test the efficacy of PA-824 at either dose, moxifloxacin, and PZA given for either four or six months in the phase III STAND, or NC-006, trial.[30] The STAND trial will also include an open-label MDR-TB arm. While shortening treatment to six months for some MDR-TB patients would represent a major advance, the lack of randomization and control for this arm will make it difficult to judge the suitability of this regimen, which also requires widespread drug susceptibility testing, as 38–54 percent of people with MDR-TB are resistant to PZA.[31,32]

SQ109, the last new compound in the meager TB pipeline, is in development by Sequella. The drug was included in the publicly funded study MAMS-TB-01—despite its lack of prior clinical data demonstrating any activity in patients with TB. SQ-109 has no early bactericidal activity.[33,34] The adaptive design of MAMS-TB-01 incorporated a planned interim analysis to allow for early termination of arms showing little treatment-shortening potential. While the SQ109-containing arms had no safety or inferiority signals, there was no evidence that either arm was superior to the standard regimen in shortening the time to a negative culture (used as a proxy for predicting the ability to shorten treatment). As such, the two SQ109 arms were discontinued.[35] Sequella previously sold the rights to SQ109 in Russia to Infectex, which in late 2012 began what Russian regulators deemed a phase III registration trial, despite the company's enrolling just 80 participants and the drug's apparent lack of clinical efficacy.[36]

Rifamycins

Many recent studies have explored the safety and potential efficacy of higher doses of drugs in the rifamycin class, especially rifampin (also commonly known as rifampicin) and the longer-acting rifapentine, to shorten treatment for DS-TB (see table 3). The HIGHRIF1 study, funded by the European and Developing Countries Clinical Trials Partnership (EDCTP) and conducted by the Pan-African Consortium for Evaluation of Anti-tuberculosis Antibiotics (PanACEA), compared increasing rifampin doses up to 35 mg/kg against the standard dose of 10 mg/kg for bactericidal activity and safety over fourteen days. The 35 mg/kg dose appeared well tolerated, safe and showed greater bactericidal activity with higher doses, though results have not yet been published in a peer-reviewed publication.[37] An extension of this study to examine use of 40 mg/kg of rifampin for 14 days ended in May 2014; the study team has approval to test arms containing 45 mg/kg, 50 mg/kg, and 55 mg/kg of rifampin, but needs more funding to do so.[38] The HIGHRIF 2 study ended in November 2013; results will be presented in October 2014. Antimicrobial activity data are being analyzed, but this study found no serious adverse events for two months of rifampin at 15 and 20 mg/kg.[39] The RIFATOX trial found that rifampin at 15 and 20 mg/kg for the first four months of the standard six-month regimen was safe, with no increase in serious adverse events. However, these slightly higher doses of rifampin did not lead to a significant increase in culture conversion (participants' sputum testing negative for TB) at eight weeks.[40] Doses of rifampin up to 35 mg/kg are being tested for longer periods (eight weeks) in the ongoing MAMS-TB-01 study to determine their potential for treatment shortening.[41] If long-term data support safety and efficacy, rifampin's widespread availability and accessibility could facilitate its incorporation into a treatment-shortening regimen for drug-sensitive TB.

Rifapentine, which has a longer half-life than rifampin and is more potent against the TB bacterium, is being explored in higher doses for its treatment-shortening capacity. TBTC study 29X, which gave daily doses of rifapentine (with or without a boiled egg, as fatty food increases absorption) up to 20 mg/kg, showed that doses as high as 1,200 mg given daily for eight weeks were safe and well tolerated. Of those receiving 20 mg/kg, 11.1% permanently discontinued their regimens, and only one experienced a serious adverse event, compared with a 12.9% discontinuation rate and two serious adverse events in those receiving standard-dose rifampin.[42] Of those receiving 20 mg/kg of rifapentine, 94.7% tested negative for TB on solid culture at eight weeks,

versus 81.3% of those receiving standard rifampin ($P < .05$).[43] Study 29X, a phase I pharmacokinetic trial in healthy volunteers, showed that body weight did not affect rifapentine clearance from the body, meaning that weight-based dosing for rifapentine is not necessary. ACTG Study A5311 stopped early after 20 of 44 subjects discontinued treatment, 12 with grade 3 or higher toxicity.[44] These participants received daily single or divided doses of up to 2,400 mg of rifapentine. It is unclear whether the increased toxicity was related to higher exposures or to more robust responses from healthy volunteers. The Johns Hopkins–sponsored RioMAR trial, which gave two months of rifapentine (7.5 mg/kg) and moxifloxacin together, stopped early for administrative reasons, with just over half of the target population enrolled. Analyses indicate that participants in the experimental arm were slightly more likely to discontinue treatment due to study withdrawal (5% vs. 2%), loss to follow-up or default (5% vs. 0%), or toxicity (6% vs. 3%), but were more likely to have negative liquid cultures at the end of the intensive phase of treatment (94.4% vs. 71.4%; $P = .01$ in the per-protocol analysis).[45]

These data cumulatively indicate that doses of rifapentine up to 1,200 mg are well tolerated in people with TB, and warrant further study as they may help shorten treatment. A planned phase III trial, TBTC 31, will explore whether 1,200 mg daily of rifapentine, with or without moxifloxacin, can allow treatment to be shortened to just four months in people with and without HIV. Posttrial access to rifapentine, however, may prove challenging, as the drug is registered only in the United States, and despite the recent price reduction, remains much more costly than rifampin.

Both rifampin and rifapentine interact with a number of drugs that are metabolized by the liver, including antiretrovirals and methadone, important for treating people with HIV or on opiate substitution therapy. A study is under way to see if rifampin interacts with buprenorphine, used for opioid substitution therapy. It is unclear how increasing doses of rifamycins may affect these known drug-drug interactions. Further research is needed.

Fluoroquinolones

Fluoroquinolones, currently one of the backbones of MDR-TB treatment, continue to be explored for their potential to shorten treatment for drug-sensitive TB. Currently, there is little resistance to fluoroquinolones among patients with newly diagnosed TB, but resistance in re-treatment TB is increasing, and the widespread use of this class for other indications raises

concerns about emerging resistance. A debate has emerged as to whether the potential impact of treatment shortening outweighs concerns over the risk of "losing" the fluoroquinolone class for MDR-TB treatment.[46,47] This debate has so far been theoretical, as data from fluoroquinolone-based treatment-shortening trials are pending or negative. The OFLOTUB study failed to show that a four-month gatifloxacin-containing regimen was noninferior to—no worse than—the standard six-month treatment regimen.[48] Participants in the gatifloxacin arm were 3.8% more likely to have an "unfavorable outcome" (relapse, treatment failure, death, or loss to follow-up) than those in the control arm (95% CI: −0.3% to 8.0%, with noninferiority bounds set to 6%), but patients treated with gatifloxacin in this trial were much more likely to experience relapse (14.6% vs. 6.9%).[49]

Results from the REMox TB trial, due to be released soon, will provide further evidence on the potential for fluoroquinolones to shorten treatment of drug-sensitive TB. REMox studied four months of daily moxifloxacin, a fluoroquinolone that is more effective than other drugs in that class against the few but persistent TB bacteria that survive even when antibiotics wipe out most of them.[50] The future role of moxifloxacin and the fluoroquinolone class in the treatment of drug-susceptible TB will depend on the outcome of REMox and TBTC Study 31(see table 3). Fortunately, moxifloxacin's formerly high price is dropping as quality-assured generics enter the market.[51]

CONCLUSIONS AND RECOMMENDATIONS

TB drug development has undoubtedly advanced, but progress is slow, the number of new compounds limited, and knowledge insufficient to dramatically improve cure rates, reduce treatment duration, and make treatment more tolerable. To resolve this:

1. **Pharmaceutical companies, public agencies and research institutions, and philanthropies must invest more in TB drug research** to speed the progress of the drugs that are in development and to bring additional compounds into development. Existing public research funders such as the NIH, the CDC, the U.S. Agency for International Development, the British Medical Research Council, the French National Agency for Research on AIDS and Viral Hepatitis, and the EDCTP can invest more.

