HIV • HCV • TB

2015 PIPELINE REPORT

Drugs, Diagnostics, Vaccines, Preventive Technologies, Research Toward a Cure, and Immune-Based and Gene Therapies in Development

TAG i-base

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JULY 2015

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RESEARCH TOWARD A CURE, AND IMMUNE-BASED AND GENE THERAPIES
IN DEVELOPMENT

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

Edited by Andrea Benzacar

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HIV i-BASE/TREATMENT ACTION GROUP

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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.

ABOUT TAG

Treatment Action Group 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.

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

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

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THIS REPORT IS DEDICATED TO

Tireless Champion of Disadvantaged and Vulnerable People

Ana Isabel Charle

(1979–2015)

and

Pioneering HIV Researcher and Activist

Joseph Albert Marie "Joep" Lange

(1954–2014)

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The Antiretroviral Pipeline

By Simon Collins and Tim Horn

INTRODUCTION

As a global community of people living with HIV, our needs from the antiretroviral (ARV) pipeline have changed considerably over the last 20 years.

Antiretroviral treatment (ART), particularly for people starting treatment, is increasingly effective, safe, and easier to take. ART now involves fewer pills and doses, with several combinations combined in a single daily pill. This may have raised the bar for drug research and development, with only those compounds with clear advantages progressing to clinical trials, but by definition, this has always been the case. Just as importantly, technological and scientific advances should enable companies to continue to design even better and more effective drugs.

Although current treatments are largely manageable, side effects continue to be a concern, especially when combination therapy will be taken for decades. Drug interactions are complex, even with some recently approved drugs. This is increasingly significant given the greater rates of complications and polypharmacy as we grow older. Drug interactions are also important because of the increasing role played by non-HIV specialists in HIV management, especially primary care providers. The strictness required to maintain long-term adherence continues; most once-daily combinations still involve being taken every 24 hours rather than "any time," and many drugs still must be taken with food.

Critically for 2015 – and annually going forward – manufacturers need to market new drugs at prices that are not just competitive but affordable. This is particularly true given the results from the Strategic Timing of Antiretroviral Treatment (START) study, which support starting HIV therapy regardless of baseline CD4 count.[1,2] The DSMB interim analysis, demonstrating a 53% reduction in the risk of developing serious illness or death in the early-treatment group (95% CI: 0.32–0.68, $P < 0.001$) compared with those in the deferred group, is expected to change ARV treatment guidelines in high-, middle-, and low-income countries. Overnight, this will substantially increase the number of people who will be eligible for treatment and the budgets required to meet this need.

The use of generic versions of widely used ARVs in high-income countries warrants a specific focus. Although they are bioequivalent, generics are technically new formulations. The dramatically lower prices in some countries have the potential to further widen the difference between standards of care for people who are rich or well insured compared with those dependent on public health providers. With nearly all health systems under pressure to save costs, certainly in Europe, this will bring a new dynamic to HIV management.

However, at least in the United States, launch prices continue to spiral upward – directly related to the wholesale acquisition cost established for a previously approved drug, irrespective of the active pharmaceutical ingredient (API) or the potential for high-volume sales – and annual (and sometime twice-yearly) price increases far exceed all medical consumer price index categories.

It is significant that the U.S. Department of Health and Human Service's *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* 2015 update relegated Atripla to an alternative option. Although efavirenz is in now off patent in some countries in Europe, the U.S. patent has been extended to 2017, for reasons that are unclear.

Whether guideline recommendations alone will be sufficient to shift the majority of new prescriptions to one of the four integrase-based combinations or to darunavir/ritonavir plus tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) is also unclear. Similar discussions are likely to occur when TDF, which has been a preferred regimen component since U.S. approval in 2001, comes off patent in 2017. A new prodrug of tenofovir, tenofovir alafenamide fumarate (TAF), is covered later in this report to discuss whether it brings important clinical advantages for some or all patients or whether it is merely a way to extend patent exclusivity.

Even fixed-dose combinations (FDCs), clearly popular for anyone taking treatment, are undergoing more rigorous scrutiny, including whether, in the absence of evidence showing clinical benefits, the common-sense advantages of reduced pill count will be sufficient to justify continued access at higher prices than for matched generics.[3,4]Also, for the first time, branded drugs are being co-formulated with generics for high-income markets.

Against this background, the antiretroviral pipeline in 2015 is surprisingly encouraging. It features compounds in phase II/III development that might bring important improvements for treatment. These include Gilead Science's TAF, ViiV Healthcare's cabotegravir (in oral and long-acting injection formulations), and Janssen's long-acting rilpivirine formulation. Of particular interest for the important group of people with resistance to current drugs, Bristol-Myers Squibb (BMS) has an attachment inhibitor, fostemsavir, and a maturation inhibitor, BMS-955176, and Merck is progressing with the non-nucleoside reverse transcriptase inhibitor (NNRTI) doravirine.

SUMMARY OF PIPELINE PROGRESS

A summary of key developments since the *2014 Pipeline Report* is included in table 1. Study details, references, and timelines for compounds with significant advances over the past year are discussed in greater detail in the text below.

Table 1. Summary of Pipeline Compounds in 2015

Compound	Class/Type	Company	Status	Comments
tenofovir alafenamide fumarate (TAF)	NtRTI (tenofovir prodrug)	Gilead	NDA filed/ Phase III	NDA filed in U.S. for 4-drug elvitegravir/cobicistat/FTC/TAF (E/C/F/TAF) in November 2014, 2-drug FTC/TAF in April 2015, and 3-drug rilpivirine/F/TAF in July 2015. Decisions will take 12 months. Phase III studies include: E/C/F/TAF in treatment-experienced patients and darunavir/FTC/TAF
doravirine (MK-1439)	NNRTI	Merck	Phase III	Once-daily NNRTI with comparable efficacy to efavirenz. Phase III studies include head-to-head against darunavir/ritonavir in experienced patients and combined in an FDC with generic TDF and 3TC
fostemsavir (BMS-663068)	Attachment inhibitor (gp120)	BMS	Phase III	Phase II data at CROI 2015 reported comparable efficacy to atazanavir/ritonavir in experienced patients. International phase III study in people with multidrug resistance (>2 class) opened February 2015
raltegravir (once-daily formulation, 2 X 600 mg tablets)	INSTI	Merck	Phase III	Ongoing phase III noninferiority study comparing once- vs. twice-daily raltegravir has primary outcome results expected in early 2016
cenicriviroc (TBR-652)	CCR5 inhibitor (also active against CCR2)	Tobira	Phase II	No new clinical data since phase II study results in 2013. Current phase II studies are in neurocognitive impairment or NASH. Plans to study co-formulation with 3TC have not developed

Compound	Class/Type	Company	Status	Comments
BMS-955176	Maturation inhibitor	BMS	Phase II	Phase II trial in experienced patients under way. Phase III evaluations in naïve and experienced patients planned
apricitabine	NRTI	Avexa	Phase IIb	3TC-like molecule, stalled at phase IIb with no new studies since 2009; active against some NRTI resistance but limited financial backing
PRO 140	CCR5-specific humanized monoclonal antibody	CytoDyn	Phase II	No new data since 2010. Phase II trials, including adjunctive therapy and treatment substitution evaluations, are planned or under way
ibalizumab (TMB-355; formerly TNX-355)	CD4-specific humanized IgG4 monoclonal antibody	TaiMed Biologics	Phase II/III	Orphan drug designation was granted by the FDA in October 2014. Compassionate access is listed as phase III, but there are no stand-alone studies
cabotegravir oral and long-acting (LA) formulations	INSTI (follow-up to dolutegravir)	ViiV Healthcare	Phase IIb	96-week phase IIb results at CROI 2015 support once-daily maintenance therapy at 30 mg dose paired with oral rilpivirine; cabotegravir LA with rilpivirine LA in phase II studies
rilpivirine LA formulation	NNRTI	Janssen	Phase II	Follow-up data supporting daily oral dosing as maintenance therapy paired with oral cabotegravir presented at CROI 2015; rilpivirine LA with cabotegravir LA now in phase II studies
GS-9883	INSTI	Gilead	Phase II	A follow-up to elvitegravir that does not require boosting. Being compared with dolutegravir in ongoing phase II study with 24-week primary endpoint results expected early 2016
censavudine (formerly festinavir/ BMS-986001/OBP-601)	NRTI	Oncolys	Phase IIb	This d4T-like molecule had similar efficacy but increased side effects and drug resistance compared with tenofovir in a phase 2b study presented at ICAAC 2014. BMS has dropped the option to develop. May have role in HIV-2
dolutegravir plus rilpivirine (co-formulation)	INSTI plus NNRTI	ViiV Healthcare, Janssen	Phase I	A phase I bioavailability study in HIV-negative volunteers is under way for this dual formulation. The dual combination, using separate oral drugs as maintenance therapy, is the focus of several other ongoing studies
albuvirtide	Long-acting fusion inhibitor	Frontier Biotechnologies	Phase I	Though no new data have been reported since 2012, a phase III trial is currently under way in China. U.S./E.U. development and regulatory plans remain unclear
EFdA	NRTI	Merck	Phase I	No new data or studies announced since *2013 Pipeline Report*

BMS: Bristol-Myers Squibb
CROI: Conference on Retroviruses and Opportunistic Infections
FDA: Food and Drug Administration (United States)
FDC: fixed-dose combination
ICAAC: Interscience Conference of Antimicrobial Agents and Chemotherapy
INSTI: integrase strand transfer inhibitor (integrase inhibitor)
LA: long-acting
NASH: nonalcoholic steatohepatitis
NDA: new drug application
NNRTI: non-nucleoside reverse transcriptase inhibitor
NRTI: nucleoside reverse transcriptase inhibitor
NtRTI: nucleotide reverse transcriptase inhibitor
TAF: tenofovir alafenamide fumarate
TDF: tenofovir disoproxil fumarate

APPROVALS SINCE JULY 2014

Four new co-formulations were granted marketing clearance since the last *Pipeline Report* was published in July 2014.

Dolutegravir/Abacavir/3TC

The FDC of dolutegravir/abacavir/3TC, brand name Triumeq, was approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) in August and September 2014, respectively.[5,6] Approval was primarily based on previously published data from the phase III SINGLE dolutegravir registrational study plus a new bioequivalence evaluation of the FDC compared with the three single drugs.[7]

Triumeq is manufactured by ViiV Healthcare and is one of four integrase strand transfer inhibitor (INSTI)-inclusive regimens recommended as first-line therapy for antiretroviral-naive people in the April 2015 update to the U.S. Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*.[8] It is also one of three regimens recommended as first-line therapy – all INSTI-inclusive ARV combinations – in Spain's 2015 treatment guidelines.[9]

Darunavir/Cobicistat

The dual formulation of darunavir/cobicistat was approved by Health Canada in June 2014, the EMA in November 2014, and the FDA in March 2015.[10,11,12]

Manufactured by Janssen, the trade name is Prezcobix in Canada and the United States and Rezolsta in the European Union. Approval was based on phase I bioequivalence data of the FDC compared with single drugs in HIV-negative volunteers, and the decisions emphasized the continued need to take darunavir with food. Approval was also based on efficacy results from a single-arm study in 313 HIV-positive people (94% were treatment-naive) with viral load >1,000 copies/mL and estimated glomerular filtration rate (eGFR) >80 mL/min.[13,14]

Darunavir/ritonavir, combined with TDF/FTC, is the only non-INSTI third drug to remain listed as recommended for ARV-naive people in the April 2015 update to the U.S. *Guidelines*.[8] Prezcobix, however, is listed as an alternative option for use in combination with TDF/FTC or abacavir/3TC, due in part to the less stringent open-label, single-arm safety and efficacy trial completed for regulatory approval.

Atazanavir/Cobicistat

The dual formulation of atazanavir and cobicistat was approved by the FDA in January 2015.[15] EMA review was submitted in 2014 and was still ongoing as this report went to press.

The FDC is manufactured by Bristol-Myers Squibb with the trade name Evotaz. Approval was based on data from registrational studies for cobicistat and new bioequivalence data comparing the FDC with atazanavir and cobicistat coadministered as separate drugs.[16]

Atazanavir/cobicistat, combined with TDF/FTC, is ranked as an alternative component of first-line therapy in the April 2015 U.S. *Guidelines*, though only for people with pretreatment estimated creatinine clearance of ≥70 mL/min. This led to its being listed as a third-tier/"other" option and only when used in combination with abacavir/3TC.[8]

Boosted atazanavir is used less frequently than darunavir/ritonavir due to higher side effect–related discontinuations, as documented in ACTG A5257.[17]

Raltegravir/3TC

The dual formulation of raltegravir and 3TC was approved by the FDA in February 2015 with an indication for use in combination with other ARVs.[18] It was submitted to the EMA in March 2014, with a decision expected as this report went to press.

Manufactured by Merck, with the trade name Dutrebis, this is the first co-formulation containing a patent-protected originator drug (raltegravir) with a generic drug (3TC) that was previously developed by another company.

Co-formulating branded products and generics is a strategy that is expected to continue as other ARVs come off patent (see cenicriviroc and doravirine, below). That said, Merck has not marketed Dutrebis in the United States due to the lack of a clearly defined population in need; the company may market Dutrebis elsewhere.[19]

FDA approval of co-formulated raltegravir/3TC was based primarily on a study demonstrating bioequivalence between the FDC and separate raltegravir and 3TC tablets.[20] Notably, the improved bioavailability in this new formulation allows a 300 mg dose of raltegravir, compared with 400 mg in the stand-alone formulation.

Single-Drug Approvals: Elvitegravir and Cobicistat

The only new single-drug approvals in the last year were for formulations of elvitegravir and cobicistat in the United States.[21,22]

Each of these single drugs was approved by the EMA a year earlier, and demand was so low that in Europe elvitegravir is currently available only by special arrangement with the manufacturer.

CURRENT REGULATORY SUBMISSIONS

TAF Co-formulations

TAF is a new version of tenofovir and is the pipeline compound closest to regulatory approval. Development was prioritized as an FDC component rather than as a single new drug, and applications for an FDC and in a dual nucleoside reverse transcriptase inhibitor (NRTI) formulation have already been submitted to the FDA. The four-in-one combination of elvitegravir/cobicistat/FTC/TAF (E/C/F/TAF) was filed in November 2014 with a target approval date of November 5, 2015. The dual formulation of FTC/TAF (F/TAF) was filed in April 2015, with an anticipated approval in April 2016.[23,24]

Both TDF and TAF are prodrugs of tenofovir, which require phosphorylation to tenofovir diphosphate (TFV-DP), the active metabolite. TDF is first converted to tenofovir in the blood, whereas TAF largely undergoes alterations inside lymphocytes and other cells. Compared with TDF, TAF achieves intracellular concentrations of tenofovir that are four to seven times higher at plasma concentrations that are 90% lower.[25,26,27]

Low-milligram TAF dosing – either 10 mg or 25 mg, depending on the combination – together with reduced tenofovir exposure has the potential to reduce bone and kidney toxicities compared with TDF dosing. The low-milligram dosing also clearly helps with pill size for co-formulations, and using less API has the potential to reduce the cost of generic versions where the marketing price is more closely related to manufacturing costs.

It would be easier to be excited about the potential advantages of TAF over TDF if the development timeline were not based on extending the initial TDF patent despite safety concerns with TDF. Gilead Sciences presented in vitro and animal data for TAF in 2001, but phase I results in humans were not reported until

2011.[28,29] That is at least 10 years of accumulated renal and bone toxicity among people living with HIV using TDF while TAF stayed on the shelf.

This coordinated delay means that TAF will become available just as the patent on TDF expires. Using this strategy, Gilead has extended the patent on tenofovir for six years based on the primary patent on TAF – and for longer based on other co-formulations.[30]

E/C/F/TAF

The regulatory submission for E/C/F/TAF is based on noninferiority results compared with E/C/F/TDF (Stribild) at 48 weeks in two randomized, double-blind, placebo-controlled phase III studies in treatment-naive patients (studies 104 and 111). Combined analyses of both studies were reported in two separate sessions at the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) – one primarily on efficacy and the other for detailed renal, bone, and lipid results – and final 48-week results were published in April by the Lancet.[31,32,33]

In the combined studies, 867 treatment-naive participants received E/C/F/TDF, and 866 received E/C/F/TAF. Most were men (85%), and just under half were either black (25%) or Hispanic/Latino/Latina (19%). Median baseline CD4 counts and viral load were 405 cells/mm^3 and 38,000 copies/mL, respectively. Approximately 12% of participants had CD4 counts below 200 cells/mm^3, and 23% had a viral load above 100,000 copies/mL. Median eGFR was 115 mL/min/1.73 m^2 (entry criteria included eGFR >50).

For the primary endpoint of viral efficacy at week 48, viral load was <50 copies/mL in 92% of the E/C/F/TAF group compared with 90% in the E/C/F/TDF group (difference 2.0% [95% CI: 0.7%–4.7%]), meeting criteria for noninferiority. Virological failure occurred in 4% of both groups.

When stratified by baseline viral load above/below 100,000 copies/mL, results were 87% versus 89% (above; difference −1.7% [95% CI: −8.3 to 4.8]) and 94% versus 91% (below; difference 3.1% [95% CI: 0.2–6.0]) in the E/C/F/TAF versus E/C/F/TDF arms, respectively. More than 90% of people in both groups with baseline CD4 counts below 200 cells/mm^3 also had undetectable viral loads at the 48-week time point. No clear differences were reported between the two combinations in selected subgroup analyses by age, gender, and race.

CD4 count increases were similar until week 36 but by week 48 were significantly higher in the E/C/F/TAF group (+211 cells/mm^3) compared with the E/C/F/TAF group (+181 cells/mm^3) ($P = 0.024$).

Safety and drug resistance results were almost identical for the two FDCs. Moderate-to-severe side effects were rare, occurring in approximately 1% of participants in both groups, as were side effect–related treatment discontinuations. Diarrhea was the most common side effect (18%), followed by nausea (16%) and headache (13%). Discontinuation due to side effects occurred in 0.9% ($N = 8$) of the E/C/F/TAF group and 1.5% ($N = 15$) of the E/C/F/TDF group; decreased eGFR ($N = 1$), nephropathy ($N = 1$), and renal failure ($N = 2$) all occurred in the E/C/F/TDF group.