High–TB burden countries also need to fund TB R&D.[52] Additional investment in optimal strategies for treating latent TB infection is especially critical.

2. **Drug sponsors and clinical trials groups must collaborate to ensure the development not just of individual agents but also of new and better regimens.** The ACTG should expedite its study of delamanid and bedaquiline to inform the use of the two together. Sequella needs to make sutezolid available for studies with potential partners. Janssen must commit to adequate funding for its phase III program to ensure that the STREAM trial is conducted to the highest scientific and ethical standards, including that the standard-of-care arm continues to enroll throughout the trial duration. Research on drug-drug interactions is essential for bringing new regimens forward.

3. **More research must be conducted in populations disproportionately affected by TB**, including people with HIV, people who use drugs or alcohol, people with HCV coinfection, children, and pregnant and lactating women. Research in these groups is important for all new TB drugs and regimens, especially in light of their historical lack of representation in clinical trials.

4. **Trial sponsors must include community representatives throughout the research process, from early development to registration**, to ensure that planned studies reflect community interests and needs.[53]

5. **Regulatory authorities must ensure that postmarketing requirements are enforced** so that adequate safety and efficacy data are available to support the use of new tools to fight TB, particularly ones that are approved under early review mechanisms.

Limitations in research are paralleled by those on the access side, where patients, doctors, and TB programs are unable to access new and old drugs alike due to high costs, supply problems, and lack of registrations.

6. **Sponsors of new drugs must plan early on for pre-approval access programs** as soon as sufficient safety and preliminary efficacy data (phase II) are available; this includes both individual patient compassionate use programs, and expanded access trials in countries that do not have a legal mechanism to allow for compassionate use (e.g., China, Lithuania,

Moldova, Russia). Otsuka has been negligent in its already late and limited compassionate use program. The TB Alliance should develop and implement a compassionate use strategy for PA-824 as it enters into phase III trials.

7. **Sponsors of new drugs must rapidly file for registration in trial-site countries and other high–TB burden settings.** Otsuka must immediately file in countries other than the high-income, low-burden settings it has been targeting for years. Similarly, Sanofi should file for approval for rifapentine in the numerous countries where its trials have been conducted, such as South Africa and Brazil; it is unethical not to have done so years after rifapentine received approval in the United States.

8. **Drug companies must commit to affordable pricing.** Community groups have lambasted the tiered-pricing approach that does little to promote fair drug prices,[54] yet Janssen and Otsuka are insisting on this approach. Many activists advocate instead for voluntary licensing and other plans that allow competition to drive down prices and expand access in low- and middle-income countries, while tiered pricing locks in fixed, often high, prices.[55]

9. **TB programs and regulatory authorities must prepare for the registration of new drugs and regimens early**, considering risks and benefits thoroughly, and strategizing for the roll-out of numerous, rather than individual, changes to guidelines for patient care. As many treatment-shortening first-line studies are under way, programs should carefully weigh what evidence would be required to change a long-established standard of care, and to mitigate the risk of resistance when fluoroquinolones or new drugs are included.

10. **National programs and donors must finance better drug procurement, supply-chain management, and universal access to ensure access to both old and new treatment options.** Drug shortages are preventable and therefore unacceptable; better forecasting is needed to assist manufacturers in creating a stable supply; regulatory incentives may also be required. In particular, the FDA and CDC should move quickly to find ways to take advantage of the GDF model. In parallel, drug procurement budgets need expansion to enable the best treatment to reach those in need at no cost to the patient.

11. **The World Health Organization must update its Essential Medicines List.** In particular, bedaquiline, clofazimine, delamanid, linezolid, and rifapentine must be included on the list. Countries need these drugs urgently for the treatment of LTBI and active drug-resistant TB disease; their addition to the WHO's Essential Medicines List would provide critical guidance to countries to purchase these drugs.

While TB treatment and prevention research and implementation are moving forward, they are a long way from where we need them to be. With political will, commitment from the public sector and industry, smarter science, and guidance from and engagement with all affected communities, we can get there. We must.

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Playing Catch-Up: Pediatric Tuberculosis Treatment Pipeline

By Lindsay McKenna

Introduction

While the pediatric HIV drug pipeline has seen increased activity in recent years, the same cannot be said for pediatric TB. Adult-pediatric approval gaps remain an issue in HIV drug development, especially for children under two years old, including infants.[1] But HIV drugs are far ahead of TB drugs, many of which were developed over a half-century ago and still lack evidence-based dosing for children, which is critical for optimizing treatment and developing acceptable formulations, especially for very young children.

The lack of appropriate pediatric TB treatment results from the historical neglect of TB disease in children. Many TB programs, researchers, and funding agencies have not made children a priority, because they believe children do not transmit the disease and are therefore "epidemiologically insignificant." Diagnostic challenges and resultant poor recording and reporting of TB in children have further perpetuated the perception of limited disease burden and potential market for TB treatment in children. While treatment of drug-susceptible TB (DS-TB) in children is evidence-based, fixed-dose combinations (FDCs) of first-line drugs (FLDs) are not available in appropriately dosed combinations. The current treatment of multidrug-resistant TB (MDR-TB) in children is very much a guessing game: treatment practice is guided by findings extrapolated from adult data, and unpalatable pills, designed for adults, must be split or crushed and mixed with juice or foodstuffs to administer them to children. While researchers play catch-up to generate pediatric data for existing drugs, a few studies of new drugs in children are under way or planned, though progressing slowly.

New Disease Burden Estimates

The perception of a small market for pediatric TB drugs has limited interest from developers and manufacturers. In 2013, for the second time ever, the World Health Organization (WHO) included pediatric TB incidence estimates in its annual *Global Tuberculosis Report*. The WHO estimated that in 2012,

530,000 children developed TB disease.[2] However, researchers from Brigham and Women's Hospital and Harvard Medical School recently estimated that 1 million children develop TB annually—twice the number estimated by the WHO, and three times the number of children diagnosed each year—and, of those, 32,000 have MDR-TB.[3]

Existing Drugs

In 2010, the WHO released evidenced-based pediatric dosing guidelines for FLDs. Four years later, we are still waiting for appropriately dosed FLD formulations that are easy to give to children. The Global TB Alliance for Drug Development, under a grant from UNITAID, is working to speed the market introduction of pediatric FLD formulations. New pediatric FDCs for the treatment of DS-TB are expected in late 2015. For second-line drugs (SLDs), we currently lack the data necessary to develop appropriately dosed pediatric formulations, although there are plans to develop evidence-based dosing guidelines for SLDs using pharmacokinetics (PK) data from the **MDR-PK** study in South Africa (see table 1).[4]

New Drugs

Bedaquiline and delamanid, two new drugs recently approved for treating MDR-TB in adults, are now being studied in children. Otsuka, the sponsor of delamanid, which was approved by the European Medicines Agency (EMA) for DR-TB in April of this year, is already enrolling the second age cohort (6–11-year-olds) in its PK and safety study.[5] In stark contrast, Janssen, the sponsor of bedaquiline—which was conditionally approved by the U.S. Food and Drug Administration (FDA) in December 2012—has yet to begin its planned PK and safety study in children and adolescents. These discordant timelines are in part due to differing regulatory requirements between the EMA and FDA. The EMA, where Otsuka first registered delamanid, requires a pediatric investigational program (PIP), whereas the FDA, where Janssen first registered bedaquiline, offers pediatric study exemption for orphan drugs. While the FDA offers other incentives for research in pediatric populations, such as an additional six months of marketing exclusivity under the Best Pharmaceuticals for Children Act (BPCA),[6] a regulatory requirement for drug development in children is urgently needed, especially for neglected diseases like TB, where private-sector developers are few and investments are shrinking.

Planned Trials

Pediatric TB has recently gained momentum as a priority area for study; however, discourse often focuses on the well-characterized historical neglect of pediatric populations in research and development programs, without suggesting ways forward. This is slowly starting to change as the work of research and policy groups like the Sentinel Project for Pediatric Drug-Resistant TB, the Stop TB Partnership's Childhood TB Subgroup, the Tuberculosis Trials Consortium Pediatric Interest Group, the U.S. National Institutes of Health (NIH) International Maternal Pediatric Adolescent AIDS Clinical Trials Group, and a new NIH-convened multi-stakeholder panel that is promoting timely pediatric safety and dosing evidence for TB drugs and regimens is helping to improve the visibility of children with TB and to advance research in this especially vulnerable population. However, a clear and prioritized research agenda remains urgently needed. Table 1 offers an overview of ongoing and planned studies for TB prevention and treatment in children.

Table 1. Ongoing and Planned Pediatric Tuberculosis Prevention and Treatment Studies

Study/Regimen	Status	Population(s)	Sponsor(s)
PREVENTION			
P4v9 4 months of self-administered daily rifampin for prevention of TB NCT00170209*	Follow-up; results expected 2015/16	HIV-positive or -negative children 0–17 years old with LTBI	CIHR, McGill University
TBTC 26/ACTG 5259 3 months of once-weekly rifapentine and isoniazid for prevention of TB NCT00023452*	Complete; results presented 2012; PK analysis published 2014	HIV-positive or -negative children 2–18 years old with LTBI	TBTC, ACTG
ACTG A5279 4 weeks of daily rifapentine and isoniazid for prevention of TB NCT01404312*	Enrolling; primary results expected 2018	HIV-positive adults and adolescents (13+ years old) with LTBI	NIAID, ACTG, IMPAACT

Study/Regimen	Status	Population(s)	Sponsor(s)
MDR-TB Prevention Cohort 6 months of daily ofloxacin, ethambutol, high-dose isoniazid for prevention of MDR-TB	Complete; results published 2013	HIV-positive children <15 years old; HIV-negative children <5 years old exposed to MDR-TB	USAID (TREAT TB), NRF, Sir Halley Stewart Trust
IMPAACT TB-CHAMP/ A5300 Levofloxacin-based regimen for prevention of MDR-TB	Planned	HIV-positive or -negative infant, child, and adolescent household contacts with LTBI	BMRC, IMPAACT, ACTG
TBTC 35 PK and safety of rifapentine/ isoniazid FDC for prevention of TB	Planned	HIV-negative infants and children with LTBI [children <2 years old will get pediatric formulation]	TBTC, Sanofi
TREATMENT			
232 PK and safety of delamanid, OBR for treatment of MDR-TB NCT01856634*	Enrolling; primary results expected 2016	HIV-negative children 6–17 years old with MDR-TB	Otsuka
233 6 months of delamanid, OBR for treatment of MDR-TB NCT01859923*	Enrolling; primary results expected 2017	HIV-negative children 6–17 years old with MDR-TB [children <5 years old will get pediatric formulation]	Otsuka
IMPAACT 1108 PK and safety of bedaquiline, OBR for treatment of MDR-TB	Planned; opening 2015	HIV-negative children 0–18 yrs. old, HIV-positive children 12–18 years old with MDR-TB [children <12 years old will get pediatric formulation]	NIAID, IMPAACT
DATiC PK of FLDs using 2010 WHO dosing guidelines for treatment of TB and interactions with lopinavir/ritonavir and nevirapine NCT01637558*	Enrolling; interim results expected 2014	HIV-positive or -negative children 0–12 years old with TB	NICHD, UNITAID/TB Alliance
Treat Infant TB PK and safety of FLDs using 2010 WHO dosing guidelines for treatment of TB	Enrolling; interim results expected 2014	HIV-positive or -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 and interactions with nevirapine and efavirenz NCT01687504* NCT01704144* NCT01699633*	Enrolling; primary results expected 2017	HIV-positive or -negative children 3 months–14 years old with TB	NICHD
SHINE 4 vs. 6 months using 2010 WHO dosing guideline–adjusted FLD FDCs for treatment of minimal TB	Planned; opening 2015	HIV-positive or -negative infants, children, and adolescents with minimal TB	BMRC, DFID, Wellcome Trust, University College London
PATCH Safety and efficacy of levofloxacin and rifampin for treatment of TB meningitis	Planned	HIV-positive or -negative infants and children with DS-TB meningitis	NICHD (pending)
IMPAACT 1106 PK of FLDs, SLDs, and ARVs	Planned; opening 2014	HIV-positive or -negative low-birth-weight/premature infants	NIAID, IMPAACT
MDR-PK PK and safety of SLDs for treatment of MDR-TB	Enrolling; interim results presented 2013; final results expected 2016	HIV-positive or -negative infants, children, and adolescents with MDR-TB or LTBI	NICHD
IMPAACT 1101 PK and safety of raltegravir and interactions with rifampin-containing TB treatment NCT01751568*	Planned; opening 2014	ARV-naive HIV-positive children 3–12 years old on rifampin-containing TB treatment	NIAID
Rifabutin-PK PK and safety of rifabutin for treatment of TB	Planned	HIV-positive children and adults on PI-based second-line ART	ICMR, NACO
IMPAACT 5000 PK and safety of rifapentine for treatment and prevention of TB in pregnant women	Planned	HIV-positive or -negative pregnant women	NIAID

*National Institutes of Health clinical trial identifiers; for more information go to ClinicalTrials.gov.

ACTG: AIDS Clinical Trials Group, U.S. Institute of Allergy and Infectious Diseases
ART: antiretroviral therapy
ARV: antiretroviral
BMRC: British Medical Research Council
CIHR: Canadian Institutes of Health Research
DFID: Department for International Development (United Kingdom)
FDC: fixed-dose combination
FLD: first-line drug
ICMR: Indian Council of Medical Research
IMPAACT: International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group, U.S. National Institutes of Health
LTBI: latent tuberculosis infection
NACO: National AIDS Control Organization (India)
NIAID: U.S. National Institute of Allergy and Infectious Diseases
NICHD: National Institute of Child Health and Human Development, U.S. National Institutes of Health
NRF: National Research Foundation (South Africa)
OBR: optimized background regimen
PI: protease inhibitor
PK: pharmacokinetics
SLD: second-line drug
TB: tuberculosis
TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention
WHO: World Health Organization

TRIAL RESULTS

Prevention

TBTC 26 PK/ACTG 5259

In this study of rifapentine and isoniazid, which shortens treatment for latent TB infection (LTBI) to just three months of once-weekly dosing, researchers found that higher weight-adjusted doses of rifapentine were required for children 2–11 years old to achieve exposures similar to those in adults. Higher rifapentine doses were well tolerated in children. Researchers found decreased bioavailability of rifapentine with crushed tablets compared with whole tablets, emphasizing need for the pediatric formulation currently being developed by Sanofi.[7]

MDR-TB Prevention Cohort

Six months of daily ofloxacin, ethambutol, and high-dose isoniazid was well tolerated in children with household exposure to MDR-TB, and few children developed TB or died (incident TB in 6/186 children; death in 1/186 children). Children less than one year old or HIV-positive and those with poor adherence were more likely to develop TB or die.[8] While this study was not a randomized controlled trial (RCT), the findings suggest that this three-drug regimen should be considered for preventive therapy in children exposed to MDR-TB and evaluated in a future RCT.

What's Missing?

The WHO recommends that child contacts of DS-TB patients be treated with isoniazid preventive therapy,[9] but no such recommendation exists for child contacts of DR-TB patients. Children exposed to DR-TB by household contacts need to be rapidly identified, screened, and treated or put on prophylactic therapy. We urgently need to identify and validate TB drugs or regimens that can be used to prevent disease in child contacts of DR-TB patients.