Significant decreases in eGFR associated with the effect of cobicistat on renal tubular secretion of creatinine occurred by week 2 and were largely stable thereafter, but these were significantly more pronounced in the E/C/F/TDF group compared with the E/C/F/TAF group (mean −5 vs. −11.2 mL/min; $P < 0.001$). Changes in quantitative proteinuria measured by median percentage change in urine protein to creatinine ratio, urine albumin to creatinine ratio, retinol-binding protein (RBP), and beta-2 microglobulin (B_2M) were significantly higher in the E/C/F/TDF arm compared with the E/C/F/TAF arm (all $P < 0.001$). Increases in the two low-molecular-weight proteins RBP and B_2M are markers of defective proximal tubular uptake.[34]

Decreases in bone mineral density (BMD) were more pronounced in the E/C/F/TDF group compared with the E/C/F/TAF group. Though there was evidence of spine and hip BMD loss in both groups, the decreases were significantly more pronounced in the E/C/F/TDF group: −2.86 and −2.95 mean standard deviation percentage change in spine and hip BMD, respectively, versus −1.30 and −0.66 for E/C/F/TAF. Individuals in the E/C/F/TDF group were also more likely to have >3% loss in spine and hip BMD: 45% and 50% versus 26% and 17% in the E/C/F/TAF group.

Participants in the E/C/F/TAF group experienced significantly greater increases in triglyceride (114 vs. 108 mg/dL), total cholesterol (189 vs. 177 mg/dL), low-density lipoprotein (LDL) (115 vs. 109 mg/dL), and high-density lipoprotein (HDL) (51 vs. 48 mg/dL) levels compared with those in the E/C/F/TDF group, which is related to the loss of the lipid-lowering effects of less circulating tenofovir. However, the more clinically important total cholesterol:HDL ratio was similar in both groups: 3.6 at baseline versus 4.7 at week 48.

CROI 2015 also included results from a single-arm, open-label, 96-week phase III switch study to E/C/F/TAF (study 112) in an older population that was more likely to have bone, renal, and lipid concerns.[35] Entry criteria included having mild-to-moderate kidney dysfunction defined as eGFR 30–69 mL/min.

The study included 242 participants on otherwise stable treatment: 98% had viral load <50 copies/mL, median CD4 count was 632 cells/mm^3, and 65% were using TDF. At baseline, median age was 58 years (IQR 52–65), median eGFR was 54 mL/min (30% were <50 mL/min), 39% had hypertension, and 14% had diabetes.

The primary endpoint was change in eGFR at week 24, and secondary analysis included the week-48 results presented at CROI when 92% of the participants still had viral load <50 copies/mL.

There were no significant changes in eGFR (using either Cockcroft Gault or cystatin C) at week 24 or 48 or in actual GFR in the 32 patients, as measured using iohexol clearance. However, other markers of kidney function significantly improved. Median change in proteinuria at week 48 generally either remained unchanged or improved (for 87% of those with grade 1 [N = 52] and for 73% of those with grade 2 [N = 22]). Results for albuminuria status were similar and only worsened for 5%. Median percentage change in RBP and B_2M creatinine ratios reduced by 60%–80% by week 48 ($P < 0.001$ for all patients combined). These changes occurred in patients with baseline eGFR both under and above 50 mL/min.

Median BMD at week 48 significantly increased by 1.9% (IQR: −0.3 to 4.3) in spine and by 0.9% (IQR: −0.3 to 2.7) in hip ($P < 0.001$). This is notable given that BMD routinely drops due to aging, HIV, and ART, irrespective of combination. The study did not report on use of bisphosphonates or other bone management interventions that might explain this.

Median changes in lipids increased for all parameters (total cholesterol, LDL, HDL, and triglycerides) for people switching from tenofovir and decreased for people switching from non-TDF combinations. Median change in the total cholesterol:HDL ratio was minimal (0.3% and 0.2% for prior TDF and non-TDF groups).

Taken together, these results suggest that the priority for TAF will be people who already have some degree of renal dysfunction or reduced bone mineral density. This may be another example where use of newer drugs is prioritized for some patient groups.

F/TAF

According to Gilead, the regulatory application for the dual F/TAF is based on four phase III E/C/F/TAF studies (studies 104, 111, and 112 and an adolescent study 106),[33,35,36] plus bioequivalence data for F/TAF compared with E/C/F/TAF.

Not included in the new drug application (NDA) are data from study 311-1089, the only safety and efficacy trial evaluating F/TAF in combination with drugs other than elvitegravir/cobicistat, such as the boosted protease inhibitors (PIs) atazanavir, lopinavir, and darunavir and the unboosted drugs efavirenz, raltegravir, dolutegravir, and maraviroc.[37] Hence, the FDA is reviewing an NDA for a co-formulation to be used in combination with unboosted third drugs – one requiring a TAF dose (25 mg) higher than that used in E/C/F/TAF (10 mg; Gilead is developing formulations of F/TAF containing both doses) – without the availability of robust data to support this indication.

In fact, all of Gilead's registrational trials for TAF combined with drugs other than elvitegravir/cobicistat, such as FDCs containing cobicistat/darunavir and rilpivirine, as discussed below, are switch studies.

TAF is a new drug with a unique metabolism and safety profile. The near-complete reliance for approval on switch studies is unprecedented. Similarly, renal data from E/C/F/TAF studies are muddied by cobicistat's effect on estimated (if not actual) GFR, limiting a complete understanding of TAF as an individual drug.

COMPOUNDS IN PHASE II AND III

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 in advanced development or progressing in earlier stages.

Advanced: Generally Phase III

- TAF in other FDCs
  - darunavir/cobicistat/FTC/TAF
  - rilpivirine/FTC/TAF [editor's note: NDA submitted to the FDA at press time]
- doravirine
- fostemsavir
- cenicriviroc/FTC
- dolutegravir/rilpivirine
- doravirine/TDF/3TC
- raltegravir formulation for once-daily dosing

Progressing: Generally in Active Phase I or Phase II

- GS-9883
- BMS-955176
- cabotegravir (oral formulation)
- long-acting injections:
  - cabotegravir LA
  - rilpivirine LA
  - co-formulated cabotegravir/rilpivirine LA
- monoclonal antibodies (mAbs):
  - ibalizumab
  - PRO 140
  - other mAbs

Compounds with little or no progress irrespective of development phase include an entry inhibitor (albuvirtide) and the NRTIs apricitabine, censavudine, and EFdA.

Other F/TAF Co-formulations

In addition to developing E/C/F/TAF and F/TAF, Gilead is collaborating with Janssen on FDCs of darunavir/cobicistat/FTC/TAF (D/C/F/TAF) and rilpivirine/FTC/TAF (R/F/TAF) [Editor's note: an NDA supporting the approval of R/F/TAF was filed with the FDA at press time.].

Forty-eight-week data from a randomized, double-blind, placebo-controlled phase II study in ART-naive adults with eGFR $\geq$70 mL/min were published in April 2015.[38] The study randomized 153 patients (2:1) to receive the D/C/F/TAF co-formulation or separate darunavir and cobicistat plus TDF/FTC.

The primary endpoint of virological suppression (<50 copies/mL) at week 24 was reported for 75% in the D/C/F/TAF group compared with 74% in the D/C/F/TDF group (weighted difference: 3.3% [95% CI: −11.4% to 18.1%]). Though this study was not sufficiently powered for noninferiority, the standard non-inferiority margin of −12% was prespecified by the investigators (i.e., the lower boundary of the weighted difference of the CI was >−12%).

At week 48, viral-load suppression rates were 77% versus 84%, respectively (weighted difference: −6.2 [95% CI: −19.9 to 7.4], P = 0.35). This difference, the authors note, was partly due to a higher rate of loss to follow-up in the D/C/F/TAF group (6.8%) compared with the D/C/F/TDF group (2%), though for reasons other than virological failure.

Bone and renal markers suggested potential benefits for TAF. At 48 weeks, reductions in bone mineral density in both spine and hip were significantly less pronounced in the D/C/F/TAF group: −1.57% versus −3.62% (P = 0.003) and −0.84% versus −3.82% (P < 0.001), respectively. Median reduction in eGFR was also less pronounced in the D/C/F/TAF group: −2.9% versus −10.6% (P = 0.017).

An active-controlled phase III switch study of 420 patients on a boosted PI (atazanavir, darunavir, or lopinavir) plus TDF/TFC that will randomize participants to either change to the D/C/F/TAF FDC or remain on the multitablet combination is listed but was not yet enrolling as we went to press.[39] At week 48, all participants will have the option to use the FDC.

With regard to R/F/TAF, Gilead is conducting two randomized placebo-controlled phase III switch studies in people with no history of drug resistance. Both studies evaluate switching to the new FDC following more than six months of virologic suppression with either efavirenz/FTC/TDF (study 311-1160) or rilpivirine/FTC/TDF (study 311-1216) compared with remaining on these two approved FDCs.[40,41]

Because TAF can reach 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 analogue mutations (TAMs).[42] 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.[43]

Study 292-0117 is evaluating the efficacy of TAF versus placebo added to a failing regimen for 10 days, followed by treatment with atazanavir plus E/C/F/TAF.[44] The primary endpoint is viral-load reduction of $\geq$0.5 log copies/mL at day 10. The trial will recruit 100 participants with detectable viral loads (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 as K65R plus M184V, and at least one major NNRTI or PI mutation.

A clinical trial is also looking at a 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.[45] However, new data suggest that darunavir trough concentrations are reduced by approximately 80% – to subtherapeutic levels (median trough: 0.273 mg/L [interquartile range: 0.164–0.501] vs. historical population median of 1.36 mg/L with once-daily 800 mg darunavir plus 100 mg ritonavir) – when combined with E/C/F/TDF.[46]

Participants must have a history of at least two previous 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, particularly in light of the questionable added benefit of darunavir, will be worth noting.

Although they are not yet in human studies, matchstick-sized TAF implants notably produced sustained drug levels for over a month in a beagle study in the context of use for pre-exposure prophylaxis (PrEP).[47]

Doravirine (MK-1439)

Doravirine is a once-daily NNRTI being developed by Merck that can be taken with or without food. It has in vitro activity against common NNRTI resistance mutations (K103N, Y181C, G190A, E101K, E138K, and K103N/Y181C) and selects for distinct mutations in vitro (V106A, F227L, and L234I), suggesting limited cross-resistance to rilpivirine or etravirine.[48] Additional analyses noted that mutant viruses selected by doravirine are susceptible to rilpivirine and efavirenz, and mutants selected by rilpivirine and efavirenz are susceptible to doravirine.

Doravirine is primarily metabolized by CYP3A4 but is neither an inducer nor an inhibitor. In a seven-day monotherapy evaluation using 25 mg and 200 mg once-daily oral dosing, doravirine produced a median reduction in viral load of 1.3 log copies/mL.

Based on 24-week primary efficacy results from the phase IIb P007 doravirine dose-finding study (using 25 mg, 50 mg, 100 mg, and 200 mg) in 208 treatment-naive patients compared with standard dose efavirenz, the 100 mg dose was selected for phase III studies. This was reported in the *2014 Pipeline Report*.

From week 36, an additional 132 people were randomized to doravirine 100 mg or efavirenz, and the original participants all switched to the 100 mg dose. TDF and FTC were used as background NRTIs throughout. Week 48 results from this complicated group were presented at Glasgow 2014, together with a week-8 analysis of central nervous system (CNS) side effects from the 100 mg doravirine versus combined efavirenz groups.[49]

At baseline, median CD4 count and viral load for all participants was approximately 400 cells/mm^3 (range: 90–1,100) and 4.6 log copies/mL (range: 2.6–6.7). Around 10% had CD4 counts <200 cells/mm^3, and 30% had viral loads higher than 100,000 copies/mL.

Efficacy and safety results at week 48 were broadly similar to those at week 24. By intent-to-treat analysis (where noncompletion equaled failure), suppression to <40 copies/mL was achieved by 72%, 72%, 76%, and 83% in the 25 mg, 50 mg, 100 mg, and 200 mg doravirine groups (76% combined) versus 71% in the efavirenz arm. Using a 200 copies/mL cutoff, rates were 85% (doravirine combined) versus 79%.

The most common adverse events in the combined doravirine and efavirenz groups were abnormal dreams (10.2% vs. 9.5%), nausea (7.8% vs. 2.4%), fatigue (7.2% vs. 4.8%), diarrhea (4.8% vs. 9.5%), and dizziness (3.0% vs. 23.8%), and they were generally mild to moderate. The rate of discontinuation due to drug-related adverse events was twice as high in the combined efavirenz groups compared with the efavirenz group: 2.4% vs. 4.8%.

Week-8 CNS tolerability data for 216 participants randomized to 100 mg doravirine or efavirenz reported at least one CNS-related adverse event in 22.2% of the doravirine group compared with 43.5% of the efavirenz group (difference: −21.3% [95% CI: −33.2 to −8.8]; $P < 0.001$). The most common CNS adverse events were dizziness (9.3% vs. 27.8%), insomnia (6.5% vs. 2.8%), abnormal dreams (5.6% vs. 16.7%), and nightmares (5.6% vs. 8.3%); all doravirine compared with efavirenz.

A phase III study comparing doravirine to darunavir/ritonavir in treatment-naive patients started in late 2014 and includes sites in the United States, Canada, Puerto Rico, and Europe.[50]

Additional phase III studies using the FDC of doravirine plus generic TDF and 3TC are due to start in mid-2015, including one in treatment-naive patients with efavirenz as a control and a second in patients virally suppressed on PI/ritonavir-based combinations. Final results are likely to coincide with TDF's patent expiration in 2017.[51,52]

Fostemsavir

Fostemsavir (BMS-663068) is a prodrug of the attachment inhibitor BMS-626529 that produced median viral-load reductions of 0.7 to 1.5 log copies/mL after 7 days of monotherapy. It is active against both CCR5- and CXCR4-tropic HIV, but not subtype AE and group O.[53,54] Fostemsavir is an oral twice-daily drug that binds directly to gp120, causing conformational changes that block attachment to the CD4 receptor.

Forty-eight-week data from an international phase IIb dose-ranging study were reported at CROI 2015.[55] Treatment-experienced participants, all of whom had virus susceptible to raltegravir, TDF, and atazanavir, were randomized to receive fostemsavir at doses of 400 mg twice daily, 800 mg twice daily, 600 mg once daily, or 1,200 mg once daily, compared with ritonavir-boosted atazanavir, all in combination with raltegravir and TDF. Sensitivity to BMS-626529 was an entry requirement (IC50 $<$100 nM). Approximately 5% of study participants did not meet this criterion, and the PhenoSense Entry Assay did not provide a result for 26% of screening samples.

A total of 251 participants were treated. Median age at baseline was 39 years; 60% were male and 38% were white. The median pretreatment viral load was 4.85 log copies/mL (43% had viral loads $\geq$100,000 copies/mL), and CD4 count was 230 cells/mm^3 (38% with $<$200 CD4 cells/mm^3).

At week 48 in the modified intent-to-treat analysis, viral response rates to $<$50 copies/mL were comparable across all groups regardless of gender, age, and race: between 61% and 82% in the fostemsavir group and 71% in the atazanavir group. Response rates in participants with baseline viral loads $\geq$100,000 copies/mL were lower in all arms, including the atazanavir/ritonavir control group.

CD4 count gains were similar across all groups, with mean increases ranging from 141 to 199 cells/mm^3 by week 48.

Seven participants discontinued treatment due to adverse events (two in the atazanavir group, five in the different fostemsavir groups), but none of the discontinuations was believed to be directly related to the study drugs used. Abdominal pain, nausea, and headache were among the most common side effects, though most occurred in the atazanavir group. Similarly, elevations in bilirubin occurred in 29/51 (58%) of participants in the atazanavir group compared with no cases of hyperbilirubinemia or jaundice in the fostemsavir groups. Laboratory abnormalities were uncommon among those receiving fostemsavir, with no clinically relevant changes in total cholesterol, LDL, or triglycerides.

A phase III trial of fostemsavir in treatment-experienced patients started in February (study AI438-047).[56] Approximately 410 participants will be enrolled. Entry criteria include detectable viral load of $\geq$400 copies/mL on current ART and resistance, intolerance, or contraindications to drugs in at least three classes. Participants must be taking at least one, but no more than two, active approved drugs to be eligible for the randomized, placebo-controlled eight-day monotherapy arm of the study. Optimized background therapy is added after day 8, with all participants receiving open-label fostemsavir (600 mg twice daily) for at least 48 weeks.

Participants who are not taking any active approved drugs can enroll in an open-label cohort. This arm includes the option of using the experimental monoclonal antibody ibalizumab to prevent functional monotherapy, although ibalizumab has to be procured by the individual participant and is not provided as part of the study. (See the discussion below on the FDA treatment investigational new drug [IND] allowance of ibalizumab.)

The fusion inhibitor enfuvirtide (T-20, Fuzeon) can be used in both the randomized and nonrandomized arms to help construct the most viable combination.

An astonishing 137 clinical trial sites in Argentina, Australia, Belgium, Brazil, Canada, Chile, Colombia, France, Ireland, Italy, the Netherlands, Peru, Poland, Portugal, Puerto Rico, Romania, Russia, Spain, Taiwan, the United Kingdom, and the United States have been contracted to ensure adequate and prompt enrollment.

Cenicriviroc (Previously TBR-652)

Cenicriviroc is a CCR5 inhibitor that produced median viral-load reductions of 1.7 log following 10 days of monotherapy in a phase I study presented at CROI in 2010. It is also active against CCR2. In a randomized, double-blind, placebo-controlled phase IIb study comparing cenicriviroc with efavirenz in treatment-naive patients, all with background TDF/FTC, viral suppression to <50 copies/mL at week 48 was 68%, 64%, and 50% in the 100 mg, 200 mg, and efavirenz groups, respectively, when reported in 2013.[57] No new clinical data have been reported since then.

Tobira's phase III program was due to evaluate a co-formulation tablet containing 200 mg cenicriviroc and 300 mg 3TC, but no new clinical trials have been announced.