Treatment

First-line drugs

There is a nonlinear relationship between weight and drug clearance in children. As a result, the standardized mg/kg dosing under the revised WHO guidelines for FLDs may lead to underdosing in small children. Ongoing studies will confirm that the revised FLD dose recommendations actually produce drug exposures in children (especially those younger than two years old) comparable to those observed in adults and will examine how concomitant treatment with ART affects TB and HIV drug exposure in children (see table 1: **DATiC**; **Treat Infant TB**; and **PK-PTBHIV01**). As dosing needs may vary significantly for infants, where immature physiological function can lead to higher exposures and toxicity, the **Treat Infant TB** study will confirm PK and safety of the revised FLD dosing recommendations in infants less than 12 months old, and the **IMPAACT 1106** study will collect both first- and second-line drug PK data in low-birth-weight and premature infants.

Second-line drugs

Existing and forthcoming SLD PK data will eventually be combined in a systematic review, which will inform a WHO dosing recommendation required to advance the development of pediatric formulations.

MDR-PK

Thee and colleagues did an interim analysis of ofloxacin (20 mg/kg) and levofloxacin (15 mg/kg) PK, safety, and tolerability data in HIV-positive and -negative children, where the drugs were used as treatment for MDR-TB disease and as prophylaxis against it. They found low drug exposures in children relative to PK and pharmacodynamic (PD) targets and to levels of exposure achieved in adults. While both drugs were well tolerated as part of long-term treatment, their optimal doses in children have yet to be determined.[10,11,12] In an earlier analysis of PK data for ofloxacin, researchers observed lower drug concentrations in children in the disease group compared with those in the prophylaxis group. One possible explanation is that children receiving prophylaxis were generally younger and required the tablets to be crushed, which may increase drug bioavailability.[13]

Following interim analysis of PK data for ethionamide (20 mg/kg), researchers found that younger children achieved target drug levels earlier (this again may be related to increased bioavailability when tablets are crushed); overall, however, ethionamide exposures were the same between age groups and comparable to those of adults. However, children with HIV had significantly lower levels of exposure compared with children who were HIV-negative.[14]

Contrary to what researchers found with ethionamide, children exceeded adult-target drug exposures when given 20 mg/kg of amikacin.[15] There may therefore be potential to reduce the dose or frequency of administration of amikacin in children, which could reduce the drug-related hearing loss observed in at least 20 percent of children treated with existing injectable TB drugs.[16]

TRIAL STATUS UPDATES

233 (delamanid)

Otsuka is currently enrolling a cohort of 6–11-year-olds in a PK and safety study in the Philippines. The study protocol was recently approved in South Africa, and enrollment is under way. Otsuka will soon begin bioequivalence studies of its dispersible minitablet, which is under development for children less than six years old.[17,18]

P1108 (bedaquiline)

Janssen's pediatric trials are long overdue. After nearly three years of negotiations with IMPAACT and the U.S. National Institute of Allergy and Infectious Diseases (NIAID) to complete a protocol for study P1108, Janssen decided this June that it was pulling out of the collaboration.[18a] The study had planned for 12–18-year-olds to receive the adult formulation and for younger cohorts (6–12 years, 2–6 years, 6 months–2 years, 0–6 months) to receive the pediatric formulation (dispersible tablets) currently under development. The cohorts were to be enrolled sequentially from oldest to youngest, once adequate data from the preceding cohort were available. HIV-negative children were to be enrolled first in each age cohort, and similar numbers of HIV-positive children 12–17 years old would follow. Enrollment for this study was expected to begin in the first quarter of 2013, and revised to the first quarter of 2015 before Janssen's withdrawal.[19] IMPAACT may still go ahead with this or a modified design. As this report goes to press, Janssen has yet to announce plans for an alternative pediatric trial, despite its being a requirement of EMA approval. Janssen's delays in developing the protocol with IMPAACT and NIAID, and its recent withdrawal from the collaboration, have squandered public resources and investigators' effort, and needlessly slowed the collection of critical data on bedaquiline in children.

PA-824

While the Global TB Alliance for Drug Development will advance the new drug, PA-824, to phase III trials in adults, its pediatric program is not expected to start until 2016. This delay could be related to toxicology study findings that

some rats receiving high doses of PA-824 over three to six months developed cataracts.[20]

What's Missing?

Data detailed above suggest that crushing and mixing TB medicines to facilitate their administration to young children may have an affect on drug bioavailability. The Sentinel Project on Pediatric Drug-Resistant Tuberculosis is conducting a laboratory-based study to evaluate the stability and availability of SLDs when mixed with different foods. Its study includes ethionamide, cycloserine, levofloxacin, and linezolid in Plumpy'Nut (a nutrient-dense peanut-based paste), milk, vitamin syrup, and crushed banana.[21] Results, expected this summer, will inform the design of a study proposed by researchers at Stellenbosch University to examine taste and practical preferences and how different foods and food products affect drug PK.[22]

The current development model for pediatric TB drugs is similar to that for adult therapies: researchers study individual drugs sequentially and often as additions to existing regimens. Yet, what we actually need is new, shorter, all-oral regimens that are effective against all forms of TB and available in pediatric formulations (preferably dispersible tablets). The ongoing PK study in South Africa will fill many of the existing data gaps for the use of SLDs in children. However, once we have adequate PK information, we will still lack data on the optimal role of each drug in pediatric TB treatment. For example, if moxifloxacin-containing regimens (see "Tuberculosis Drug Development Hobbles Forward," p. 197) show favorable results, we will still lack a pediatric formulation for moxifloxacin (the tablet is not scored and is bitter when crushed). In addition, we lack data and consensus on the role of fluoroquinolones in treatment shortening for pediatric DS-TB.

We need a pediatric TB treatment research agenda that analyzes planned and ongoing studies in adults, determines what pediatric data remain to be gathered, and identifies adult studies where adolescents can and should be included. Until such an agenda is established, children will remain an afterthought, and researchers will be stuck in a never-ending game of catch-up.

RECOMMENDATIONS

1. Integrate adult and pediatric TB drug research.

The existing model, in which TB treatment research in adults and children is conducted sequentially, needs to shift toward integration. Failing to study, or delaying the study of, TB treatments in children leaves us with no safety or efficacy data and no guidelines for dosing: every child remains an experiment.[23]

2. Mandate earlier inclusion of children in TB drug development.

The earlier inclusion of children in TB research is critical to developing appropriately dosed and formulated drugs for children. In a forthcoming consensus document, an NIH-convened group of experts recommends a parallel development pathway for pediatric TB drugs. The development of pediatric formulations should follow phase IIa studies so that once efficacy and adequate safety have been established in adults (phase IIb studies), PK, safety, and tolerability studies in children can begin.[24]

3. Include adolescents in phase III TB drug trials.

Adolescents more than 10 years old who can tolerate adult formulations should be included in phase III trials. The protocol for TBTC phase III study 31, currently in development (see "Tuberculosis Drug Development Hobbles Forward," table 3, p. 201), will include adolescents more than 13 years old.[25] Individual site Institutional Review Boards (IRBs) may pose a barrier to the inclusion of adolescents in phase III trials on the basis of age. Differing expertise and populations between sites may also affect the recruitment of adolescents. It is important that local IRB decisions be driven by community consultation.

4. Conduct progressive clinical trials to speed research on and access to TB drugs for children.

For studies in children less than 10 years old, cohorts should be recruited in parallel, as sequential enrollment does not necessarily offer any additional

protection for the younger age groups, whose physiology differs from that of older children.[26] However, enrollment of older cohorts should not be delayed while pediatric formulations are developed; it should start early on.

TBTC study 35 (see table 1), will recruit all age cohorts in parallel. Janssen should follow the TBTC and Sanofi's lead as it revises its pediatric trial plans following its sudden withdrawal from the collaboration with IMPAACT and NIAID. If IMPAACT moves forward with its plans to study bedaquiline in children independent of Janssen, it should revise the protocol for P1108 to recruit all age cohorts in parallel. If Janssen and IMPAACT go ahead with plans for sequential enrollment, it will only further delay the gathering of data urgently needed to inform the inclusion of bedaquiline in pediatric DR-TB regimens.

5. Develop a pediatric TB treatment research agenda.

We need a pediatric TB treatment research agenda that analyzes planned and ongoing studies in adults, determines what pediatric data are missing, and identifies adult studies where adolescents can and should be included.