Cenicriviroc may also be active against HIV-2 in CCR5-tropic patients.[58] It is also being studied as a potential treatment for mild-to-moderate HIV-associated neurocognitive decline, based on the hypothesis that dual CCR5 and CCR2 blockade will lead to reductions in monocyte activation, a potential inflammation-related driver of neurocognitive impairment.[59] CCR5 and CCR2 blockade may also be associated with antifibrotic activity; hence, cenicriviroc is currently being evaluated as a potential treatment for nonalcoholic steatohepatitis (NASH).[60]

Raltegravir (Once-Daily Formulation)

Once-daily dosing of Merck's INSTI was not approved after the QDMRK trial, which failed to show that once-daily dosing of raltegravir (800 mg) was noninferior to twice-daily dosing (400 mg) for first-line therapy.[61]

Several newer formulations have led to a 600 mg version (total daily dose 1,200 mg)[62] that is currently being compared in a phase III randomized, double-blind noninferiority study (onceMRK) with the approved twice-daily formulation in treatment-naive participants. Primary endpoint results at 48 weeks from this 96-week study are expected in early 2016.[63]

Clinical results, not just pharmacokinetics (PK)/pharmacodynamics data, appear to be a requirement of once-daily dosing approval.

BMS-955176 (BMS-176)

BMS-176 is a second-generation maturation inhibitor that targets the final stage of HIV Gag processing and inhibits release of the fully formed capsid. Maturation inhibitors are a new class of antiretrovirals that may have an important role for people with resistance to currently approved drugs.

The first-generation maturation inhibitor bevirimat (PA-457) was discontinued in June 2010 due to limited antiviral activity against HIV with common (in 30%–40% of treatment-naive patients) polymorphisms at positions 369, 370, or 371 in Gag.

BMS's compound has greater potency and coverage of Gag polymorphisms compared with bevirimat,[64] along with a half-life supportive of once-daily dosing and no significant safety issues identified in phase I studies.[65]

Preliminary results from a 10-day dose-ranging monotherapy study of BMS-176 were reported at CROI 2015.[65] BMS-176 doses of 5, 10, 20, 80, and 120 mg were evaluated in six dosing groups, each composed of 10 HIV-positive, treatment-naive participants (two in each group received matching placebo). All but one participant were men; only three were nonwhite.

At each of the three higher doses, comparable reductions of −1.4 logs were reported at day 10, with HIV RNA declines sustained for approximately a week after the drug was discontinued. Maximum median reduction in viral load was 1.7 log copies/mL in the 40 mg arm. Results were broadly similar for each group irrespective of baseline polymorphisms.

Side effects reported by >5% of participants included headache, abnormal dreams, night sweats, and diarrhea, but they were broadly similar between active drug and placebo recipients with no treatment discontinuations. No serious side effects or laboratory abnormalities were reported other than two single cases of transient grade 3 neutropenia (one each in the 80 mg and 120 mg groups).

Clinical trials currently planned or under way include a food effect trial, a second dose-finding study further evaluating 60 and 120 mg BMS-176, and a phase IIb study evaluating the safety and efficacy of the maturation inhibitor combined with atazanavir (either with or without ritonavir) and dolutegravir in 200 treatment-experienced participants.[66,67,68]

GS-9883

GS-9883 is a second-generation INSTI in development by Gilead that, unlike elvitegravir, does not require PK boosting.

A phase Ib dose-ranging study using doses from 5 mg to 100 mg for 10 days of monotherapy in treatment-naive HIV-positive participants has been completed; results are expected shortly.[69]

A phase II trial comparing GS-9883 with dolutegravir in approximately 75 HIV-positive, treatment-naive participants, with all participants using separate background FTC/TAF, is currently under way in the United States.[70]

Cabotegravir

Cabotegravir (formerly S/GSK-744) is an INSTI and an analogue of dolutegravir. It is being developed as an oral tablet for once-daily dosing and a long-acting parenteral administration formulation (cabotegravir LA).

Cabotegravir has a low nanomolar potency to treat wild-type HIV infection, with a >2-log impact on viral load after 10 days of monotherapy. It has activity against a broad range of single integrase-associated drug mutations that can overcome early resistance to raltegravir and elvitegravir, but it loses significant sensitivity in the presence of E138K/Q148K and Q148R/N155H complexes. Also similarly to dolutegravir, it has a high barrier to resistance that makes resistance in integrase-naive patients rare. The half-life of the oral drug is >40 hours, easily allowing once-daily dosing, and is >40 days for the long-acting formulation, allowing monthly or quarterly injections depending on dose and formulation.[71]

Phase I and IIa studies reported low PK variability, generally good tolerability, and limited drug interactions. Injection-site reactions were common with the long-acting formulations. The current intramuscular (IM) formulation requires two 2 mL gluteal injections (four injections for the initial loading dose and two injections subsequently). This was associated with moderate pain in 20% of participants lasting, on average, five days (range: 1–30). [72,73]

Clinical efficacy and safety of cabotegravir come from a phase II dose-ranging study that used oral cabotegravir and oral rilpivirine as two-drug maintenance therapy, with 96-week data presented at CROI 2015.[74]

The LATTE study enrolled 243 treatment-naive HIV-positive participants, mostly in early infection. Median baseline viral load and CD4 count were 20,000 copies/mL (14% >100,000) and 410 cells/mm^3 (<5% were <200). For the 24-week induction phase, participants were randomized to cabotegravir (10, 30, or 60 mg) or efavirenz, plus investigator choice of TDF/FTC or abacavir/3TC. If viral loads were <50 copies/mL at week 20, then those receiving cabotegravir substituted their NRTIs for 25 mg oral rilpivirine at week 24 for a further 72 weeks of maintenance therapy. The efavirenz control arm continued the NRTI backbone.

At week 24, viral load was <50 copies/mL in 87% of those in the combined cabotegravir/rilpivirine groups compared with 74% in the efavirenz group. In the week-96 analysis, which included those who did and did not meet the maintenance therapy requirement, 76% of those in the cabotegravir/rilpivirine groups, compared with 63% of those in the efavirenz group, had viral loads of <50 copies/mL. The difference between doses – 68%, 75%, and 84% in the 10 mg, 30 mg, and 60 mg groups – was related to nonvirological discontinuations.

Limiting the analysis to the 47 participants in the efavirenz group and the 160 in the cabotegravir/rilpivirine groups who met the viral-load criteria for continuing in the maintenance phase of the study, 86% in the cabotegravir/rilpivirine arm, compared with 83% of the efavirenz arm, had viral loads <50 copies/mL at week 96. The rate of virological failure in the maintenance population was 3% in the combined cabotegravir groups, compared with 4% in the efavirenz arm.

Three participants originally randomized to the 10 mg cabotegravir group developed treatment-emergent NNRTI mutations during the study; one also developed an INSTI mutation.

Participants were more likely to withdraw from the study due to adverse events in the efavirenz group compared with the combined cabotegravir groups (15% vs. 4%, respectively), usually before the start of the maintenance therapy phase of the trial. CNS effects were more commonly seen in the efavirenz arm. Headache was more common in the cabotegravir groups. Most adverse events were mild to moderate in intensity.

The 30 mg dose of cabotegravir was selected for further development of the oral formulation. A study evaluating the bioavailability of different 30 mg tablet formulations is now under way.[75]

Long-Acting Formulations: Cabotegravir LA and Rilpivirine LA

The availability of both cabotegravir and rilpivirine in long-acting injectable formulations led to a development program that will co-formulate both drugs as a monthly IM injection.

Long-acting drug formulations allowing monthly or less frequent dosing have the potential to improve clinical outcomes in all patient groups where adherence continues to be difficult. For this reason, many patient groups find long-acting formulations preferable to having to take daily pills. These slow-release formulations might have better tolerability, especially reduced gastrointestinal and other side effects.

Additionally, they may be cheaper than oral formulations to produce, given that they use less API and packaging, generate fewer distribution costs, and could potentially help overcome a key global concern of stock-outs in low-income countries.

The INSTI cabotegravir (S/GSK1265744) and the NNRTI rilpivirine are already being combined in phase II/III clinical trials. They employ nanoformulation technologies to overcome the bioavailability, water solubility, and stability weaknesses of oral antiretrovirals. These formulations also have an exciting potential for use as PrEP (see "Preventive Technologies," page 57, for details).

Challenges remain, however:

- Oral lead-in dosing is currently necessary to safeguard against serious adverse events, including hypersensitivity reactions.
- A minimum period with undetectable viral load in the induction phase might be important prior to the dual-therapy maintenance therapy.
- It is not known how to manage drug interactions after long-acting antiretrovirals have been given (e.g., if rifampin-inclusive treatment is necessary for tuberculosis if it is diagnosed later).
- It is not known how to manage the PK "tail" at the end of the dose with compounds that have such extremely long half-lives. Unless treatment is switched to an oral combination, vulnerability to drug resistance to both INSTIs and NNRTIs is high when drug concentrations fall below their inhibitory concentrations. This raises concerns relating to missed injections, whether from adherence or supply issues.
- Patient acceptability may be low if the volume of injections for both drugs is high, if the drugs are given by multiple injections, or if monthly clinic visits are necessary to receive the injections.

A phase IIb maintenance therapy trial employing the long-acting injectable formulations of cabotegravir and rilpivirine is now under way.[76] The study will consist of three phases: an induction phase, a maintenance phase, and an extension phase. Importantly, there is also a long-term follow-up phase for participants who withdraw from the study and have received at least one dose of cabotegravir LA and rilpivirine LA, in order to study and ensure adequate follow-up during the PK tail period following administration of both long-acting drugs.

In the induction phase, participants will receive oral cabotegravir (30 mg) plus abacavir/3TC once daily for 20 weeks and will then add oral rilpivirine for an additional four weeks. In the maintenance phase, beginning at week 24, eligible participants will be randomized 2:2:1 to one of the following treatment arms:

- IM regimen of cabotegravir LA (400 mg) + rilpivirine LA (600 mg) every four weeks for 96 weeks (the first dosing clinic visit will require loading doses of two 400 mg cabotegravir LA injections and one 600 mg rilpivirine injection);
- IM regimen of cabotegravir LA (600 mg) + rilpivirine LA (900 mg) every eight weeks for 96 weeks (the first dosing clinic visit will require loading doses of two 400 mg cabotegravir LA injections and one 900 mg LA injection; the second dosing clinic visit, four weeks later, will require an additional 600 mg loading dose of cabotegravir LA); or
- continuation of the oral induction phase regimen of cabotegravir plus abacavir/3TC once daily for 96 weeks (or 104 weeks if continuing on to the extension period).

The trial is now fully enrolled with 265 participants.

Long-Acting Rilpivirine

Rilpivirine has undergone several PK, safety, and efficacy evaluations, which include phase I studies exploring oral and long-acting parenteral coadministration with cabotegravir.[72]

ViiV Healthcare, in collaboration with Janssen, is primarily conducting the clinical development of long-acting rilpivirine for therapeutic purposes.

Dolutegravir/Rilpivirine

Based in part on the encouraging data from the LATTE study, ViiV and Janssen are developing an FDC containing standard doses of dolutegravir (50 mg) and rilpivirine (25 mg) as a single-tablet, two-drug, NRTI-free maintenance regimen.[77] Should the FDC prove durable and safe, its approval and availability may serve as a stopgap until the long-acting formulations of cabotegravir and rilpivirine are approved, as an oral maintenance therapy alternative to long-acting cabotegravir/rilpivirine injections, or as an oral option to be initiated should long-acting cabotegravir/rilpivirine injections need to be discontinued.

A number of clinical trials of this oral maintenance regimen are planned or now under way. These include an FDC formulation study and three switch clinical trials.[78,79,80,81]

Censavudine (OBP-001, formerly festinavir/BMS-986001)

This molecule has a similar structure to the NRTI d4T (stavudine) but with in vitro data that suggested it may have none of d4T's problematic side effects.

Results from a phase IIb study presented at the Interscience Conference of Antimicrobial Agents and Chemotherapy in 2014 comparing once-daily BMS-986001 with TDF (with background efavirenz plus 3TC) reported similar efficacy at weeks 24 and 48 with higher doses, but with higher rates of drug resistance in people experiencing virological failure.[82] Slight differences in bone changes and increases in peripheral fat were reported with BMS-986001, but no statistical analysis was performed to support this.[83]

A potential role for censavudine in treating HIV-2 was suggested in a poster at the 2015 International Drug Resistance Workshop that reported greater in vitro activity against HIV-2 compared with HIV-1 and the ability of the drug to overcome key NRTI resistance mutations.[84]

Despite this, BMS has since dropped its option to develop the compound, and the rights have reverted to Oncolys.

Monoclonal Antibodies

Research into the potential therapeutic role for monoclonal antibodies in management of HIV has been ongoing for well over a decade. Although progress was slow with the earliest compounds, more recent discoveries of a number of more potent and more broadly neutralizing monoclonal antibodies (bNAbs) has led to greater optimism that they might play an important role in both treatment and cure research.

A meeting cosponsored by the U.S. National Institute of Allergy and Infectious Diseases (NIAID) and the Bill & Melinda Gates Foundation in June 2015 brought together more than 140 scientists, researchers, industry, regulators, advocates, and funders to review the current state of this research and to encourage collaborations that would bring advances more rapidly to clinical studies.

In addition to discussing ibalizumab and PRO140, discussed separately below, the meeting reported on more recently developed compounds, including VRC01, which is being developed by the U.S. National Institutes of Health (NIH) Vaccine Research Center, and 3BNC117, which is being developed by the Rockefeller University with support from the NIH. Both are bNAbs with activity against many diverse HIV strains. In addition to their possible use for therapeutic purposes, they are being eyed for their prevention potential as passive immunization and their curative potential in combination with latency-reversing drugs (for more, see "Preventive Technologies," page 57, and "Research Toward a Cure and Immune-Based and Gene Therapies," page 81).

In a recently published study, 12 HIV-negative and 17 HIV-positive individuals received single infusions of 1, 3, 10, or 30 mg/kg of 3BNC117.[85] The infusions were well tolerated, and the HIV-positive participants in the two highest dose groups, particularly the eight individuals in the 30 mg/kg group, experienced viral-load reductions between 0.8 and 2.5 log copies/mL, which persisted for at least 28 days in some cases. Baseline resistance to 3BNC117 was documented in one individual, as well as evolving resistance to the antibody among some participants in the lowest dose groups.

Indeed, a key theme from the Bethesda meeting was the need for future research to use multiple bNAbs from an extensive panel of isolates in combination to ensure sufficient coverage and to minimize the risk of resistance, which paralleled learning from the experience of early ART.

Ibalizumab (TMB-355)

Ibalizumab (TMB-355) is a monoclonal antibody that binds to CD4 and blocks HIV entry post-attachment. It is being developed, albeit slowly, by TaiMed Biologics and was recently granted orphan designation by the FDA due to its limited but important treatment potential. It has been studied primarily as an intravenous (IV) formulation and is being looked at principally as a regimen component for people with cross-class-resistant HIV.

In phase I and II studies completed to date, there were mean viral-load reductions of −0.95 to −1.96, with no severe drug-related adverse events reported among the 247 participants who received the drug via IV administration.

No additional phase II or phase III treatment protocols have been announced other than an ongoing one (investigator-sponsored) that allows participants in the phase IIb clinical trial to continue received ibalizumab with optimized background therapy.[86] For treatment-experienced patients requiring ibalizumab to construct a viable or tolerable antiretroviral regimen, TaiMed is providing the IV formulation of the drug through a treatment IND program, which requires each patient and his or her health care provider to apply for access to the drug through regulatory agencies.[87] Additionally, in response to advocates' requests, BMS has agreed to allow heavily treatment-experienced patients enrolled in the nonrandomized arm of its phase III evaluation of the attachment inhibitor fostemsavir to use ibalizumab to help optimize treatment outcomes.[56]

Ibalizumab has been reformulated for subcutaneous administration, with encouraging safety and PK data reported in September 2014.[88]

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.[89,90] Weekly (162 mg and 324 mg) and biweekly (324 mg) subcutaneous administration have also been evaluated, yielding mean viral-load reductions of 1.37 log to 1.65 log copies/mL and no serious adverse events.[91]

Though no new PRO 140 data have been reported since 2010, phase II studies are planned or under way. These include an ongoing evaluation of 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), as well as a study of subcutaneous injections of PRO 140 added to an optimized antiretroviral regimen for HIV-positive injection drug users with viral rebound and documented poor adherence that was announced in 2011 and has yet to open to enrollment.[92,93]

CONCLUSION

The antiretroviral drug pipeline remains robust, with significant advancements of several compounds now in late-stage development and the entry of new compounds with potential for both treatment-experienced and treatment-naive populations. TAF continues to show well in clinical trials, demonstrating its promise as a new version of a drug that remains a backbone of treatment regimens throughout the world; doravirine is now in phase III evaluations as a generic-backed co-formulated, single-tablet regimen; and data continue to support the exploration of long-acting dual-drug injectable regimens as maintenance therapy. For treatment-experienced individuals, the advancement of fostemsavir – particularly into a highly ambitious, multinational phase III clinical trial with an open-label arm for patients in desperate need of new treatment options – and the entrance of BMS-955176 are encouraging, as is the orphan designation for ibalizumab.

This is not to say that all pipeline contenders are advancing in a seamless fashion, nor are their launch and commercial successes yet being viewed against the backdrop of increasingly perilous cost and access considerations.

RECOMMENDATIONS

- Manufacturers must commit to drug prices required to achieve cost-contained HIV care and service delivery in high-income countries.
- Manufacturers developing new oral drugs are strongly encouraged to follow the emerging trend of evaluating co-formulations with historically potent and safe generic antiretrovirals, notably TDF and 3TC. However, these fixed-dose combinations must be priced accordingly.
- Gilead Sciences should commit to a more robust research program for TAF that covers three main concerns:

    1. Head-to-head comparisons of TAF- versus TDF-inclusive regimens, including those with drugs that do not require boosting, in treatment-naive individuals (i.e., not just switch studies).
    2. Evaluations of lower-dose TAF (e.g., 2 mg and 10 mg in cobicistat-boosted and cobicistat-unboosted regimens, respectively), in light of data suggesting that the increased intracellular concentrations associated with 10 and 25 mg dosing do not confer potency advantages compared with TDF in treatment-naive populations. This may have potential for further improved safety and API requirements.
    3. Collaboration with the FDA and other regulatory agencies to fully validate intracellular, versus blood plasma, drug concentrations as a bona fide PK marker. This is key to supporting bioequivalence data requirements for generic co-formulations in low-income countries (e.g., fixed-dose combinations containing 3TC instead of FTC).