6. Increase funding for pediatric TB drug development.

Greatly increased funding is critical to hastening the development of correctly dosed formulations of new and existing TB drugs designed for use in children.

The recently published *Roadmap for Childhood Tuberculosis*, which outlines key actions and investments needed to address pediatric TB, estimates that US$200 million between 2011 and 2015 is needed for research and development (R&D) projects to provide new tools to prevent, diagnose, and treat TB in children.[27] Yet, in 2012, TAG reported only US$10.3 million in pediatric TB R&D investments from 14 donors—just two percent of the US$627.4 million that 84 funders invested in overall TB R&D in 2012.[28] Out of US$237.8 million in total TB drug R&D funding, only US$3.8 million was invested in pediatric TB drug development. Pediatric TB R&D investments follow the larger trend of decline in TB R&D funding overall described in TAG's *2013 Report on Tuberculosis Research Funding Trends, 2005–2012*.[29]

7. Mandate the development of pediatric TB drugs.

While the FDA offers some incentive for research in pediatric populations (six months' additional marketing exclusivity under the BPCA), a regulatory requirement is urgently needed for sponsors seeking approval for new TB drugs, especially as private-sector developers are few and investments are shrinking. Under the Pediatric Research Equity Act of 2003, the FDA can require that companies conduct pediatric studies after receiving marketing approval; however, drugs with orphan status (for diseases that affect <200,000 people in the U.S., like TB) are exempt from this requirement. Other stringent regulatory authorities should also consider mandating pediatric investigational program submissions alongside new drug applications as has been done successfully by the EMA.

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The Tuberculosis Vaccines Pipeline

Back to basic science

By Mike Frick

The last year in tuberculosis (TB) vaccine research has demonstrated how setbacks can sometimes produce the potential for unexpected progress. Dominant hypotheses have yielded to new investigative directions, and unresolved questions have returned to center focus in the wake of disappointing results from the first efficacy trial of a TB vaccine since 1968. The announcement in February 2013 that TB vaccine candidate MVA85A did not confer significant added protection against TB to infants vaccinated with the existing TB vaccine, bacille Calmette-Guérin (BCG), delivered unwelcome news in a field eager for success.[1] One month after the publication of these results, TB vaccine researchers gathered in Cape Town, South Africa, at the Third Global Forum on TB Vaccines, where conversation focused on the lessons the historic MVA85A trial holds for future vaccine discovery efforts.

Discussions in Cape Town and during the following year have led researchers to revisit topics ranging from the predictive value of animal models used in preclinical development to the tradeoffs of different clinical trial endpoints to the complex contextual factors that affect risk of *Mycobacterium tuberculosis* (MTB) infection and TB disease. Driving these intersecting lines of inquiry is the urgent need to better understand host–pathogen interaction, or the interplay between MTB and the human immune system.

Answering these questions will require embracing new approaches in preclinical and clinical research as well as forging stronger connections between clinical research and development (R&D) and laboratory advances in basic science. Over the past year, developers have introduced new study designs in phase II trials, although not every TB vaccine candidate is taking advantage of these innovations. Findings from basic research have cast doubt on the core assumptions that steered TB vaccine R&D from its revitalization in 2000, when the pipeline sat empty,[2] to the present day, when the pipeline now has 16 candidates or vaccine combinations under active clinical development.

Table 1. Vaccine Candidates under Active Development

Agent	Strategy	Type	Sponsor(s)	Status
M. indicus pranii	Immunotherapeutic	Whole-cell M. indicus pranii	Ministry of Science and Technology (Government of India), Cadilla Pharmaceuticals	Phase III
M. vaccae	Immunotherapeutic	Whole-cell M. vaccae	AnHui Longcom	Phase III
MVA85A	Prime-boost	Viral vector	Oxford University, Aeras, European & Developing Countries Clinical Trials Partnership (EDCTP)	Phase IIb
M72 + AS01	Prime-boost	Protein/adjuvant	GlaxoSmithKline, Aeras	Phase IIb
VPM1002	Prime	Live recombinant rBCG	Vakzine Projekt Management GmbH, Max Planck Institute for Infection Biology, TuBerculosis Vaccine Initiative (TBVI), Serum Institute of India	Phase IIb pending
Crucell Ad35	Prime-boost	Viral vector	Crucell, Aeras	Phase IIa
Hybrid 1 + IC31	Prime-boost	Protein/adjuvant	Statens Serum Institut (SSI), TBVI, EDCTP, Valneva	Phase IIa
Hybrid 4 + IC31	Prime-boost	Protein/adjuvant	SSI, Sanofi, Institut Pasteur, Aeras	Phase IIa
Hybrid 56 + IC31	Prime-boost	Protein/adjuvant	SSI, Valneva, Aeras	Phase IIa
RUTI	Immunotherapeutic	Fragmented MTB	Archivel Farma	Phase IIa
Ad5Ag85A	Prime-boost	Viral vector	McMaster University, CanSino	Phase I
ChAdOx1 85A + MVA85A	Prime-boost	Viral vector	Oxford University	Phase I
Combination Crucell Ad35 + MVA85A	Prime-boost	Viral vector	Crucell, Oxford University, Aeras	Phase I
DAR-901	Prime-boost	Whole-cell M. obuense	Dartmouth University, Aeras	Phase I
ID93 + GLA-SE	Prime-boost	Protein/adjuvant	Infectious Disease Research Institute, Aeras	Phase I
MTBVAC	Prime	Live genetically attenuated MTB	University of Zaragoza, Biofabri, TBVI	Phase I

The composition of the TB vaccine pipeline remains virtually unchanged from the picture presented in TAG's *2013 Pipeline Report*.[3] The pipeline includes vaccines designed to replace BCG (prime vaccines), improve the limited immunity conferred by BCG (prime-boost vaccines), and shorten TB chemotherapy (immunotherapeutic vaccines). Candidates under the prime strategy seek to either modify BCG or genetically attenuate MTB itself to produce a safer, more effective vaccine that could replace BCG altogether. Within the prime-boost strategy, viral-vectored and adjuvanted subunit vaccines aim to augment the limited immunity conferred by BCG. Viral-vectored vaccines use weakened, nonreplicating viruses to transport MTB DNA into human cells, where it is transcribed into antigens (proteins that provoke an immune response). Adjuvanted subunit vaccines combine different MTB antigens with adjuvants that boost the body's natural immunity. The pipeline also contains several whole-cell vaccines constructed from inactivated mycobacteria related to MTB such as *Mycobacterium vaccae*.

OLD QUESTIONS IN BASIC SCIENCE

The lack of biomarkers that correlate with protective immunity against TB disease or MTB infection remains the central challenge of TB vaccine R&D. The word biomarker refers to genes, biological processes, or clinical phenotypes that act as precursors or signals of a particular disease or response to immunization or treatment.[4] Biomarkers can help researchers improve the selection of candidates to advance to late-phase trials by giving glimpses of efficacy earlier in a vaccine's development. The term is so frequently invoked as a stand-in for the many unanswered questions in TB immunology that it has become a too-convenient shorthand conflating distinct immunological questions that will not be solved by easy, unitary solutions. Context matters: researchers will need to identify unique markers for different stages of infection and disease, or define "biosignatures" comprising markers associated with both host and pathogen response.[5]

Ultimately, biomarkers are tools that may be helpful in selecting better candidates and designing shorter, faster trials, but whose identification will depend on answering lingering questions about the dynamics of host–pathogen interaction. Even when found, potential biomarkers will not shorten the clinical pipeline overnight, as any markers of immunity will require the clinical validation that hinges on confirming vaccine efficacy in large phase III

trials. In the meantime, much work remains unfinished on the basic-science front, beginning with improving our understanding of BCG, the TB vaccine we already have.