- Long-acting antiretrovirals for parenteral administration continue to hold tremendous promise for treatment and prevention. Though safety and efficacy trials should be prioritized, research to more fully evaluate potential implementation challenges of these drugs – such as dosing and clinical follow-up acceptability and feasibility evaluations – should be planned.
- The development of new drugs for treatment of cross-class-resistant HIV should remain a priority. It is very encouraging to see progress in this area. For drugs with limited indications, including those without clear marketing potential for treatment-naive individuals, the Orphan Drug Designation program should be explored and engaged.
- Manufacturers should continue to closely collaborate with, and invest heavily in, evidence-based research, implementation science, policy advocacy, and service delivery aimed at improving HIV diagnosis and clinical care engagement rates. Their efforts should aim to maximize virological suppression rates required to improve disease-free mortality and prevent ongoing transmission of the virus.

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Fit For Purpose: Antiretroviral Treatment Optimization

By Polly Clayden

The most striking news since the *2014 Pipeline Report* is from the START (Strategic Timing of AntiRetroviral Treatment) study.[1] We now have evidence from a large, randomized, controlled trial to show that CD4 count is no longer a barrier to starting antiretroviral treatment (ART).

START results mean that guidelines worldwide should soon recommend ART to all HIV positive people. This will bring on the mammoth task of starting and keeping 35 million on treatment.[2] If ever there was a time when ART needs to be optimized – that is safe, effective, tolerable, durable, simple and affordable – it is now.[3]

One way to optimize antiretrovirals is by dose reduction.[4] The rationale is that when new drugs are developed, the highest tolerated doses in phase II are often selected for phase III and approval. In some cases lower doses might have equivalent efficacy and better tolerability. It might also be possible to reduce the amount of active pharmaceutical ingredient (API) with improved bioavailability through reformulation – and reduced API means reduced cost.

Since discussions on treatment optimization began the field has evolved and newer antiretrovirals have been approved.[5, 6, 7] Focus has shifted from merely making older drugs more efficient. Speeding up the introduction of generic versions of newer drugs – in appropriate regimens and formulations – into low-and middle-income countries is likely to produce the best options.[8, 9, 10]

Treatment optimization is one critical component to achieving universal access to ART. Last year's report provided more background on optimizing treatment and how this might be achieved.[11]

Important steps towards optimized treatment over the past year include:

- The first generic version of dolutegravir (DTG) submitted to the US Food and Drug Administration (FDA) for tentative approval.[12]
- Published 96-week data from ENCORE1 – continuing to show that a lower dose of efavirenz (EFV) is non-inferior to the currently approved one. [13, 14]
- A new formulation of tenofovir alafanemide fumarate (TAF)[15] submitted to the FDA and the European Medicines Agency (EMA) – albeit within a fixed dose combination (FDC) and a co-formulation with agents that complicate its recommendation in low- and middle-income settings. [16, 17, 18]

This chapter gives an update on antiretroviral treatment optimization trials and strategies – both ongoing and planned – and pipeline products for low- and middle-income countries. It also looks at missing evidence that is needed to change current recommendations.

Can We Do Better With What We Have?

As we go to press, discussions about the recommendations for the 2015 World Health Organization (WHO) guidelines are afoot. For adults the current (2013) guidelines include the regimens in Table 1.[19]

Table 1. WHO recommended adult ART regimens 2013

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 preferredm(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.

Several dose optimization trials and a reformulation program, relevant to these recommendations, are ongoing or have been completed. Some require more information before the new dose or formulation can be widely recommended. See Table 2.

TABLE 2. Antiretrovirals with potential for optimization

Compound/Approved dose	Class	Sponsor/approach	Outcomes	Status
TDF 300 mg once daily	NtRTI	CHAI in partnership with generic companies Reformulation	Approx 33% reduction anticipated Target 200 mg TDF-containing FDC tablet	TDF (xb) Bioequivalence completed Results available August 1015
AZT 300 mg twice daily	NRTI	Geneva University Hospital Dose optimization RCT	Dose reduced to 200mg twice daily	MiniZID Phase III Completed January 2014 No difference between arms in overall anemia rate at 24 weeks
d4T 30 mg twice daily	NRTI	Wits Reproductive Health Institute Dose optimization and comparison with TDF RCT	Dose reduced to 20mg twice daily	WHCS-001 Phase III To be completed end 2015/early 2016
EFV 600 mg once daily	NNRTI	Kirby Institute Dose optimization RCT	Dose reduced to 400 mg once daily	ENCORE 1 400 mg non-inferior to 600 mg at 96 weeks
ATV/r 300/100 mg once daily	PI	HIVNAT/Kirby Institute RCT	Dose reduced to 200/100	LASA III Phase IV to be completed June 2015

ATV/r, atazanavir/ritonavir; AZT, zidovudine; d4T, stavudine; EFV, efavirenz; TDF, tenofovir disoproxil fumarate.

NRTI, nucleoside reverse transcriptase inhibitor; NRtI, nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor,

With the exceptions of TDF (xb), EFV 400 mg and darunavir/ritonavir (DRV/r) – discussed in the following section – since the trials began, optimizing existing antiretrovirals has become less relevant.

Lower dose AZT (400 mg) did not show an improvement in overall anaemia rate – the primary endpoint – compared with the standard dose (600mg) in a randomized trial conducted in Cameroon.[20]

The trial that dare not speak its name – of lower dose d4T (20 mg) – will yield more data from a low- or middle-income country on TDF. But d4T has not been recommended at higher doses anywhere for some time and we are not anticipating a revival. By 2018, d4T is expected to be only 2% of the nucleos(t)ide reverse transcriptase inhibitor (NRTI) market.[21]

The results of the low dose atazanavir/ritonavir (200/100 mg) trial are not expected to be applicable outside Thailand, where it is being conducted. [22]

What Are The Ones To Watch?

In the Clinton Health Access Initiative's (CHAI) *2014 ARV Market Report* the authors write: "The global community is coalescing around a short list of products that have shown superior or non-inferior efficacy compared to existing alternatives but also offer improved durability and tolerability, higher bioavailability, lower pill burden, and the potential for lower frequencies of adverse events." [23]

These products are: EFV 400 mg, DTG, TDF(xb), TAF and DRV/r, which have also featured annually in this Pipeline Report chapter.

Despite having coalesced for quite a while now, at a WHO Think Tank convened in February 2015, [24] the expert group recognized that a greater body of evidence supports the use of EFV 600 mg first-line (an estimated 15 million patient years when combined with TDF/XTC – meaning either FTC or 3TC).[25] The group suggested that this evidence provides a level of confidence that is not currently there with the alternatives: EFV 400 mg and DTG.

Both TDF (xb) and TAF are still in development and a WHO recommendation for DRV/r has been delayed due to a lack of a heat stable co-formulated generic version (which has been delayed due to a lack of a WHO recommendation).

Efavirenz 400 mg

EFV 600 mg fulfils many of the characteristics in the target product profile as part of an ideal ART regimen. For those who tolerate the drug, it is safe and effective, can be used in pregnancy and in people receiving concomitant TB treatment and needs minimal laboratory monitoring.

But it has a low genetic barrier to resistance. It is also associated with central nervous system (CNS) side effects, which can lead to drug discontinuation, reported in as many as half the people receiving it in settings with access to alternatives.[26] There is also an interaction between EFV and some hormonal contraceptives that can reduce their efficacy.[27]

A recent meta-analysis found that over 90% of treatment-naive people remained on an EFV-based first line regimen after an average follow up of 78 weeks.[28] But CNS side effects were more frequent with this antiretroviral compared to a number of others. People with HIV and activists have reported these adverse events as flaws of EFV since it was first approved.[29]

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 2014.[30] There have been no surprises at 96 weeks. [31]

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 participants at 48 weeks. It was conducted in Europe, Australasia, Latin America, Asia, and Africa.

Significantly fewer participants (2% versus 6%, p=0.01) discontinued treatment due to EFV-related side effects (rash, CNS, gastrointestinal, but not psychiatric) in the 400 mg arm compared to the 600 mg arm and 10% fewer reported these side effects.

A very high proportion (approximately 90%) of participants had an undetectable viral load in this study. Extended follow up to 96-weeks continued to demonstrate non-inferiority of 400 mg EFV.

Results from a pharmacokinetic sub-study of ENCORE 1 suggest that the current targets for EFV could be too high.[32] There has also been a suggestion from the FDA that the original approved dose might be too high.[33]

Since the announcement of the trial results in 2013, there has been much discussion about recommending the reduced dose, particularly in low- and middle-income countries where the resulting cost savings would be considerable.

Questions about whether or not 400 mg would be robust in the third trimester of pregnancy and with TB treatment have delayed recommendations from WHO and national guidelines.

There are six 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.[34] The results suggest that pregnancy has slight if any clinically important effects on EFV pharmacokinetics.

A South African study of 97 pregnant women (44 with TB) found that pregnancy increased the rate of low EFV plasma concentrations, but vertical transmission was rare.[35] A detectable viral load at delivery was more common among pregnant women with TB, but antiretroviral treatment was generally started later in this group. Another small study also found lower EFV plasma concentrations during pregnancy but the authors suggested that the clinical implications are unknown.[36]

For rifampicin, there have been seven short-term pharmacokinetic studies with EFV 600 mg (less than two weeks) showing reduction in plasma concentrations. It is unclear how useful these results are when EFV has not reached steady state. Five longer-term studies in HIV-positive people have shown increased Cmin or no effect.[37]

In order to make a universal recommendation for EFV 400 mg results from pharmacokinetic studies with rifampicin and in pregnant women are necessary.

Results from a pharmacokinetic substudy of ENCORE1 suggest that although 400 mg gives cerebrospinal fluid exposure (CSF) exposure of EFV above that required for HIV suppression, exposure of metabolites might still be within the concentration range associated with toxicities.[38] Although significant, the reduction in EFV-associated adverse events was modest in ENCORE1 and the pharmacokinetic study suggests this possible explanation.

Last year, three leading HIV doctors suggested that the dominant role of EFV in first-line therapy should be reconsidered.[39] They wrote that "this should not only happen in high-income countries but ideally also in low-income settings, if alternative drugs are available, and this recommendation should be reflected in the treatment guidelines of the WHO and both governmental and non-governmental organisations".

But for low- and middle-income countries, EFV is likely to remain a recommended first-line antiretroviral for a while. For countries where generics are not accessible until a drug is off patent this is likely to be for

some time. While EFV remains an option, it is important that the pharmacokinetic studies to look at TB and pregnancy are funded and conducted to ensure that the most optimized dose is given.

CHAI is working with suppliers to develop and file EFV 400 mg as part of an FDC with TDF and 3TC.[40] ENCORE1 data will be filed as an Investigational New Drug (IND), be cross-referenced in the suppliers' New Drug Applications (NDA) and be used as the basis for FDA tentative approval. The first filing is anticipated in the first quarter of 2016. FDA has agreed to the filing strategy for the product.

Dolutegravir

Excitable reviewers have found it hard to swerve from describing DTG as: "game-changing".[41] With a low 50 mg once daily dose that does not require boosting, a very high barrier to resistance, good efficacy, minimal toxicity, pregnancy category B, and the potential to be low-cost and co-formulated, it looks like it will be an important potential option for use in low- and middle-income countries. It could replace EFV first-line. It is also predicted to cost about US$30 per patient per year (pppy) to manufacture.

DTG was superior to EFV at 48 weeks in antiretroviral naive patients in phase III trials (and remained so at 96 weeks).[42, 43] At 48 weeks the proportion of participants who discontinued treatment due to adverse events was lower in the DTG group than in the EFV group (2% vs 10%). Rash and CNS events frequently associated with EFV were significantly more common in the EFV group.

Data from this comparison and from studies comparing DTG to raltegravir (RAL) and in people with resistance to other integrase inhibitors [44, 45] were used to gain approval for a broad indication in adults and adolescents aged 12 and above.[46] The indication for 12 to 18 year olds is based on a 24-week open-label label study in integrase inhibitor-naive participants.

DTG studies have not yet included significant numbers of people who would be treated in low-and middle-income countries. The registrational trials for DTG comprised approximately 80% men and few non-white participants and hardly anyone co-infected with other diseases (a few with hepatitis B and none with TB or malaria). People with baseline NRTI resistance were not included.

Information about treating HIV/TB coinfection with a DTG-based regimen is limited. A phase I study has been conducted in healthy volunteers of DTG given with rifampicin and with rifabutin.[47] The study 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.

As yet information about DTG in pregnant women is scarce. Although animal reproduction studies are not always predictive of human response, no safety issues were revealed in preclinical studies. So far only one first trimester and four second/third trimester exposures have been reported to the Antiretroviral Pregnancy Registry (APR) to 31 July 2014.[48]

For DTG to be recommended in WHO guidelines without restriction, more information is needed on how it is likely to perform in real world, low- or middle-income settings. Populations in these settings include larger proportions of women of childbearing age, children, and people with TB, malaria, and other coinfections.[49]

ViiV Healthcare (the originator of DTG), Aurobindo Pharma, and CHAI recently announced that Aurobindo has submitted an Abbreviated New Drug Application (ANDA) for generic DTG 50mg, to the FDA for tentative approval.[50]

This is the first ANDA for a generic version of DTG and has been made within two years from FDA approval of originator DTG for the US. ViiV has provided a selective waiver to the FDA for the five-year period of New

Chemical Entity exclusivity, which would have prevented tentative approval of Aurobino's ANDA. This product is expected to gain tentative approval in the first quarter of 2016. Several generic manufacturers are working on FDCs of DTG /TDF/3TC.

ViiV has also licensed DTG to the Medicines Patent Pool (MPP).[51] The agreements for both adult and pediatric treatment were signed just two months after DTG was approved by the EMA and eight months after FDA approval.

New and Better Versions of Tenofovir

TDF (xb)

Tenofovir disoproxil fumarate (TDF) – the current formulation of tenofovir – is recommended globally as part of first-line treatment and used widely in high-, low- and middle-income settings.

The downside of TDF is its potential for renal and bone toxicity. There are limits to the lowest possible price of TDF with the current formulation, due to its high milligram dose (300 mg).

CHAI is developing a dosage form of TDF called TDF (xb) in partnership with companies performing the preclinical work, formulation screening and Good Manufacturing Practice (GMP), and a generic manufacturer. [52]

With the current TDF 300 mg formulation only 25% of tenofovir is absorbed into the bloodstream. By reformulating the excipients CHAI aims to increase bioavailability and, in turn, lower the dose to an anticipated 200 mg, while maintaining equivalent exposure to that achieved with the current formulation.

Bioequivalence studies will compare TDF (xb) to the 300 mg originator formulation of TDF to provide evidence for tentative FDA approval of TDF (xb)-containing FDCs. The goal is to reach the market with a TDF (xb)-containing FDC in 2017.

TAF

Gilead Sciences has developed a new version of tenofovir: tenofovir alafenamide fumarate (TAF).

TAF is not yet approved but it has been submitted to the FDA and EMA as a component of an FDC with elvitegravir/cobicistat and FTC (E/C/F/TAF) and a co-formulation with FTC (F/TAF).[53, 54, 55, 56] The FDA applications were filed in November 2014 with expected approval November 2015 and April 2015 with expected approval November 2016, respectively.

Besides Gilead's incestuous combinations, other TAF-containing FDCs in development are collaborations with Janssen: darunavir/cobicistat/FTC/TAF (D/C/F/TAF) and rilpivirine/FTC/TAF (R/F/TAF).

Both TDF and TAF are prodrugs of tenofovir. TAF doses are one tenth or less than that of TDF and give intracellular levels of the active metabolite, tenofovir diphosphate, which are four to seven times higher and plasma concentrations that are 90% lower than those with TDF.[57, 58, 59]

It is possible that the reduction in plasma concentrations with TAF could mean less tenofovir accumulation in bone and kidneys and, in turn, fewer bone and kidney associated toxicities compared with TDF. [8]

Due to a drug-drug interaction between TAF and cobicistat (or ritonavir) that increases the levels of tenofovir 2.5-fold, a dose of 10 mg is being used in regimens with boosting agents and 25 mg in un-boosted ones.

F/TAF will be produced in 10 mg and 25 mg TAF plus 200 mg FTC co-formulated tablets.

The reduced dose means less API and potentially considerable reductions in generic prices (this could eventually be an annual patient cost of less than US$20);[60, 61] it will also mean smaller tablet sizes.

The regulatory applications for F/TAF (described in the antiretroviral chapter of this *Pipeline Report*) are supported by the phase III trials of E/C/F/TAF [62] and an adolescent study,[63] plus bioequivalence data for F/TAF and E/C/F/TAF.

Results from these trials might not be sufficient to inform the production of generic FDCs without boosting agents, as identified as a potential optimized first-line regimen in several expert consultations.[64, 65]

Ongoing studies combining F/TAF with third agents are switching participants on stable treatment from TDF to TAF.[66, 67] Although DTG might be the third agent in the open label switch study, it would probably not generate appropriate data in treatment-naive people to allow WHO recommendation for first-line regimens. So even if the FDA and EMA approve TAF in 2015/2016, guidance and uptake in low- and middle-income countries could be delayed.

Independent investigators, generic manufacturers and organizations such as CHAI and UNITAID might be better placed to establish this evidence and take on the development of a DTG and TAF-based FDC than the originator manufacturers. One study is in the planning stage.

There are potential licensing hurdles with possible combination products under the current Gilead/MPP license.[68] CHAI is working with Gilead and MPP to clarify the licensing of TAF to allow specific FDCs for low- and middle-income countries.

At least one generic manufacturer plans to develop and file a DTG-containing FDC with FTC and TAF, anticipated in 2018.

Darunavir/ritonavir

Darunavir/ritonavir (DRV/r) is generally considered to be the most potent and tolerable protease inhibitor, but as yet there is no generic formulation, and cost has been a barrier to its wide use. WHO has not yet recommended DRV/r for second-line treatment and there has been limited work on its optimization.

This drug has different approved doses for treatment-naive (and treatment- experienced without 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.