BCG: the old friend we barely know

First introduced in 1921 and now the most widely given vaccine in the world, BCG protects infants and children from tuberculous meningitis and severe forms of disseminated TB.[6] The protection afforded by BCG declines in adolescence, although the biological mechanisms behind this waning remain unknown—a mystery revisited in multiple publications in the past year.[7,8,9] A systematic review of 21 randomized controlled trials comparing BCG with placebo (all of them conducted decades ago) reinforces several earlier suspicions about BCG's adolescent disappearing act and variable protection. The review found that BCG conferred greater protection in northern latitudes, where vaccine recipients face less exposure to non-MTB mycobacteria (NTM), which are commonly found in the soil in equatorial regions. The average protection conferred by BCG also appeared greatest in trials that enrolled MTB-naive subjects (either neonates or school-aged children with negative MTB skin tests). Notably, the strain of BCG used in different trials did not appear to explain variability in BCG efficacy.[10]

Understanding the nuances of BCG is essential given the pipeline's preponderance of candidates designed to boost BCG. An old question in TB vaccine R&D asks whether prior exposure to NTM masks or blocks the efficacy of BCG. The "masking" hypothesis speculates that exposure to mycobacteria confers some level of protection against TB, and so BCG vaccination offers limited additional protective effect.[11] In contrast, the "blocking" hypothesis proposes that exposure to NTM produces antigens that block the replication of BCG (as a live attenuated vaccine, BCG must replicate to be effective).[12] Clarifying the effects of NTM exposure on BCG efficacy may help researchers predict whether candidate vaccines will be similarly compromised. One approach would be to explicitly model NTM exposure in preclinical animal studies.[13] Another strategy would be to take NTM exposure as a given and, rather than try to predict its effects preclinically, treat it and BCG as "background noise" on top of which developers prime and boost with new candidates.

The role of NTM exposure has raised questions since the earliest days of the World Health Organization (WHO)'s BCG vaccination program in 1948,[14] and is unlikely to yield to simple answers. Solidifying consensus that NTM exposure underlies part of BCG's variable performance does, however, open the door to related questions that may be easier to answer. For one, the optimal times to administer and boost BCG remain unclear. One study suggests that the immune response to BCG in infants peaks at 10 weeks after vaccination. Consequently, the best time to boost BCG may come 14 weeks after vaccination, when the body has had time to develop greater cellular memory of BCG, and the effector CD4 and CD8 T cells provoked by BCG are no longer in a state of peak activity.[15] One tension underlying this and related work is that most studies of BCG are conducted in infants, while most vaccines in the pipeline are being developed with adolescents in mind. BGC dynamics in infants might differ from the immune responses required to boost BCG in more immunologically mature young adults. Research on BCG and trials of candidate vaccines are focusing on different age cohorts, with unknown consequences for new product development.

Dangerous liaisons: host–pathogen interaction and the missing markers of immune response

Work to understand BCG might also bring the misunderstood interplay between human host and MTB pathogen into sharper focus. TB vaccine R&D has focused on achieving cell-mediated immunity by triggering Th1 cytokines (e.g., IFNγ, TNFα, and IL-2) produced by either CD4 or CD8 T cells. These cytokines are small proteins that act as signaling molecules that help direct the body's immune response by changing the behavior of other cells. The emphasis on inducing Th1 immunity draws from both animal-model data suggesting a connection between T-cell expression of IFNγ, TNFα, and IL-2 and protection against TB disease,[16] as well as observations that CD4 T-cell depletion places people with HIV at a higher risk of developing TB.[17] Yet mounting evidence suggests that invoking a strong Th1 response alone is not sufficient for a new vaccine to outperform BCG; researchers will need to look beyond IFNγ and its cytokine cousins when evaluating the immunogenicity of candidate vaccines.

An elegant study in South Africa measured the BCG-specific CD4 and CD8 T-cell response in nearly 6,000 infants. The authors found no correlation between the magnitude of expression of Th1 cytokines and protection against

TB disease.[18] These results echo earlier concerns about the poor predictive value of IFNγ as a marker of protective immunity.[19] Only recently have these findings gained critical mass, with multiple voices calling on vaccine developers to look beyond cell-mediated immunity and IFNγ readouts as primary measures of immunogenicity.[20,21,22,23]

New genetic analyses of MTB strains from across the world raise an even more uncomfortable notion: not only is Th1 immunity insufficient for achieving protection, but triggering it may actually play into MTB's hand.[24,25] MTB has coevolved with humans for at least 70,000 years,[26] giving it ample time to learn the tricks of our immune system and turn them against us. The suggestion that MTB has conserved the very epitopes that our immune system recognizes[27] means that vaccine candidates constructed to overexpress these epitopes may actually work against protection. This is exactly how most candidates in the pipeline are designed. In most pathogens, antigens recognized by the immune system show the greatest genetic variability in order to help the organism evade detection by the host. In MTB, however, genes coding for the epitopes recognized by human T cells appear the least changed over time. Detection by T cells may actually benefit MTB in several ways, including aiding transmission to future hosts given the role T cells appear to play in the formation of cavitary TB (a highly contagious condition in which MTB infection and subsequent inflammation destroy lung tissue). Future vaccination strategies may need to target more variable parts of the MTB genome, rather than the T-cell epitopes that MTB has conserved.[28]

Even the central tenet of TB pathogenesis—that infection and disease exist as binary states—has come under scrutiny.[29] Much TB drug, diagnostic, and vaccine research has proceeded from the long-held idea that latent TB infection and active TB disease exist as mutually exclusive worlds. Emerging consensus that infection and disease lie along a continuum requires recognizing related immunologic states with greater nuance behind them rather than a simple distinction between active and latent. Driving this conceptual shift is work suggesting that MTB may be more extracellular than assumed.[30] Dominant thinking portrays MTB as an intracellular organism that sequesters itself in fortress-like granulomas in the lung in a dormant state of low activity until an "event" (e.g., a weakened immune system owing to diabetes, aging, or HIV infection) provides an opportunity for escape. New thinking suggests that even when checked into latency by the immune system, some bacteria persist outside of the cell.[31] More than a point of scientific clarification, better characterizing

the intracellular/extracellular nature of MTB along the continuum of infection and disease holds important implications for the TB vaccine pipeline. Most vaccines in the pipeline are designed to trigger T-cell responses, yet extracellular bacteria live beyond the reach of T cells.[32]

Our understanding of how MTB behaves—even within the cell—is being overturned. New work points to substantial variability in the activity of MTB across individual granulomas within the same host. Macaques with active and latent TB both appear to have granulomas containing live bacteria and others that are sterile (the immune system has already killed the bacteria).[33,34] Understanding why the immune system produces different results in different granulomas may illuminate biomarkers correlating with progression to active or reactivated disease.[35] In the meantime, acknowledging the gray scale between latent infection and active disease may guide researchers in targeting vaccines to account for MTB's ability to be resting/active, intracellular/extracellular all within the same person.

Preclinical screening: lost in the animal kingdom

All of these advances in basic science point to one word: diversity. Whether discussing different strains of BCG, the mycobacterial exposures in dissimilar climates, or the genetic and biological differences within and across human populations, the component parts of TB immunology can no longer be taken as uniform. Acknowledging diversity holds major implications for the preclinical testing of TB vaccine candidates in animal models and how researchers employ these results to select candidates for future testing in humans.

First, MTB itself, like many bacterial pathogens, is not a uniform organism, but instead exists as many strains actively evolving in response to environmental pressures. The rise of drug-resistant strains of MTB—and the recent discovery that some drug-resistant strains may even be developing "compensatory mutations" enabling them to spread faster[36,37]—signals the need to create a TB vaccine that can act against all forms of TB. Yet most preclinical programs continue to screen vaccine candidates against weaker laboratory strains (H37Rv, Erdman) instead of clinical isolates of MTB that are circulating in communities and making people sick.[38,39,40]

In addition to screening vaccine candidates against clinical MTB isolates—including drug-resistant strains—vaccine developers should take advantage of

other opportunities to optimize animal modeling. Since TB manifests differently in animals than in humans,[41] animal models will always contain an element of art. Yet even recognizing these biological differences, the field could do more to align animal and human testing. First, animals are typically challenged with a single, high-dose MTB lab strain while people in TB endemic countries face repeated, low-dose exposures to more virulent strains.[42] The immune system may respond quite differently to these dissimilar levels of exposure. Second, the endpoints of animal and human trials are misaligned. Animal studies look at whether a candidate vaccine reduces the burden of TB disease as measured by bacterial load. By contrast, clinical trials measure whether candidate vaccines can prevent either MTB infection or TB disease.[43] How results tied to these different endpoints translate across the already sizable species gap remains unclear.