No dose-finding studies have ever been conducted with DRV/r in treatment- naive people and the original studies were conducted in people who were highly protease inhibitor-experienced.[69, 70] Results from these trials of DRV/r, as well as two with 600/100 mg,[71, 72] suggest that a dose reduction to DRV/r 400/100 mg might be feasible.

There are also potential cost efficiencies to be gained through process chemistry and reformulation.

Several generic manufacturers have been developing a co-formulation of DRV/r 400/50 mg (800/100 mg once daily, two pills). As ritonavir is tricky to make in a heat stable formulation there have been technical hitches with this product development. One manufacturer seems to have overcome these obstacles and anticipates an FDA filing for tentative approval in the second quarter of 2016.[73]

What Is Planned Or Needed To Recommend The New Drugs And Formulations?

Several trials are underway or planned (see table 3) that should fill some of the remaining evidence gaps.

TABLE 3: Ongoing or planned ART optimization trials

Trial	Implementer/ Sponsor	Design	Status	Information gained
LOW DOSE EFAVIRENZ				
EFV 400 mg pregnancy	SSAT/Mylan	PK EFV 400 mg in third trimester pregnancy and post partum in 25 women Sites in London and Kampala	Starting July 2015	Supporting data to ENCORE1
EFV 400 mg TB	SSAT	PK EFV 400 mg with isoniazid and rifampicin in 26 participants Sites in London and Kampala	Funding application stage	Supporting data to ENCORE1
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 application stage	Further experience with EFV400mg plus 200 mg
DOLUTEGRAVIR				
DTG/FTC/TDF vs DTG/FTC/TAF	Wits RHI	DTG/FTC/TDF vs DTG/FTC/TAF in 600 ART-naive participants Phase III Few exclusion criteria – adults according to WHO 2015 guidelines No baseline resistance testing Percentage with HIV RNA<200 copies/mL at 48 Weeks (FDA snapshot algorithm) South Africa	Funding application stage	Data on safety and efficacy of DTG-based regimens first line Comparison TAF vs TAF 25 mg Support inclusion in 2017 WHO guidelines
NAMSAL ANRS 12313	HIV OPD (Central Hospital) and CNPS Hospital (Yaounde) ANRS	DTG vs EFV 400mg, both plus 3TC/TDF in 550 ART-naive participants Phase III Few exclusion criteria – adults according to WHO 2013 guidelines No baseline resistance testing Percentage with HIV RNA<200 copies/mL at 48 Weeks (FDA snapshot algorithm) Two sites in Cameroon	Fully funded by ANRS Awaiting DTG supply	Data on TDF/3TC/DTG as 1st line ART in low-income country
DolPHIN1 (dolutegravir in pregnant HIV mothers and neonates)	University of Liverpool/ Makere University/ ViiV	DTG PK in pregnant women in third trimester and post partum during breastfeeding Phase II 60 late presenting women (after 28 weeks gestation) Women randomised 1:1 to receive DTG (50 mg once daily) or standard of care (EFV) plus two NRTIs Sites in Uganda	Start July 2015 Completion July 2016	Data on 3rd trimester PK Secondary outcomes include: safety and tolerability of DTG up to 6 months post partum and VL at delivery

Trial	Implementer/ Sponsor	Design	Status	Information gained
ARIA	ViiV	DTG/ABC/3TC FDC vs ATV/ r +TDF/FTC in 474 treatment naive women Phase IIIb Pregnancy and breast feeding are exclusion criteria but women who become pregnant in ARIA can rollover to ING200336 Multinational, sites in South Africa 48 weeks	Underway Start August 2013 Completion April 2018 Primary completion September 2015	Data on women
ING200336 Pharmacokinetic and safety study in pregnant women with HIV	ViiV	PK and safety single arm study of women with unintended pregnancies while participating in ARIA Estimated enrolment 25 (approx 237 receive study drug in ARIA) Multinational, sites in South Africa	Start October 2014 Completion February 2019	Data on 2nd/3rd trimester PK
IMPAACT 1026s V9 Pharmacokinetic properties of antiretroviral and related drugs during pregnancy and postpartum	NIH	PK Phase IV Pregnant women > 20 weeks gestation receiving DTG as part of clinical care Each study arm 12 to 25 (target) women with evaluable 3rd trimester PK data Open to all IMPAACT sites	September 2014 May 2016	Data on 2nd/3rd trimester PK
PANNA Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women	PANNA Network	PK, safety and efficacy Pregnant women receiving DTG as part of clinical care Target 16 women Open to all PANNA sites	June 2015 until target	PK data from 3rd and at 4 to 6 weeks post-partum.
Open label study of DTG vs EFV for HIV/TB coinfection	ViiV	50 mg DTG twice daily vs 600 mg EFV (randomised 3:2 ratio) during TB treatment (rifampicin, isoniazid, pyrazinamide and ethambutol) in 125 treatment naive participants Phase IIIb 48 weeks Multinational, sites in South Africa	Start November 2014 Completion December 2018 Primary completion 2016 Not yet enrolling	Data on HIV/TB first line co-treatment

Trial	Implementer/ Sponsor	Design	Status	Information gained
TENOFOVIR ALAFENAMIDE 25 MG				
Switch study to evaluate F/TAF in HIV positive participants who are virologically suppressed on regimens containing FTC/TDF	Gilead	Double blinded study in 660 virologically stable adults receiving FTC/TDF plus open label 3rd agent randomised to continue vs switch to FTC/10mg or 25mg TAF (dosing will be dependent on 3rd agent) Phase III 48/96 weeks Sites in US, Canada and Europe	Start May 2014 Completion October 2016 Primary completion November 2015	Data on unboosted TAF (dolutegravir, efavirenz, raltegravir and rilpivirine allowed) Total number of participants receiving unboosted dose unknown
Switch study to evaluate the safety and efficacy of FTC/RPV/TAF FDC in HIV positive adults who are virologically suppressed on FTC/RPV/TDF	Gilead	Double blinded study in 550 virologically stable adults receiving RPV/FTC/TDF FDC randomised to continue vs switch to RPV/FTC/ 25mg TAF FDC Phase IIIb 48 weeks Sites in US, Canada and Europe	Start January 2015 Completion June 2017 Primary completion June 2016	Data on 25 mg TAF
IMPAACT 1026s V9 Pharmacokinetic properties of antiretroviral and related drugs during pregnancy and postpartum	NIH	PK Phase IV Pregnant women > 20 weeks gestation receiving TAF as part of clinical care Each study arm 12 to 25 (target) women with evaluable 3rd trimester PK data Open to all IMPAACT sites	September 2014 May 2016	Data on 2nd/3rd trimester PK
SECOND LINE LOW DOSE DRV/R (INCLUDING PLUS DTG)				
DRV/r 400/100 mg South Africa	Wits RHI/ SA DoH	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	Seeking DRV/r supply	Clinical experience of low dose DRV in switch study
DRV/r 400/100 mg France	ANRS	Single arm 100 stable participants switch to DRV 400/100 once daily plus 2 NRTI	Ongoing	Clinical experience of low dose DRV in switch study
SL2 pilot	SSAT	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 naive participants 48 weeks	Funding application stage	Preliminary data to support registration study
SL2 registration	SSAT	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 application stage	Data for FDA, PEPFAR and WHO approval

First-line

Experts agree that a DTG-based preferred first-line regimen is the current goal. In combination with TAF and FTC the total daily dose would be 275 mg compared to 1200 mg with the current WHO preferred first-line: EFV 600 mg/TDF/3TC. For people who cannot access (or tolerate) DTG, EFV 400 mg based regimens should be an alternative first-line.

While data gaps remain, both compounds should, at the very least, have an honorable mention in the WHO 2015 guidelines.

ViiV is sponsoring a number of trials to help to address some of the evidence gaps with DTG – including use in pregnant women and people receiving TB treatment. An open label study of regimens containing 50 mg DTG twice daily or EFV 600 mg once daily during first-line TB treatment, begun enrolling early 2015.[74]

Another trial is enrolling ART-naive women only and comparing first-line DTG regimens to boosted atazanavir (ATV/r) ones.[75] Women who become pregnant in the trial will remain on their randomly assigned regimen and roll over into a pregnancy study.[76]

A number of investigator-led studies are also planned in closer-to-real-life African settings. These include a randomized comparison between DTG and EFV 400 mg regimens, and another with two DTG-based regimens, one with TDF and the other TAF and FTC. NAMSAL, the trial of DTG versus EFV 400 mg regimens is fully funded but has been delayed now for some time due to the DTG supply (or lack of). The TAF versus TDF study is at the funding application stage and dependent of TAF being approved. A DTG pregnancy pharmacokinetics study is funded and scheduled to start enrollment in July 2015.[77]

IMPAACT P1026s and PANNA[78, 79] – the respective American and European studies that look at pharmacokinetics of antiretrovirals in pregnancy and post-partum – are both starting to enrol women receiving DTG (and TAF is planned).

For EFV 400 mg, a pharmacokinetic study in pregnant women is scheduled to start enrolment in July 2015. Funding for the TB pharmacokinetic study is still under discussion.

Un-boosted TAF for adults is only being investigated in two Gilead trials [80, 81] – so in order to recommend this drug widely the investigator-led study is important.

IMPAACT P1026s and PANNA will provide some pharmacokinetic data on TAF in pregnant women. For co-treatment of TB, TAF is a minor CYP3A4 substrate and a substrate of P-glycoprotein, both of which are induced by rifampicin, so there might be an interaction. Gilead has not looked at this.

If DTG/TAF/FTC fulfils its early promise, is recommended, and generic FDCs are made available, there will be questions to be answered on the pros and cons of a wholesale switch from the current EFV-based first-line versus a gradual transition.

Second-line

For people failing EFV-based first-line treatment – and this population is expected to swell with greater access to viral load testing – discussions about a one-pill, once daily, second-line regimen with DRV/r 400/100mg and DTG are underway. [82] Studies to investigate this regimen are designed and seeking funding.

A regimen of DRV/r plus DTG has the potential to be once daily, heat stable, co-formulated second-line option with no cross-resistance to an EFV/TDF/3TC first-line. Market forecasts suggest that such an FDC might be available at low cost: US$250 pppy. Making recommendations for DTG first- and second-line depending on the initial regimen is not mutually exclusive.

If DTG becomes preferred first-line, research into the best option for second-line following this regimen is needed. Early discussions have included the possibility of DRV/r with rilpivirine or doravirine. It might also be possible to use NRTIs again.[83, 84]

What Needs To Be Done?

The 2015 revised WHO guidelines must reflect recent research and approvals. DTG and EFV 400mg should be included as alternative first-line recommendations with restrictions where data are missing. DRV/r is overdue as a recommended second-line option. A recommendation from WHO is the biggest signal and incentive to generic manufacturers to produce new formulations and FDCs suitable for low- and middle-income countries.

Research must be funded. Donors need to step up and fund the trials that will generate data to fill the current knowledge gaps. We need the missing information to make first-line recommendations without restriction. We need information to guide switching from EFV to DTG regimens. We need studies to support recommendations for optimized second-line regimens.

Sustainable supply of generic antiretrovirals must be maintained. Three manufacturers (Mylan, Cipla, and Hetero) accounted for 51% of antiretroviral volume and 56% of revenue in low- and middle-income countries in 2013.[85] Mylan had the highest share of revenue at 24%. The company also has 30% of South African public sector market (the largest ART program in the world); and it supplies many of the APIs for antiretrovirals produced by South African generic companies.[86] So the recent moves by the Israeli pharmaceutical company Teva for a hostile takeover of Mylan are alarming.[87] Should this come about Teva must continue with the commitment to people with HIV in low- and middle-income countries.

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The Pediatric Antiretroviral Pipeline

By Polly Clayden

Introduction

The big news since the *2014 Pipeline Report* is that there is finally a solid form of lopinavir/ritonavir (LPV/r) suitable for infants and young children.

On 21 May 2015, the United States Food and Drug Administration (FDA) tentatively approved LPV/r pellets, manufactured by Cipla, for infants and young children less than three years old.[1, 2]

A few months before, in December 2014, the Medicine Patent Pool (MPP) signed a licensing agreement with AbbVie – that holds the patent for LPV/r. This agreement will help to make the new formulation available for children in low- and middle-income countries. The next hurdles will be getting it approved by regulatory agencies and used in programs in these countries.[3]

There has not been a lot of activity in the pediatric pipeline over the last year. This year's chapter confirms (again) the need for priority generic products and highlights the ones to watch in the originator pipeline. It also includes a few new ones: the non-nucleoside reverse transcriptase inhibitor (NNRTI) doravirine, and long acting formulations cabotegravir and rilpivirine.

Lopinavir/Ritonavir Pellets Tentatively Approved

The World Health Organization (WHO) recommends LPV/r-based regimens as preferred for infants and young children.[4] Compliance with the recommendation has been hard as this boosted protease inhibitor was previously only available as syrups, which are too complicated to use for most programs in low- and middle-income countries. The new formulation consists of a finite number of LPV/r 40/10 mg pellets in a capsule, which is opened and sprinkled on soft food.

Although it is quite a step forward from syrup, the new formulation of LPV/r is still not ideal. The pellets are much easier to transport and store (no cold chain), and for this reason programs are keen to start using them. But acceptability data from the CHAPAS-2 trial[5] – that showed similar LPV/r exposure with pellets and syrups – revealed that pellets were not more acceptable than syrups by 48 weeks.[6] For infants and young children overall, the trial found pellets were more acceptable than syrups at week 12 but not by week 48. The main problem was taste.

Infants less than three months old have not yet been treated with the pellets. As they cannot be stirred, dissolved/dispersed or crushed in liquids it is important to make sure that infants can swallow them. For the youngest infants (three to six months old) in CHAPAS-2, the pellets were either added to a small amount of expressed breast milk in a spoon and given to the infant, or put on the infant's tongue before breastfeeding.

DND*i* is waiting for the production of the clinical batch of the pellets to begin the LIVING study (implementation study using the new formulation) in Kenya.[7] All the necessary local regulatory approvals are in place to start the study.

DND*i* is also working on an improved taste masked granule formulation of LPV/r (as part of a fixed dose combination [FDC] 4-in-1 regimen).

WHO Recommendations and Current Priority Formulations

WHO 2013 guideline recommendations for adults are simple: two preferred first line regimens and two alternatives. Recommendations for children are more complicated (see Table 1). Only one regimen, AZT plus 3TC plus nevirapine (NVP) is currently available as an FDC. There is still some way to go with formulations and regimens appropriate to children. Despite some advances in the last few years, innovation and access in antiretrovirals for children still lags behind that for adults.

Table 1: 2013 WHO Guidelines Pediatric Recommendations

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 years 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.

NRTI, nucleos(t)ide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; TB, tuberculosis

Missing Pediatric Formulations

Several gaps remain in available products for children that need to be filled before the 2013 WHO guidelines (and the 2015 ones that are on the way) can be implemented in most low- and middle-income settings.

Where possible these should be 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 and inappropriate for most low- and middle-income countries. [8]

The WHO 2014 supplement to the 2013 guidelines include a pediatric chapter: *Optimizing Antiretroviral Drugs for Children: Medium- and Long-Term Priorities*. [9] WHO highlights two priority formulations needed to treat children according to the 2013 guidelines:

AZT or abacavir (ABC) plus 3TC plus LPV/r. These formulations are in development and are needed to make it possible to give FDCs to children younger than three. Better solid forms could overcome palatability issues with the currently available nasty tasting LPV/r syrup (although taste masking is complicated and can limit drug absorption and the recently approved solid form still needs improving). Many barriers with supply chain – transport, storage and distribution – could be addressed by these formulations.

Supported by UNITAID, DND*i* is working on a more palatable version of LPV/r – which will be produced in combined 4-in-1 granule formulations (finer than the newly approved 0.8mm pellets and more sand-like in texture). [10] The plan is to have the optimized 4-in-1 LPV/r-based FDCs by 2016.

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 (less than 35 kg) 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.

These two formulations have been a priority for some time now and are still unavailable.

Recommendations From the Second Pediatric Drug Optimization Meeting

The first Pediatric Antiretroviral Drug Optimization (PADO1) meeting, held in Dakar in 2013, brought together researchers, clinicians, activists and other experts to identify medium- and long-term priority drugs and formulations for children. The recommendations from this meeting were summarized in the WHO 2014 supplement,[11] and continue to inform formulation development.

The Second Pediatric Antiretroviral Drug Optimization (PADO2) meeting,[12] held in December 2014 was conducted to build on the PADO1 agenda and provide technical advice to the WHO 2015 guidelines development group. Among the topics discussed at the meeting were the needs for children at both ends of the age spectrum: newborns and adolescents.

For newborns, less than four weeks, the participants noted that there was currently no alternative to NVP plus 3TC plus AZT. Although very early treatment is being explored for infants, data for this very young age group are scarce. See Table 2. Some missing data will be provided by ongoing International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) trials:

- P1026s – phase IV, prospective, pharmacokinetic study in pregnancy and post partum, that obtains infant antiretroviral washout data.[13]
- P1093 – phase I/II, open label, non-comparative, intensive pharmacokinetics and safety study of dolutegravir (DTG) down to four weeks.[14]
- P1097 – washout pharmacokinetic study of raltegravir (RAL) including in low birth weight (<2500 g) infants.[15]
- P1106 – phase IV prospective pharmacokinetic study in low birth weight infants receiving NVP prophylaxis, tuberculosis (TB) prophylaxis or treatment and/or LPV/r-containing ART.[16]
- P1110 – phase I open label, non-comparative pharmacokinetic dose-finding study of RAL in high risk, HIV-exposed neonates.[17]
- P1115 – phase I/II proof of concept study of very early intensive antiretroviral therapy (ART) in infants to achieve HIV remission.[18]

Table 2: Newborn Treatment Options
(including ongoing and planned IMPAACT trials)

Compound	Preterm	Term	2 weeks
Nucleos(t)ide Reverse Transcriptase Inhibitor			
ABC	P1106 < 2500 g		
AZT	√	√	√
ddI			√
d4T	P1106 < 2500 g	√	√
FTC		√	√
TAF	P1026s washout	P1026s washout	
3TC	P1106 < 2500 g	√	√
Non-nucleoside Reverse Transcriptase Inhibitor			
Doravirine	P1026s washout	P1026s washout	
EFV	P1026s washout	P1026s washout	
ETR	P1026s washout	P1026s washout	
NVP	P1106 < 2500 g	P1115 >34 weeks GA	√
RPV			
Protease Inhibitors			
ATV			
DRV	P1026s washout	P1026s washout	
LPV	P1026s washout P1106 <2500 g	P1026s washout	√
Integrase Inhibitors			
DTG	P1026s washout	P1026s washout P1093 dosing (in development)	P1093 dosing (in development)
EVG	P1026s washout	P1026s washout	
RAL	P1097 washout	P1097 washout P1110 dosing	
CCR5 Receptor Antagonist			
Maraviroc		In development	

Adapted from Ruel T. IMPAACT 2015.