The preclinical development of MVA85A, which reported good results in at least four animal models, demonstrates that achieving "modest" protection in animals does not predict the level of efficacy required in human studies.[44] Aeras has indicated that future work will emphasize having "robust" preclinical data from nonhuman primate models before moving a vaccine into clinical testing.[45] While encouraging, this raises questions about the harmonization of animal models; for example, nonhuman primate models alone employ three species of macaques.[46] Harmonization may simplify the selection of candidate vaccines for human trials by increasing the comparability of results, but reliance on a few models may elide key insights about MTB diversity. Animal modeling is the crucible where basic research and product development reveal themselves as allied yet distinct enterprises. Negotiating this tension will require, if not harmonization per se, at least greater collaboration between preclinical and clinical developers, and a willingness to learn from the work of both.

NEW APPROACHES IN CLINICAL TRIALS

With so many unanswered questions in basic science, clinical trials of TB vaccines must be designed to help scientists learn about the biology of host–pathogen interaction at each step of human testing. One approach entails building hypothesis testing into larger clinical trials so that biological questions can be answered alongside traditional tests for safety and vaccine response (a strategy some have called "experimental medicine studies").[47] This might help alleviate the pressure to predict everything preclinically by

mainstreaming opportunities to learn about human disease dynamics into the traditional clinical development pathway. An upcoming phase II trial of TB vaccine candidate **M72 + AS01**, an adjuvanted subunit vaccine developed by GlaxoSmithKline, will adopt this approach. Alongside the larger trial evaluating the safety and efficacy of M72 + AS01 in adults,[48] Aeras will run a parallel study collecting biological samples to inform biomarker research.[49]

New trial designs may offer other ways forward. In 2013, Aeras supported the first trial combining two vaccine candidates, and began the first trial looking at prevention of MTB infection rather than TB disease as the primary endpoint.

New endpoints: faster, cheaper, smaller trials?

To date, most trials (including the phase IIb study of MVA85A) have used prevention of TB disease as the primary endpoint. Recognition that MTB infection is much more common than TB disease, however, has encouraged a shift to using prevention of infection as the primary endpoint in clinical evaluation. Since rates of MTB infection are typically three times higher than those of TB disease in any given population, prevention-of-infection trials will be smaller and less costly, enroll more quickly, and require shorter lengths of follow-up.[50] **Hybrid 4 + IC31** is the first TB vaccine candidate to be studied using the new prevention-of-infection paradigm.[51]

Developed jointly by Aeras, Sanofi Pasteur, and the Statens Serum Institut (SSI) of Denmark, Hybrid 4 + IC31 contains a fusion of the antigens Ag85B and TB10.4 in the adjuvant IC31. The vaccine has completed four phase I studies establishing its safety among healthy adult volunteers. The new prevention-of-infection trial will take place at the South African Tuberculosis Vaccine Initiative (SATVI) in the Western Cape region of South Africa and enroll 990 adolescents; results are expected by the end of 2015.[52] The trial contains three arms: one-third of participants will be revaccinated with BCG; one-third will be vaccinated with Hybrid 4 + IC31; and the final third will receive a placebo.[53] The inclusion of a BCG-only arm will offer the first randomized controlled trial data on whether or not BCG acts against infection in this age cohort.

Other candidates will soon begin prevention-of-infection trials, including **Hybrid 56 + IC31**, an adjuvanted subunit vaccine developed by SSI. Future work on Hybrid 56 + IC31 reflects SSI's decision to discontinue development of a related candidate, **Hybrid 1 + IC31**. Hybrid 56 + IC31 appears more

immunogenic than Hybrid 1 + IC31 as measured by polyfunctional T-cell response, including IL-2 and TNFα dominance over IFNγ.[54] The vaccine combines three antigens—Ag85B, ESAT-6, and Rv2660c—of which the last is considered a "latency antigen" (believed to be upregulated during periods of nutrient deprivation standing in for latent infection).[55] SSI recently concluded a dose-finding study of Hybrid 1 + IC31 in 240 MTB-positive and -negative adolescents in South Africa; results are expected by late 2014.[56]

Although heralded as a "new paradigm,"[57] candidates studied under a prevention-of-infection approach with favorable results will likely enter later-phase trials assessing their ability to prevent TB disease. The idea is to take advantage of the speed of prevention-of-infection studies to obtain better information on potential efficacy before initiating larger, more expensive confirmatory trials.[58] Of course, protective mechanisms associated with prevention of infection may appear quite distinct from those associated with prevention of disease. The bridge between prevention-of-infection and disease work may not present a straightforward crossing.

Prevention-of-infection trials must traverse several other uncertain terrains. Prevention of infection represents a "fragile" endpoint—difficult to assess and sensitive to "force of infection" in a given area (an indication of how many susceptible individuals become infected with MTB in a given period). Moreover, MTB infection is measured using interferon gamma release assay (IGRA) diagnostic tests, themselves imperfect technologies with sometimes "fragile" results. The use of QuantiFERON Gold In-Tube (QFT), a type of IGRA test, to assess infection makes use of the best available tool, but QFT is hardly ideal. The repeatability of QFT results have come under increasing scrutiny,[59,60] and at least one study suggests that QFT variability may be inherent to the test itself and not due to biological factors related to host or pathogen.[61] In the context of TB vaccine trials, using QFT conversion to determine incidence of infection may overestimate true incidence when based only on the least stringent definition of QFT conversion: negative to positive.[62]

To allay these concerns, investigators at SATVI have conducted a small study of QFT assay reproducibility to develop stricter laboratory protocols within the manufacturer's specifications. The trial will also collect data on stable conversion as a secondary endpoint.[63] The prevention-of-infection trial with Hybrid 56 + IC31 will also evaluate sustained QFT conversion over many months rather than relying on a single conversion result.[64] While these

strategies work around concerns about QFT, they illustrate how diagnostic R&D limitations hold back TB vaccine research.

The phase I prom: TB vaccines meet their matchmakers

In addition to its prevention-of-infection trials, the TB vaccine field initiated the first study combining two new vaccine candidates. Sponsored by Aeras, a phase I study begun in 2013 pairs **Crucell Ad35** with **MVA85A** in 50 healthy adult volunteers at Oxford University.[65] Each candidate is undergoing separate phase II trials—Crucell Ad35 in nearly 600 infants and MVA85A in 650 adults with HIV.[66,67] The rationale for combining these candidates derives from the distinct immune response each induces. MVA85A appears to act primarily through CD4 T cells, while Crucell Ad35 demonstrates a more robust CD8 T-cell response. In the combination trial, Crucell Ad35 will be administered first and then boosted with MVA85A.[68] The decision to use this order was based on malaria vaccine work suggesting that vaccines built using modified vaccinia virus Ankara (like MVA85A) seem capable of boosting prime vaccines that employ adenovirus platforms (Crucell Ad35).[69] MVA85A is also serving as the boosting vaccine in a phase I study with a new TB vaccine candidate that uses a simian adenovirus vector: **ChAdOx1 85A**. The combination trial of ChAdOx1 85A + MVA85A is sponsored by Oxford University and is currently recruiting participants.[70]

A motley crew: other candidates make noise in phase I

Other candidates continue to advance through the pipeline, with some of the most interesting work happening in phase I. **MTBVAC**, the first live vaccine constructed from attenuated MTB, entered a phase I study in 2013 and showed good safety results at the interim analysis point.[71] Weakened by deleting two virulence genes from MTB, MTBVAC could replace BCG if successful in future trials.