ABC, abacavir; ATV, atazanavir; AZT, zidovudine; ddI, didanosine; DTG, dolutegravir; d4T, stavudine: EFV, efavirenz; FTC, emtricitabine; ETR, etravirine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide fumarate; 3TC, lamivudine. GA, gestational age.

For infants two weeks and above, the immediate priority first-line is still LPV/r-based regimens and for older children EFV-based FDCs. An alternative to the liquid formulation of ritonavir (RTV) is needed to make double boosting (adding extra RTV to overcome pharmacokinetic interactions with TB drugs during co-treatment) easier with LPV/r.

For second-line treatment a generic, co-formulated, heat stable version of darunavir/ritonavir (DRV/r) was prioritized. Children who fail on LPV/r-based first-line regimens particularly need a robust option second-line.

Current dosing recommendations for DRV/r (approved by regulators in the United States and Europe) need to be simplified to reduce the number of different formulations and minimize pill burden for children in low- and middle-income countries. A 240/40 mg DRV/r tablet for twice daily dosing is a priority for children in weight bands 10 kg and above. DRV/r is not approved for children less than three years old and will not be investigated in this age group due to toxic levels in pre-clinical studies.

Discussion about adolescents focused on adherence and more tolerable alternatives to EFV.

The priority antiretrovirals in the medium-term (five years) are: DTG, RAL and tenofovir alafenamide fumarate (TAF). Although the PADO2 participants did not expect RAL to be used widely when DTG comes to the market (and it has not been identified as a priority for adults) a better formulation of RAL might offer an alternative for infants.

The Pipeline

Pediatric investigation plans (PIPs) will be in place or under discussion for all compounds in early phases of development by originator manufacturers (described in the adult antiretroviral chapter). Although a generic company and DND*i* are developing the LPV/r-based 4-in-1 FDC, the list of pipeline pediatric drugs and combinations also includes this.

There are considerable incentives and/or penalties from regulatory agencies to ensure that any new drug that might benefit children must be studied in this population. Pediatric research and development of new drugs is mandatory. The European Medicines Agency (EMA) enforces penalties for companies that do not provide a PIP as part of their application (or request a waiver). The FDA also extends six month patent protection to companies that perform the requested pediatric studies – though companies are not required to do this.

A PIP can be waived for specific drugs or classes of drugs that are likely to be ineffective or unsafe in all or some pediatric age groups. A waiver can also be obtained for products that are intended for conditions that only occur in adults, or that do not represent a benefit over existing pediatric treatments. In some cases, studies can be deferred until after the adult studies have been conducted.

Manufacturers must include pharmacokinetic data for all age groups of children, efficacy, tolerability, and differences in side effects. They must have stability and palatability data for formulations and demonstrate that they are able to achieve pharmacokinetic targets associated with efficacy in adults.

Studies are conducted in children as soon as there are sufficient data from those in adults. Most pediatric development programs take a staggered approach, starting with the older cohorts of children and working in de-escalated 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. As the youngest age group is last to be studied and approved there are considerable delays in availability of new drugs for this population.

Whether this process could be accelerated and age groups studied simultaneously, where possible, has been discussed for some time. It would be interesting to see if doses for younger children have changed dramatically from predicted milligrams per kilogram ones due to pharmacokinetic data from older cohorts.

The current pediatric antiretroviral pipeline is shown in Table 3.

Table 3. The Pediatric Antiretroviral Pipeline

Compound	Sponsor	Formulation/s and dose	Status and comments
Nucleotide reverse transcriptase inhibitor and combinations			
Tenofovir alafenamide fumarate (TAF)/ /emtricitabine (FTC) elvitegravir (EVG)/ cobicistat (COBI) (E/C/F/TAF)	Gilead	Reduced dose FDC tablets in development	Phase II/III single arm, open label E/C/F/TAF treatment-naive children and adolescents 6 to <18 years PK within adult range at 24 weeks in 12 to <18 years Waiver <6 years
FTC/TAF (F/TAF)	Gilead	Reduced dose, co-formulated tablets and non-solid formulation in development	Switch study in children and adolescents stable on FTC/TDF plus 3rd agent Study in infants and children 4 weeks to <6 years planned
Rilpivirine (RPV)/FTC/TAF	Gilead/Janssen	Reduced dose, FDC tablets planned	Dependent on development of RPV and F/TAF Initial indication adolescents >12 years
Non-nucleoside reverse transcriptase inhibitors			
Etravirine (ETR)	Janssen	Dispersible tablets 25 (scored), 100 mg	FDA/EMA approval for children and adolescents 6 to <18 years Phase I /II treatment-experienced infants and children 2 months to <6 years and treatment-naive 2 months to <2 years enrolling Waiver <2 months
Rilpivirine (RPV)	Janssen	Tablet 25mg Granules 2.5 mg /g	Submitted to FDA and EMA for adolescents 12 and above with viral load < 100,000 copies/mL 2 to <12 years planned
Doravirine	Merck	Single agent and FDC with TDF/3TC planned	Pediatric plans under discussion with EMA and FDA
Protease inhibitor and combinations			
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	Booster with ATV, DRV and as part of E/C/F/TDF and E/C/F/TAF
Atazanavir/cobicistat (ATV/c)	Gilead/BMS	Reduced dose and dispersible tablets planned	Phase II/III treatment experienced children 3 months to <18 years (ATV/c) 3 to < 18 years (DRV/c)
Darunavir/cobicistat (DRV/c)	Gilead/ Janssen		

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 and older Passive PK study ongoing: neonates born to women who received RAL in pregnancy and during labor Neonates PK and safety study for prophylaxis ongoing in high-risk HIV-exposed neonates from birth to six weeks
Elvitegravir (EVG)	Gilead	Reduced dose 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 dose tablets in development	Studies underway in treatment-naive 12 to <18 years 6 to <12 years planned Waiver <6 years
E/C/F/TAF See TAF above	Gilead	Reduced dose tablets in development	Studies underway in treatment naive 12 to <18 years 6 to <12 years planned Waiver <6 years
Dolutegravir (DTG)	ViiV Healthcare	Granule formulation (for studies) Dispersible tablets in development 10 mg and 25 mg tablets	Approved for adolescents 12 to <18 years weighing ≥40kg in US and EU Phase I/II study, 6 weeks to <18 years treatment-naive and -experienced children, ongoing In a PK study, exposures from granules were moderately higher than with tablets and highest with formula milk
DTG/ABC/3TC (572-Trii)	ViiV	Pediatric formulation development planned	FDA/EMA approval for adolescents >12 years and >40 kg Dependent on ongoing studies confirming DTG dose in children and ability to establish appropriate dosing ratios for components
DTG/RPV	ViiV/Jansen	Reduced dose co-formulation	PIP in development Studies planned in children and adolescents 6 to <18 years
Cabotegravir/RPV long acting (LA)	ViiV/Janssen	Age appropriate liquid formulation for induction Intramuscular nanosuspension as for adults	PIP approved October 2014 (to be completed by 2018) Waiver <2 years Deferral 2 to <18 years
CCR5 Receptor Antagonist			
Maraviroc (MVC)	ViiV	Suspension 20 mg/mL	Phase IV Treatment-experienced CCR5 tropic 2 to <18 years

NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITOR

Tenofovir Alafenamide Fumarate

TAF is considered to be a priority for future generic FDCs for children. Early data in adults suggests that it might have a better safety profile than TDF. This has yet to be confirmed in children. TAF also has a low milligram dose: 25 mg without a boosting agent and 10 mg boosted.

For children TAF might be an alternative to ABC. It could help to harmonize pediatric and adult ART regimens, particularly if it could be co-formulated with DTG and 3TC or FTC.

The originator company Gilead Sciences is not developing TAF as a single agent for adults or children. The development of an FDC of elvitegravir (EVG)/cobicistat (COBI)/FTC/TAF (E/C/F/TAF) is the company's priority.

As with adults, Gilead is also investigating a co-formulation with FTC (F/TAF), which hopefully will provide data to inform the dose of TAF as part of future un-boosted generic regimens.

E/C/F/TAF and F/TAF are currently under regulatory review for adults.[19, 20, 21]

F/TAF

TAF is being investigated co-formulated with FTC in a phase II/III switch study will enroll children down to six years of age.[22]

Adolescents aged 12 to 18 years will switch their current two nucleoside reverse transcriptase inhibitor (NRTI) containing regimen to F/TAF (while continuing on their third antiretroviral agent) for 96 weeks. After review of the pharmacokinetic and safety data from the older cohort, children aged six to 12 years will be randomized to receive either F/TAF or FTC/TDF (continuing on their third agent) for 96 weeks.

A study in infants and children aged four weeks to six years is planned. Reduced dose tablets and a non-solid formulation are in development. As with the pediatric formulation of TDF, the taste of TAF is bitter and will need masking. Because of TAF's low milligram dose, taste masking might be easier than it was for TDF.

E/C/F/TAF

A phase II/III, single arm, open label study of once-daily E/C/F/TAF in treatment-naive children and adolescents aged six to18 years is ongoing.[23] There is a waiver for children less than six years old.

Data were recently presented from the phase II/III for 48 treatment-naive 12 to 18 year olds with a median age of 15 years receiving E/C/F/TAF for 24 weeks.[24]

Steady-state pharmacokinetic parameters of EVG, COBI, FTC, TAF and tenofovir (TFV) were compared to adult exposures. The study found TAF (as well as TFV, EVG, COBI, and FTC) pharmacokinetic parameters in adolescents to be consistent with those associated with safety and efficacy in adults.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Etravirine

A scored 25 mg etravirine (ETR) tablet with dosing recommendations for treatment-experienced children and adolescents aged six to 18 years and weighing at least 16 kg is currently approved.[25] The recommended dose is based on 5.2 mg/kg twice daily.

IMPAACT P1090 is evaluating the drug in treatment-naive and -experienced children aged two months to six years.[26] 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 treatment of adults 18 years old and above with viral load less than 100,000 copies/mL. The originator company Janssen has submitted applications for an adolescent indication (12 to 18 years) to the FDA and EMA.

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.[27]

Based on pharmacokinetics, tolerability and efficacy data at four weeks, a dose of 25mg RPV once daily with food was selected[28] – providing comparable exposure to that in adults. This dose was effective and generally well tolerated over 24 weeks for the treatment of ART-naive adolescents with viral load less than 100,000 copies/mL.[29] PAINT is ongoing.

IMPAACT P1111 is planned in children from two weeks to less than 12 years of age.[30] A granule formulation of RPV is in development.

RPV is also being developed as an intramuscular long acting formulation for treatment and prevention (see cabotegravir below).

Doravirine

Once-daily 100 mg doravirine looks promising in adults (see antiretroviral pipeline chapter).

The originator company Merck has submitted pediatric plans to FDA and EMA for doravirine as a single agent and as an FDC: doravirine plus TDF plus 3TC. The plans are being discussed with the regulatory agencies. The current aim is to enroll populations similar to those in adult phase III studies: treatment-naive and stable experienced patients for switch studies.

PROTEASE INHIBITOR

Lopinavir/ritonavir

As described above, the FDA has recently tentatively approved LPV/r pellets for young children. DND*i* and Cipla are now developing a more palatable version of LPV/r granules in 4-in-1 FDCs with two NRTIs, ABC or AZT, plus 3TC. The granule formulation of LPV/r will be tested in HIV-negative adults very soon. The plan is to have the 4-in-1 by 2016.

INTEGRASE INHIBITORS

Raltegravir

RAL is approved for infants and children from four weeks of age.[31] For the youngest age group (four weeks to less than two year olds, weighing 3 kg to 20 kg) it is formulated as an oral suspension. This comes in single-use packets of banana-flavored granules containing 100 mg of RAL, which is suspended in 5 mL of water giving a final concentration of 20 mg/mL.

For older children there is an orange-banana flavored, chewable pediatric formulation. Because the formulations are not bioequivalent, chewable tablets and the oral suspension are not interchangeable and have specific guidance.

The pediatric program is ongoing including in neonates below four weeks of age (both HIV-infected and exposed) infants. [32,33, 34, 35, 36, 37]

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). It is also being developed as part of E/C/F/TAF.

Exposures in adolescents 12 to 18 years old receiving 150 mg once daily EVG plus a RTV-boosted protease inhibitor-optimized background regimen, showed comparable exposures to those seen in adults.[38]

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.[39]

In this study, both pediatric formulations were bioequivalent to the adult formulation. The RTV-boosted formulations are being evaluated in children in an ongoing phase II/III study in children aged 4 weeks to 18 years of age.[40]

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

E/C/F/TDF

EVG is also being studied in treatment-naive adolescents aged 12 to 18 years as part of the adult FDC, E/C/F/TDF containing EVG 150 mg, COBI150 mg, FTC 200 mg and TDF 300 mg.[41] Early data has shown similar exposures of all the individual agents to adults and good virologic suppression. [42] Study of E/C/F/TDF in adolescents and children continues.

Dolutegravir

DTG is manufactured by ViiV and is approved for adults and children aged 12 years and above. It is currently under investigation 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.

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 in age de-escalated cohorts. [43] Preliminary (24 week) data from the first cohort of the study were included with the adult regulatory submissions and led to the recent approvals.

Twenty-four week data have been presented for children aged 6 to 12 years and 48-week data for children and adolescents aged 12 to 18 years.

Treatment-experienced but integrase inhibitor-naive children (n=11) with viral load greater than 1000 copies/mL were enrolled in an intensive pharmacokinetic evaluation.[44]

Participants received DTG tablets (10, 25, 50mg) dosed at 1 mg/kg once daily (based on weight bands) added to a stable, failing ART regimen, with optimized background therapy added after the pharmacokinetic evaluation performed between days 5 and 10.

Children were a median age of 10 years, had received prior ART 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 exposures comparable to those in adults with the pediatric weight band dose.[45] Both age groups showed good short-term safety and tolerability.

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 to less than 400 copies/mL and 61% less than 50 copies/mL. There were no serious adverse events.[46]

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

A granule formulation is being used for early studies. In a phase I pharmacokinetic study in healthy adult volunteers 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.[47]

Participants received a single dose of DTG as a 50 mg tablet (adult formulation) and as 10 g of granule given: with no liquid; with purified water; with mineral water; or with 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 years of age cohort of IMPAACT P1093. It will be used in the two to six years of age cohort that has begun screening.

The company is developing a dispersible tablet formulation that will be used in future studies and marketed. The granules will not be available commercially.

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

Dolutegravir timeline:

Dispersible tablet formulation end 2015

Pharmacokinetic data from IMPAACT P1093

- from 2 to 6 years mid 2017
- from 4 weeks to 2 years mid 2019

Comparative efficacy

- ODYSSEY (PENTA 20) opens early 2016

DTG/ABC/3TC

Development of a pediatric formulation of the FDC of DTG/ABC/3TC,– currently approved for adults and adolescents aged 12 years and above [48, 49] - is also planned.

The DTG/ABC/3TC PIP requires data from IMPAACT P1093 in two to 12 year old children to inform DTG dosing. Results from the ARROW trial[50] (that found once-daily dosing of ABC and 3TC non-inferior to twice-daily in children) will provide data for ABC/3TC once-daily dosing.

The investigation plan also requires the completion of a DTG/ABC/3TC FDC pediatric study in two to 12 year olds. This will be an open-label, switch design and enroll children who are fully suppressed on ART and integrase inhibitor-naive.

DTG/RPV

The current plan for a pediatric DTG/RPV FDC is as a maintenance regimen in children and adolescents aged six to 18 years and virologically suppressed.

Data from planned adult phase III studies and existing adolescent data from single agents will be used for the 12 to 18 years age group. Providing the adult data supports the maintenance strategy, dosing studies and pediatric FDC development will then go ahead in the 6 to 12 age group.

Cabotegravir and Rilpivirine Long-Acting

Cabotegravir is under investigation as a long-acting formulation with RPV. An age appropriate formulation will be developed for induction and the intramuscular nanosuspension will be the same as for adults.

The final PIP was approved October 2014 and includes pharmacokinetics, safety, tolerability, durability, acceptability and maintenance of cabotegravir and rilpivirine in two to 18 year olds.

There is a waiver for children less than two and a deferral for two to 18 year olds. The PIP will be completed by 2018, so although the idea of long acting formulations might be appealing for children and adolescents, it is some way off.

PHARMACOKINETIC BOOSTER

Cobicistat

COBI is a CYP3A inhibitor with no antiretroviral activity. COBI 150 mg is approved for adults as a booster of atazanavir (ATV) 300 mg or DRV 800 mg, including in co-formulated tablets.[51, 52] It is also under investigation for children and adolescents aged at least six years as a part 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.

COBI is being studied in treatment-experienced children aged three months to 18 years who are suppressed and on RTV boosted ATV- or DRV-containing regimens.[53] The study will switch children from RTV to COBI 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. Reduced dose co-formulations are planned.

CCR5 RECEPTOR ANTAGONIST

Maraviroc

The pediatric maraviroc (MVC) study is still ongoing in children aged two to 18 years who are infected with CCR5-tropic virus (virus variants that use the CCR5 receptor for entry). This drug will not work for people with CXCR4-tropic virus or in dual- or mixed-virus (CCR5/CXCR4) populations.[54]

Dosing of MVC is complex and determined by body surface area and concomitant medications. [55] Wide use of MVC is not expected.

What Needs to be Done?

With a few modifications, most of the recommendations from previous years remain:

Implement WHO recommendations. As simpler formulations identified to implement the guidelines become available (most topically this year LPV/r pellets), countries must ensure that they are swiftly approved and distributed, with appropriate training for health workers.