Ad5Ag85A also completed a phase I trial in 12 BCG-vaccinated and 12 BCG-naive adults in Canada. The study showed the vaccine to be safe, well tolerated, and capable of invoking CD4 and CD8 T-cell responses in both groups, although the magnitude of this response appeared greater in BCG-vaccinated participants.[72] Safety concerns surrounding HIV vaccines constructed using adenovirus serotype 5 vectors (Ad5) have cast a cloud over Ad5Ag85A's

prospects, as this candidate also uses an Ad5 platform. Three studies using Ad5 HIV vaccines were stopped early, with two showing an increased risk of HIV infection among vaccine recipients.[73] The U.S. National Institutes of Health convened a meeting to discuss adenovirus HIV vaccines in September 2013. A subsequent meeting summary stated that "future HIV vaccine studies testing Ad5 vectors are not appropriate," although the authors dodged the question of what this means for adenovirus vaccines for related diseases such as TB.[74] In any case, Aeras has indicated that it does not plan to develop Ad5Ag85A for the market. Future work will use Ad5Ag85A to explore new routes of aerosol vaccine delivery, where it has the potential to make a valuable contribution.[75] A phase I study of Ad5Ag85A administered by inhalation has been submitted to Health Canada for approval and will likely begin before the end of 2014.[76]

Developed by the Infectious Disease Research Institute, the adjuvanted subunit vaccine **ID93 + GLA-SE** is currently undergoing a phase I trial assessing its safety and tolerability among BCG-vaccinated adult volunteers in South Africa. A phase IIa study in South Africa planned for 2015 will evaluate whether ID93 + GLA-SE can prevent recurrence of TB disease when given to BCG-vaccinated adults previously treated and cured of TB.[77] This reflects a prevention-of-recurrence strategy that would benefit a very different population than the prevention-of-infection approach being pursued by other adjuvanted subunit vaccines.

Finally, as reported last year, the whole-cell mycobacteria vaccine first studied in the phase III DarDar trial as SRL-172 re-entered the pipeline as **DAR-901**. New, more accurate phenotypic methods have identified the organism used in DAR-901 as *Mycobacterium obuense*, not *Mycobacterium vaccae* as previously believed.[78] DAR-901 differs from the SRL-172 vaccine used in the DarDar trial only in terms of a new, more scalable production method developed by Aeras that uses broth rather than agar. A phase I trial of DAR-901 in 76 foreign-born adults with prior BCG vaccination, begun in April 2014 and cosponsored by Aeras and the Geisel School of Medicine at Dartmouth University, is under way in the United States.[79]

RECOMMENDATIONS

In 2012, funding bodies spent just US$86.6 million on TB vaccine research, well short of the US$380 million called for by the Stop TB Partnership's *Global Plan to Stop TB 2011–2015*.[80] This inadequacy of resources reinforces the imperative to take advantage of each trial to learn about the biology of TB and to build stronger linkages between lab and clinic. The following recommendations outline strategies for making the most of limited resources:

1. **Increase funding for TB basic science research.** Basic science research remains the most urgent priority for the TB vaccine field. Yet funding for basic science is inadequate, totaling just US$129.6 million in 2012, nearly US$300 million short of the Stop TB Partnership's funding target in this area.[81] Fully funding basic science research at the level recommended by the Stop TB Partnership will speed progress in the clinical pipeline by deepening our understanding of host–pathogen interaction, the genetic adaptations of MTB, BCG immune kinetics and the related systems biology work that may shed light on correlates of immunity at different points along the continuum from MTB infection to TB disease. Building closer, mutually reinforcing relationships between lab bench and clinic will only become more important as old ideas about the interplay between MTB and the human immune system come under revisionary scrutiny.

2. **Create deeper channels of communication between research programs conducting animal modeling and human testing.** Screening vaccine candidates against clinical isolates of MTB, including drug-resistant strains, should become more common. Better aligning endpoints between animal and human studies would also strengthen preclinical development programs, in part by encouraging preclinical researchers to design animal studies with enough power to detect the same magnitude of vaccine efficacy as clinical trials. The phase IIb trial of MVA85A was designed to detect a 60 percent improvement over BCG alone, but most animal evaluations of TB vaccine candidates have demonstrated lower levels of improvement.[82] Some decisions will require trade-offs: agreement among labs to use only certain species of animals may benefit product development, but risks limiting research to insights gleaned from just a few

models of a complex disease. Striking the right balance between extensive modeling in animals and learning from how vaccines perform in the clinic will require more direct ties between preclinical and clinical development. Experimental medicine studies that nest biological hypotheses in clinical trials, with subsequent back-translation of findings to animal models, offer one framework for achieving this.

3. **Promote innovation within clinical trials and harness the potential of new study designs.** In addition to saving time and money, prevention-of-infection trials may offer clues about biological mechanisms of protection useful for future phase III studies. Still, the question must be asked: what is driving the shift to prevention of infection—science or cost savings? Although an intriguing avenue of research, prevention-of-infection trials come with several limitations, most importantly how to measure infection and then apply results from these trials back to prevention-of-TB disease work. Trials that combine different vaccines introduce a twist on the dominant prime-boost strategy to take advantage of the respective merits of candidates that previously traversed the pipeline singly and separately. The option to become even more adaptive in trial design—for example, moving from phase I to II to III as part of the same protocol—may offer another way forward.[83] Developers should also consider head-to-head trials comparing vaccine candidates in early-phase studies.

4. **Empower and support TB-affected communities to engage in TB vaccine research.** Growing consensus supports community engagement as a pillar of ethical medical research.[84,85] Efforts to incorporate greater community participation in TB vaccine R&D are long overdue, and the field can no longer rely on the exemplary efforts of a few individual trial sites to engage communities. While sites such as SATVI have formed thoughtful community partnerships,[86] TB vaccine R&D lacks the global community advisory structures seen in TB drug development. Vaccine researchers have an abundance of examples from which to draw, including, on the global level, the Community Research Advisors Group, an advisory body to the Tuberculosis Trials Consortium, and the robust site-level community engagement supported by the TB Alliance. Frameworks such as the *Good Participatory Practice Guidelines for TB Drug Trials* could easily be adapted to inform TB vaccine R&D.[87]

The recent agreement in principle between the mining company Anglo American and Aeras to conduct future phase III TB vaccine trials in South African mines illustrates the imperative for stronger community engagement in TB vaccine R&D.[88,89] Miners are a particularly vulnerable study population owing not only to their hugely disproportionate risk of MTB infection, but also to their exposure to the exploitative labor practices, social deprivation, and history of living under extractive-industry and settler colonialism that aggravate this risk.[90] It was striking to read press statements from the agreement in which Brian Brink, chief medical officer of Anglo American, said: "You [Aeras] have got vaccine candidates. We have to go to the next leg now, the big phase III clinical trials, where you need big populations. We are in the mining industry, and we have big populations."[91] Unfortunately, no community representative or miner shared the stage with Brink and his Aeras counterparts—a lost opportunity to hear how these "populations" might envision their participation in future TB vaccine research.

Successful TB vaccine R&D will require investments of money and talent well into the next decade. Even if the current candidates in the pipeline never reach the market, their setbacks and successes in trials will lay critical groundwork for new TB vaccine development. While the immunologic particularities of future TB vaccines remain hard to predict, the general features needed in such vaccines are already clear. A safe vaccine that provides a high degree of lasting protection against developing active TB, blocks MTB infection, or achieves complete elimination of MTB after exposure would dramatically speed progress toward achieving the goals of zero TB deaths, new infections, and suffering.[92,93] New TB vaccines must meet the needs of the communities and health systems that use them. They must be small, easy to transport, heat-stabilized, needle-free, and designed to address developing-country epidemiology.[94] Even as researchers sort out the intricate details of immunity, the field must keep this bigger picture in mind. There is no shortage of complex, careful scientific work to be done, but the ultimate goal remains a safe, effective vaccine that can end the TB epidemic in the world's most vulnerable and hard-hit communities.

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