Ensure that patents are not an obstacle. The MPP is putting a lot of emphasis on pediatric antiretrovirals and has now negotiated patent sharing agreements with ViiV, Gilead, Bristol-Myers Squibb, Merck/MSD and Abbvie – which takes care of the priority products in most low- and middle-income countries with large pediatric HIV epidemics. Licenses for the drugs in development need to make it easy to transfer patent agreements from one age band to another as approval is gained.

Speed up approval. The gap needs to be narrowed between approval of new drugs for adults, children, and neonates. An evidence base to support not always taking a de-escalated age band approach when studying new drugs is needed. Harmonization of regulatory requirements (including age categories and weight bands) between stringent authorities, WHO prequalification, and national authorities is needed to help speed up approval.

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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Preventive Technologies: Antiretroviral and Vaccine Development

By Tim Horn and Richard Jefferys

Though global HIV incidence has declined by an estimated 33% since 2001, more than 2 million people continue to be infected with the virus every year – approximately 6,000 new infections every day.[1] Efforts to reduce infectiousness through the scale-up of testing, engagement in care and supportive services, and access to safe and effective antiretroviral therapy can be credited, in large part, to the annual reductions in new infections that have been observed in many (but certainly not all) regions and populations. And though efforts to optimize HIV care continuum outcomes continue both domestically and internationally, the need for biomedical interventions to protect those most vulnerable to the virus is indisputable.

The development and implementation of, and continuing research on, pre-exposure prophylaxis (PrEP) have brought us significantly closer to a watershed in efforts to end HIV as a global epidemic. Current antiretroviral-based biomedical prevention tools, including approved oral PrEP and microbicide gels in late-stage trials, are not without significant challenges – adherence among them. However, the efficacy data are encouraging, even those limited to subsets of study volunteers: antiretroviral-based biomedical prevention can be highly effective if it is used consistently and correctly.

To address these challenges, which also include potential safety issues, ease of administration, and products that may not be scalable due to cost, there is tremendous interest in antiretrovirals in the preventive technologies pipeline, including agents for oral use, long-acting injectables, and a robust portfolio of products for vaginal and rectal administration: gels, tablets, rings, films, and nanofibers. Knowledge and support of this work are critical, not only because of its epidemic-shifting potential, but because much of it is being led by nongovernmental organizations and academic institutions, both of which are dependent on limited public and philanthropic funding.

An effective HIV vaccine could undoubtedly make a massive contribution to curtailing new infections, but a potentially licensable candidate remains a decade away at best. Recent good news is that key steps have been taken toward an efficacy trial designed to build on the slight but significant success obtained in the RV144 study, which showed a 31% reduction in HIV incidence associated with receipt of a prime-boost vaccine regimen. The new trial will take place in South Africa, and a long-awaited preparatory clinical evaluation of the vaccine components got under way in that country in February.

In a significant development for the field, a collaboration known as the mosaic HIV vaccine research program – involving subsidiaries of a major pharmaceutical company, Johnson & Johnson – is also planning efficacy trials of a combination strategy involving viral vectors and a new, improved gp140 envelope protein boost. As the name of the collaboration indicates, the vectors will encode mosaic HIV antigens, which amalgamate components from diverse viral variants.

As yet, no vaccine has proved capable of inducing the production of broadly neutralizing antibodies (bNAbs), which is the most desired goal. There are potential workarounds, however: an increasing number of highly potent bNAbs have been discovered, and there is great excitement about the possibility of delivering these antibodies by intermittent subcutaneous injections or infusions, an approach called passive immunization. Another idea currently under evaluation is the use of a gene therapy–type strategy described as antibody gene transfer, in which an adeno-associated virus (AAV) vector is employed to deliver a gene encoding a bNAb (or bNAbs) into muscle tissue. The aim is to have the vector churn out a constant supply of the bNAb into the circulation after just a single injection.

Antiretrovirals for Prevention

Table 1. PrEP and Microbicides Pipeline 2015

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
dapivirine (TMC120)	Reverse transcriptase inhibitor	Vaginal ring	International Partnership for Microbicides/ Microbicide Trials Network	Phase III
tenofovir	Nucleotide reverse transcriptase inhibitor	Vaginal gel	CONRAD	Phase III
Truvada (tenofovir DF/emtricitabine) event-driven 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
GSK1265744	Integrase strand transfer inhibitor	Long-acting injectable	ViiV Healthcare/HIV Prevention Trials Network	Phase II
maraviroc, maraviroc + tenofovir DF, maraviroc + emtricitabine	CCR5 inhibitor	Oral	HIV Prevention Trials Network/AIDS Clinical Trials Group	Phase II
rilpivirine (TMC278)	Non-nucleoside reverse transcriptase inhibitor	Long-acting injectable	PATH/HIV Prevention Trials Network	Phase II
tenofovir	Nucleotide reverse transcriptase inhibitor	Rectal gel	CONRAD	Phase II
dapivirine	Reverse transcriptase inhibitor	Vaginal gel	International Partnership for Microbicides	Phase I/II
dapivirine	Reverse transcriptase inhibitor	Thin film polymer	International Partnership for Microbicides	Phase I
maraviroc	CCR5 inhibitor	Vaginal ring	International Partnership for Microbicides/Microbicides Trials Network/U.S. National Institute of Allergy and Infectious Diseases (NIAID)/U.S. National Institute 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
tenofovir	Nucleotide reverse transcriptase inhibitor	Vaginal ring	CONRAD	Phase I
tenofovir	Nucleotide reverse transcriptase inhibitor	Vaginal tablets	CONRAD	Phase I
tenofovir DF	Nucleotide reverse transcriptase inhibitor	Vaginal ring	Albert Einstein College of Medicine	Phase I
tenofovir/emtricitabine	Combined nucleoside and nucleotide reverse transcriptase inhibitors	Vaginal tablets	CONRAD	Phase I
tenofovir + SILCS diaphragm	Reverse transcriptase inhibitor	Vaginal gel, barrier contraception	CONRAD	Phase I

Oral PrEP

Following U.S. Food and Drug Administration (FDA) approval of co-formulated tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) as PrEP in July 2012, two broad objectives have emerged:

- Continued development and implementation of demonstration projects;[2] cost-benefit analyses; educational and messaging campaigns to increase awareness among populations and individuals most at risk for the virus; training and guidelines to shepherd expert and culturally competent prescribing and follow-up practices in a variety of clinical care and community-based settings;[3] 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, drug concentrations in blood and tissues, and, ultimately, effectiveness – the primary focus in this chapter.

TDF/FTC (Truvada)

Topline results from several clinical trials, reported in previous editions of the *Pipeline Report*, have demonstrated the safety and efficacy of co-formulated TDF and FTC as PrEP among men and transgender women who have sex with men, HIV-discordant heterosexual couples, and high-risk HIV-negative heterosexual individuals.[4,5,6,7] These data formed the basis of the July 2012 FDA approval of TDF/FTC as PrEP to reduce the risk of sexually acquired HIV and, along with results from other pivotal clinical trials, the foundation of U.S. clinical practice guidelines supporting PrEP for the prevention of sex- and injection drug use–associated transmission of the virus.[8,9,10]

Though TDF/FTC is available in many countries for the treatment of HIV, it has received regulatory approval as PrEP only in the United States. Applications for approval have been filed in Australia, Brazil, South Africa, and Thailand. In other countries, including those that participated in the regulatory trials that led to U.S. approval (e.g., Botswana, Canada, Ecuador, France, Germany, Kenya, Peru, Tanzania, Uganda, and the United Kingdom), formal requests for regulatory approval have not yet been filed.[11] In the United Kingdom, based in part on the high degree of PrEP efficacy demonstrated in the recently reported PROUD study involving 545 men and transgender women who have sex with men attending sexual health clinics in England (86% efficacy; 90% CI: 58%–96%; P = .0002), advocacy efforts pushing for TDF/FTC's availability as PrEP through the National Health Service are now under way.[12] Encouraging (and superimposable) results from the French National Agency for AIDS Research IPERGAY study have also prompted groups to press the French Agency for the Safety of Health Products to approve a temporary recommendation for the use of TDF/FTC as PrEP.[13]

IPERGAY was a pilot investigation of a somewhat novel dosing strategy for TDF/FTC as PrEP: "event-driven" use, in which two TDF/FTC tablets are taken two to 24 hours before anticipated sexual activity and continued every 24 hours until 48 hours after the last sexual experience.[14] The randomized, placebo-controlled study, which enrolled 414 men and transgender women who have sex with men – 70% of whom reported condomless anal sex within two months prior to study entry – began in 2012 and was unblinded in November 2014 following a favorable interim review of the data. During the nine-month median follow-up, there were two infections in the TDF/FTC group (an annual incidence of 0.94%) and 14 infections in the placebo group (an annual incidence of 6.75%), which translated into an 86% relative reduction in the incidence of HIV infection (95% CI: 40%–99%; P < .002).

On average, IPERGAY volunteers used 16 TDF/FTC (or placebo) tablets a month, or roughly three to four tablets every week; approximately 35% used between 18 and 30 pills a month, or roughly five to seven pills a week. This observation is consistent with data from the iPrEx open-label extension study, which found that PrEP was 100% effective in volunteers using TDF/FTC at least four times a week.[15] In effect, it remains unclear to what extent event-driven oral PrEP is effective in lowering HIV infection risk among men and transgender women who have sex with men and use TDF/FTC less frequently.

Also available are preliminary data from the ADAPT study (HPTN 067).[16] The randomized, open-label trial is exploring three TDF/FTC PrEP dosing schedules: daily use of TDF/FTC; time-driven, involving twice-weekly dosing along with post-sex dosing; and event-driven, involving dosing before and after sex. All three dosing strategies followed a four-week period of once-weekly directly observed dosing. The study has enrolled approximately 500 men, transgender women, and non-transgender women who have sex with men.

The data reported at the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) – limited to TDF/FTC coverage, adherence, and tolerability outcomes – come from the cohort of South African non-transgender women enrolled in the trial. Daily dosing resulted in better full coverage of sex acts (75%) and adherence (76%) compared with time-driven (56% and 65%, respectively) and event-driven (52% and 53%, respectively) dosing. There has been one infection in the daily dosing group and two infections each in the time-driven and event-driven groups; these differences are not statistically significant ($P = 0.87$). The authors suggested that daily dosing may foster better habit formation and provide the most forgiveness for missed doses at observed adherence levels, ultimately supporting current recommendations for daily use of TDF/FTC PrEP in non-transgender women.

Analyses of the other ADAPT study cohorts are ongoing.

Maraviroc (Selzentry)

CCR5-tropic HIV – virus that utilizes the CCR5 coreceptor on CD4 cells to gain entry and establish infection – is responsible for more than 95% of new sexually transmitted infections of the virus.[17,18] Thus, there has been interest in studying the CCR5 antagonist maraviroc for potential use as PrEP. Compared with TDF/FTC, 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.

Findings from laboratory research exploring maraviroc's potential activity as PrEP have been mixed. Administered systemically, the drug penetrates and concentrates well in cervical, vaginal, and rectal tissues.[19,20] A microbicide gel formulation of maraviroc has also been found to be approximately 85% effective at blocking HIV infection of rectal tissues, with drug concentrations similar to those achieved following standard oral dosing.[21] And while oral maraviroc has been reported to prevent HIV infection in a humanized mouse model involving vaginal challenges with the virus,[22] a macaque study did not find that maraviroc protected against rectal challenges with SHIV, despite high concentrations of the drug in rectal tissue.[23] More recently, single doses of maraviroc taken by HIV-negative study volunteers failed to inhibit replication in biopsied rectal tissues incubated with the virus – protection was documented in only a subset of vaginal tissues – as determined by measurements of p24 antigen levels (the validity of which remains unclear).[24]

Three clinical trials of maraviroc 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).[25] It has an estimated enrollment of 600 HIV-negative men who have sex with men and at-risk women, with an anticipated completion date of November 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.

The second trial is MVC-PREP, which is being conducted at Emory University and is evaluating concentrations of maraviroc in the blood and genital tract of HIV-negative women.[26]

The third study, MARAVIPREX, has been concluded, though data are not yet available. It was conducted by the Fundació Lluita contra la SIDA in Barcelona and evaluated the capacity of maraviroc to protect against HIV in samples of rectal mucosa from HIV-negative volunteers.[27]

Tenofovir Alafenamide Fumarate (TAF)/FTC

TAF is a prodrug formulation of tenofovir. Unlike the currently approved 300 mg TDF, another prodrug converted in the blood to the active drug tenofovir diphosphate (TDF-DP) and then taken up into cells, TAF is primarily metabolized and converted to TDF-DP inside cells. Thus, at a much lower dose (25 mg), TAF achieves plasma tenofovir levels that are roughly 90% lower but intracellular concentrations that are approximately four to seven times higher.[28,29] The reduced systemic elimination has the potential for fewer renal- and bone-related toxicities compared with TDF. Though these have not emerged as common or severe adverse events among people using TDF/FTC as PrEP,[30,31] co-formulated TAF/FTC is being eyed as a potentially valued alternative to Truvada.

Gilead Sciences has been primarily focused on developing TAF as a component of co-formulated multidrug tablets for the treatment of HIV. Its TAF/FTC co-formulation, for use in combination with other antiretrovirals for treatment purposes, is being evaluated in a phase III study, with a new drug application (NDA) filed with the FDA in early April requesting approval of the tablet.

Evaluations of TAF/FTC's pharmacokinetics (PK) and pharmacodynamics (PD) as PrEP in animals are being conducted, and data from these studies are expected sometime in the second half of 2015.[32] Information pertaining to TAF/FTC's development is expected from the company following the release of the animal data.

Also of interest is a subdermal implant – a sustained-release delivery system similar to that used for insertable contraceptive rods (e.g., Norplant) – containing TAF. It is being developed by the Monrovia, California–based Oak Crest Institute for Science, with encouraging animal PK data – including TFV-DP concentrations in peripheral blood mononuclear cells that are 30 times higher than those associated with oral daily TDF/FTC PrEP dosing in humans – recently published.[33]

Long-Acting (LA) Formulations

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 nanosuspension formulations of antiretrovirals with PrEP potential, which may allow for monthly or quarterly, rather than daily, dosing. The drugs furthest along this development path are long-acting cabotegravir (CAB LA), ViiV Healthcare's integrase strand transfer inhibitor (and dolutegravir analog), and long-acting rilpivirine (RPV LA), Janssen's non-nucleoside reverse transcriptase inhibitor. Both are administered via intramuscular (IM) injection.

Four nonhuman primate studies have demonstrated CAB LA's protective effects against repeated intrarectal and intravaginal SHIV challenges.[34,35,36,37] Two of the four studies have confirmed a relationship between plasma drug concentrations (specifically the protein-adjusted 90% inhibitory concentration) and protection against intrarectal and intravaginal protection.[36,37] In humans, concentrations of CAB in vaginal, cervical, and rectal tissues following both oral dosing and long-acting IM injections are significantly reduced, compared with plasma levels, and plasma concentrations can vary based on body weight and sex (the drug is more rapidly eliminated from men's versus women's bodies).[38] It is not expected that these findings will affect CAB LA's protective effects; an 800 mg dose (two 400 mg IM injections) every 12 weeks – the dose currently being

evaluated in PrEP clinical trials – results in drug levels that are significantly higher than the concentration plasma targets previously established for protection.[39]

Two phase II studies of CAB LA are ongoing. ÉCLAIR, being conducted in the United States by ViiV Healthcare, enrolled approximately 120 at-risk men (60% men who have sex with men).[40] Volunteers are receiving 30 mg daily oral dosing or placebo for four weeks. Following a one-week washout period, IM injections of 800 mg CAB LA or placebo will be administered every 12 weeks for a total of three injections. The second study, HPTN 077, is currently enrolling approximately 176 HIV-negative volunteers – 60% of the participants will be women – in the United States, South America, and sub-Saharan Africa and will be evaluating three 800 mg IM injections 12 weeks apart.[41] The primary objective of both studies is to assess the safety, tolerability, and acceptability of CAB LA; only men and women at low to minimal risk of HIV infection are being recruited.

Encouraging phase I results from a study evaluating the PK of RPV LA in plasma, the genital tract in women, and the rectum in men were published last year.[42] More recently, however, preliminary data reported at the 2014 HIV Research for Prevention conference in Cape Town suggest that RPV LA's activity in rectal versus cervicovaginal tissues may differ considerably.[43] Though RPV levels following single 600 mg and 1,200 mg (2 $\times$ 600 mg) doses were higher in vaginal fluids versus rectal fluids, rectal tissues were found to have twice the concentrations of RPV compared with vaginal tissues. In fact, biopsied rectal cells were fully resistant to HIV nearly two months after the 1,200 mg RPV LA injections were given, whereas the vaginal and cervical cells appeared to be no better protected from HIV following either dose of the drug.

The implications of these findings, particularly those based on ex vivo pharmacodynamic testing, are not clear. It is possible that women require multiple doses to achieve cervicovaginal tissue concentrations required for protection. A phase II clinical trial being conducted by the HIV Prevention Trials Network (HPTN 076) and now open to enrollment will therefore need to proceed cautiously.[44] Following an oral lead-in period, 132 HIV-negative women considered to be at low risk for HIV infection will receive IM injections of 1,200 mg RPV LA or placebo, once every eight weeks, over a 40-week period. The study is to be conducted at four sites in the United States, South Africa, and Zimbabwe.

Microbicides: Vaginal and Rectal Gels

Phase III testing of a gel containing 1% tenofovir – the only vaginal microbicide to reach late-stage clinical trials – has yielded disappointing results. The preliminary data from FACTS 001, which was conducted to confirm the results from the phase IIb trial CAPRISA 004 demonstrating a 39% reduction in HIV risk among women using the gel,[45] were reported at the 2015 CROI in Seattle.[46]

The FACTS 001 trial was conducted by CONRAD in collaboration with the Follow-on African Consortium for Tenofovir Studies (FACTS) and the U.S. Agency for International Development (USAID). The trial enrolled 2,059 women at increased risk for HIV in South Africa. The median age at study entry was 23 years; 89% of participants were unmarried; 42% were seropositive for herpes simplex virus 2 (HSV-2); roughly 30% reported having used condoms consistently in the four weeks prior to their baseline visit; and 62% lived with their parents. As in CAPRISA 004, FACTS 001 volunteers were instructed to use the tenofovir gel or matching placebo within 12 hours before and 12 hours after intercourse (BAT-24 regimen); the VOICE study required daily microbicide use, which may have contributed to the poor adherence outcomes and null findings.[47]

A total of 123 HIV infections occurred: 61 in the tenofovir group and 62 in the placebo group (incidence rate ratio: 1.0; 95% CI: 0.7–1.4). Both groups had a 4% incidence rate of infection (95% CI: 3.1%–5.2%).

Participants used the gel during an average of 50%–60% of sex acts per month, based on returned applicators and self-reported number of sex acts, with 13% of participants using the gel during intercourse more than

80% of the time. A substudy analysis of 214 women in the tenofovir-treated group showed that detection of drug in genital fluids – notably a drug level consistent with having used the microbicide within the past 10 days – was associated with a 52% reduction in HIV acquisition (hazard ratio: 0.52; 95% CI: 0.27–0.99; P = .04). Participants with no tenofovir detected in genital samples were five times more likely to become infected. Thus, while it is possible to conclude that the gel was effective for those who used it consistently, use in the overall study population was too low to confirm the gel's effectiveness in the gold-standard intention-to-treat analysis.

Some scientists have argued that these results call into question the practicality and acceptability of gel-based microbicides and may signal the end of the line for the approach.[48]

Additional results from FACTS 001 are anticipated, including HSV-2 transmission risk data; in CAPRISA 004 and VOICE, 1% tenofovir gel use was associated with a 51% and 46% reduced risk of acquiring HSV-2, respectively.[45,49] Also forthcoming are data from CAPRISA 008, an open-label study providing additional safety data and an evaluation of the feasibility and effectiveness of providing 1% tenofovir gel to HIV-negative women through family planning clinics in KwaZulu-Natal, South Africa.[50]

A reduced-glycerin 1% 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 help minimize gastrointestinal side effects.[51] The trial is evaluating the safety and acceptability of daily or episodic (applied before and after receptive anal intercourse) reduced-glycerin 1% tenofovir gel, compared with daily oral tenofovir/emtricitabine, in 105 HIV-negative men who have sex with men and transgender women in Peru, South Africa, Thailand, Puerto Rico, and the United States.[52] Results, along with plans for an efficacy trial, are expected in early 2016.

The Population Council is developing PC-1005, 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.[53,54] Gels containing zinc acetate and carrageenan have also been shown to protect against HSV-2 vaginal and rectal challenges in mice and human cervical tissue samples.[55,56] Additionally, carrageenan has activity against human papillomavirus (HPV) infection.[57,58,59,60]

A phase I safety, PK, and acceptability evaluation of PC-1005, compared with a placebo gel, is under way with an estimated enrollment of 35 HIV-negative women.[61]

Compounds in preclinical development include a gel containing griffithsin (University of Pittsburgh), a lectin derived from algae that has activity against HIV and HSV; SR-2P (Stanford Research Institute), a gel composed of two polymers and containing tenofovir and the antiherpetic acyclovir; and IQP-0528, a pyrimidinedione analogue with non-nucleoside reverse transcriptase and entry inhibitor activities (ImQuest BioSciences).

Microbicides: Intravaginal Rings (IVRs)

With a growing body of data suggesting that antiretroviral-based prevention modalities are effective for women vulnerable to HIV infection, provided that adherence levels consistent with protection can be achieved, there has been considerable interest in more user-friendly technologies. Polymeric IVRs, similar to those used to control the release of estrogens or progestogens that provide contraceptive protection, are one such technology and are currently in various stages of clinical and preclinical development.

The most clinically advanced candidate is a silicone elastomer IVR containing 25 mg dapivirine (TMC120), a non-nucleoside reverse transcriptase inhibitor licensed to the International Partnership for Microbicides (IPM)

by Janssen Pharmaceuticals. IPM has studied the compound in 16 phase I/II clinical trials in Africa, Europe, and the United States. In all studies, dapivirine has been found to be safe and well tolerated, providing the basis for larger studies that will determine whether IPM's dapivirine IVR is safe and effective in preventing HIV.

Two late-stage clinical trials are fully enrolled and ongoing: the Microbicide Trials Network's ASPIRE study (MTN 020) and the IPM's Ring Study (IPM 027).[62,63] ASPIRE, a phase III trial being conducted at sites in Malawi, South Africa, Uganda, Zambia, and Zimbabwe, has randomized approximately 3,500 HIV-negative women to receive the dapivirine IVR or a matching placebo IVR, which is replaced once a month for a year. The Ring Study, a phase II/III evaluation taking place in South Africa and Uganda, is comparing the dapivirine IVR to a placebo IVR, inserted once every week over 24 months, in nearly 2,000 HIV-negative women in South Africa and Rwanda. Open-label extensions of ASPIRE and the Ring Study are expected to begin after both trials are completed next year.

A rationale for developing IVRs 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.[64] 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, were mixed, due largely to unsatisfactory levels of maraviroc in cervical tissues and plasma samples.[65] The IPM has been redeveloping the combination IVR with plans for a second phase I study.

More recently, there have been encouraging data from the European Combined Highly Active Antiretroviral Microbicides (CHAARM) program's preclinical evaluations of silicone elastomer IVRs containing dapivirine or the protease inhibitor darunavir.[66] In macaques, all drugs were detectable in blood and vaginal fluid samples, as well as all tissue samples, with the highest concentrations in vaginal and cervical tissues and the lowest concentrations in uterine and rectal tissues. Based on these results, and given the continued progress of the dapivirine vaginal IVR, the authors recommended continued development of a co-formulated dapivirine/darunavir ring as a second-generation HIV microbicide candidate.

Antiviral IVRs in various stages of preclinical development include those containing tenofovir and acyclovir (Auritec Pharmaceuticals); tenofovir and IQP-0528; and griffithsin and carrageenan (Population Council).

Microbicides: Vaginal Tablets, Films, and Nanofibers

Groups are evaluating the potential utility of vaginal tablets and novel delivery systems, such as dissolvable films and nanofibers, which may be easier to use and cheaper to manufacture than 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.[67,68,69] A phase I placebo-controlled safety and PK 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 is ongoing.[70]

Preliminary results from a phase I clinical trial (FAME 02) comparing the safety, drug absorption, and drug distribution of a dapivirine film with dapivirine gel were reported at CROI 2014.[71] Plasma levels of dapivirine were comparable across the film and gel arms, suggesting that both products can deliver drugs with similar efficacy. 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.[71]

A cellulose-based film containing tenofovir is in a phase I trial (FAME 04).[72] The study, being conducted by CONRAD in collaboration with investigators at Magee-Womens Hospital of the University of Pittsburgh Medical Center, is evaluating 10 mg and 40 mg formulations of the film compared with 1% tenofovir gel, matching placebo gel, and matching placebo film. Approximately 80 women are to be enrolled in the trial.

The University of Washington, in collaboration with the Population Council, is evaluating the potential utility of biodegradable electrospun nanofibers containing agents including tenofovir, griffithsin, or carrageenan with activity against HIV, HSV, and HPV.

Contraceptive-Inclusive Multipurpose Prevention Technologies (MPTs)

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 cross-protective options that women can easily use and that do not require the cooperation, consent, or knowledge of their sexual partners. In turn, there is tremendous interest in the development of MPTs that can double as contraception and biomedical prevention against HIV and other 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 two MPT IVRs – all of which employ the contraceptive hormone levonorgestrel, a synthetic progestogen that has been studied and used extensively and is therefore considered 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 (MZCL) over a 90-day period: it is being developed by CONRAD.[73] A phase I safety, PK/PD, and acceptability study is under way.[74]
- A vaginal ring containing MIV-150, zinc acetate, carrageenan, and levonorgestrel to protect against pregnancy, HIV, HSV-2, and human papillomavirus (HPV): preclinical evaluations by the Population Council are ongoing, with one recent analysis finding that the four-way ring protected 11 of 12 macaques against SHIV challenges and resulted in a 30% reduction in HSV-2 infection.[75]

On-demand products include:

- A reformulated 1% 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 are being undertaken by CONRAD.
- Polyphenylenecarboxymethylene (PPCM), a polymer-based gel being developed by Scottsdale, Arizona–based Yaso Biotech, has activity against HIV, HSV, HPV, chlamydia, and gonorrhea and has contraceptive activity as a nonsurfactant spermicide.[76,77,78] It has been in preclinical development for several years.

Providing PrEP in Prevention Trials

The clear efficacy of PrEP has implications for the conduct of clinical trials of HIV prevention interventions. The approach up until now has been for all participants to be offered a standard-of-care prevention package including counseling and condoms, and the effect of a given intervention is evaluated against this background. The question of how to incorporate PrEP into the standard of care now needs to be considered.

When the first PrEP efficacy data emerged, researchers conducting an ongoing vaccine efficacy trial, HVTN 505, initiated extensive consultations with community and other stakeholders, and ultimately, "the preferred option was to reintensify education and counseling about PrEP and develop a referral system rather than to provide the drug directly at trial sites as part of the study."[79] Ethicists have since suggested that PrEP should be offered as part of the standard-of-care prevention package,[80] and investigators planning future vaccine trials have indicated that this will be the case as long as agreement can be obtained from relevant local health authorities.[81]

Issues also arise for the design of trials aiming to assess the efficacy of biomedical alternatives to TDF/FTC PrEP. Researchers have suggested that noninferiority trial designs would be feasible but would probably require large sample sizes, and the results could be challenging to interpret.[82] The same authors note that in some settings where TDF/FTC efficacy has been reported to be low, it may be possible to evaluate the superiority of alternatives.

Preventive Vaccines, Passive Immunization, and Antibody Gene Transfer

Table 2. HIV Vaccines, Passive Immunization, and Antibody Gene Transfer Pipeline 2015

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
HIV VACCINES			
pGA2/JS7 DNA + MVA/HIV62	**Prime:** DNA vaccine **Boost:** modified vaccinia Ankara strain (MVA) vector Both encoding Gag, Pol, and Env proteins from HIV-1 clade B	GeoVax/NIAID	Phase IIa
ALVAC-HIV vCP1521	Canarypox vector encoding HIV-1 CRF01_AE Env, clade B Gag, the protease-encoding portion of the Pol protein, and a synthetic polypeptide encompassing several known CD8+ T-cell epitopes from the Nef and Pol proteins	Sanofi Pasteur/U.S. Military HIV Research Program (MHRP)/NIAID	Phase II
AIDSVAX B/E	AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	U.S. Army Medical Research and Materiel Command	Phase II
HIVIS 03 DNA + MVA-CMDR	**Prime:** HIVIS DNA encoding Env (A, B, C), Gag (A, B), reverse transcriptase (B), and Rev (B) proteins **Boost:** MVA-CMDR encoding Env (E), Gag (A), and Pol (E) proteins	Vecura/Karolinska Institutet/Swedish Institute for Infectious Disease Control/ MHRP	Phase II
LIPO-5	Five lipopeptides composed of cytotoxic T lymphocyte (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 composed 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
Ad26.Mos.HIV MVA-Mosaic gp140 protein	Adenovirus serotype 26 (Ad26) vectors encoding mosaic Env, Gag, and Pol MVA vectors encoding mosaic Env, Gag, and Pol gp140 protein boost	CruceII/NIAID/MHRP/International AIDS Vaccine Initiative (IAVI)/Beth Israel Deaconess Medical Center	Phase I/IIa
ALVAC-HIV (vCP2438) + bivalent subtype C gp120/MF59	Canarypox vector encoding HIV-1 clade C gp120, clade B gp41, Gag, and protease + protein boost comprising two clade C Env proteins (TV1.Cgp120 and 1086.Cgp120)	NIAID/HIV Vaccine Trials Network (HVTN)/Bill & Melinda Gates Foundation/South African Medical Research Council/Sanofi Pasteur/ Novartis Vaccines	Phase I/II

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
DNA-C + NYVAC-C	**Prime:** DNA vaccine encoding clade C Env, Gag, Pol, and Nef proteins **Boost:** NYVAC-C attenuated vaccinia vector encoding clade C Env, Gag, Pol, and Nef proteins	GENEART/Sanofi Pasteur/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	Phase I/II
DNA-HIV-PT123 AIDSVAXB/E	DNA vectors encoding HIV-1 clade C Gag, gp140, and Pol-Nef AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	NIAID	Phase Ib
Ad26.ENVA.01	Adenovirus serotype 26 vector encoding the HIV-1 clade A Env protein	CruceII/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 encoding the HIV-1 clade A Env protein	CruceII/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 encoding HIV-1 clade A Gag, reverse transcriptase, integrase, and Nef, the other encoding HIV-1 clade A Env (gp140)	IAVI/University of Rochester	Phase I Prime-boost Phase I w/ GSK HIV vaccine 732461 (F4)
Ad5HVR48.ENVA.01	Hybrid adenovirus vector consisting of a backbone of serotype 5 with the hexon protein from serotype 48; encodes HIV-1 clade A Env	CruceII/NIAID	Phase I
Cervicovaginal CN54gp140-Hsp70 conjugate (TL01)	HIV-1 clade C gp140 protein with heat shock protein 70 (Hsp70) adjuvant, 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	NIAID/IPPOX/EuroVacc/HVTN	Phase I
DNA + Tiantan vaccinia vector	Prime: DNA vector, with or without electroporation Boost: Replication-competent recombinant Tiantan vaccinia strain vector Both encoding Gag, Pol, and Env proteins from HIV-1 CN54	Chinese Center for Disease Control and Prevention/National Vaccine and Serum Institute/Peking Union Medical College	Phase I
EN41-FPA2	Gp41-based vaccine delivered intranasally and intramuscularly	PX'Therapeutics/European Commission	Phase I
GEO-D03 DNA + MVA/HIV62B	**Prime:** DNA vaccine with granulocyte-macrophage colony–stimulating factor (GM-CSF) adjuvant **Boost:** MVA vector Both vaccines encode Gag, Pol, and Env proteins from HIV-1 clade B and produce virus-like particles (VLPs)	GeoVax/NIAID	Phase I
GSK HIV vaccine 732461 (F4)	Gag, Pol, and Nef fusion protein in proprietary adjuvant AS01	GlaxoSmithKline	Phase I Prime-boost Phase I w/ Ad35-GRIN

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
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	Multiantigen DNA vaccine encoding 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 encoding HIV-1 clade A Gag, reverse transcriptase, integrase, and Nef, and the other encoding HIV-1 clade A Env (gp140)	IAVI/Profectus Biosciences/ Ichor Medical Systems	Phase I
MAG-pDNA, $rVSV_{IN}$ HIV-1 Gag	Multiantigen DNA vaccine encoding the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVAX, IL-12 pDNA adjuvant, attenuated replication-competent recombinant vesicular stomatitis virus (rVSV) vector encoding HIV-1 Gag	Profectus Biosciences/HVTN	Phase I
MV1-F4-CT1	Recombinant measles vaccine vector encoding HIV-1 clade B Gag, Pol, and Nef	Institut Pasteur	Phase I
MVA.HIVA	MVA vector encoding HIV-1 clade A Gag protein and 25 CD8+ T-cell epitopes	Impfstoffwerk Dessau-Tornau/ University of Oxford/Medical Research Council/University of Nairobi/Kenya AIDS Vaccine Initiative	Phase I in infants born to HIV-positive (PedVacc002) and HIV-negative (PedVacc001) mothers
MVA HIV-B	MVA vector encoding HIV-1 Bx08 gp120 and HIV-1 IIIB Gag, Pol, and Nef	Hospital Clinic of Barcelona	Phase I
PENNVAX-G DNA + MVA-CMDR	**Prime:** DNA vaccine encoding HIV-1 clade A, C, and D Env proteins and consensus Gag protein **Boost:** MVA-CMDR live attenuated MVA vector encoding HIV-1 clade CRF_AE-01 Env and Gag/Pol proteins DNA component administered intramuscularly via either Biojector 2000 or CELLECTRA electroporation device	NIAID/MHRP/Walter Reed Army Institute of Research	Phase I
PolyEnv1 EnvDNA	Vaccinia viruses encoding 23 different Env proteins and DNA vaccine encoding multiple Env proteins	St. Jude Children's Research Hospital	Phase I
pSG2.HIVconsv DNA + ChAdV63.HIVconsv or MVA.HIVconsv	**Prime:** DNA vaccine pSG2 **Boost:** chimpanzee adenovirus vector ChAdV63 or MVA vector All contain the HIVconsv immunogen, designed to induce cross-clade T-cell responses by focusing on conserved parts of HIV-1	University of Oxford	Phase I
Ad35-ENVA	Adenovirus serotype 35 vector encoding HIV-1 clade A Env	Vaccine Research Center/NIAID	Phase I
$rVSV_{IN}$ HIV-1 Gag	Attenuated replication-competent rVSV vector encoding HIV-1 Gag	Profectus Biosciences/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, and 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 encoding HIV-1 clade A Gag, reverse transcriptase, integrase, and Nef	IAVI/DNAVEC	Phase I
LIPO-5, MVA HIV-B, GTU-MultiHIV	Five lipopeptides comprising CTL epitopes from Gag, Pol, and Nef proteins MVA vector encoding Env, Gag, Pol, and Nef proteins from HIV clade B DNA vector encoding fusion protein comprising elements from six different HIV proteins Given in four different prime-boost combinations	INSERM-ANRS	Phase I Phase II

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 or as an aqueous formulation for tonsillar administration	NIAID/PaxVax	Phase I
DNA Nat-B Env, NYVAC Nat-B Env DNA CON-S Env, NYVAC CON-S Env DNA mosaic Env, NYVAC mosaic Env	**Prime:** DNA vector encoding Nat-B, CON-S, or mosaic Env proteins **Boost:** NYVAC vectors encoding Nat-B, CON-S, or mosaic Env proteins	HVTN/IPPOX/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, U.K.	Phase I
DNA, MVA-C, CN54rgp140 + GLA-AF	DNA vectors encoding a Gag-Pol-Nef polypeptide and gp140 Env protein, both from clade C MVA-C vector encoding Gag-Pol-Nef and gp120 Env protein from clade C HIV-1 clade C gp140 protein and GLA-AF, delivered intramuscularly	Imperial College London/Medical Research Council/Wellcome Trust	Phase I
GTU-MultiHIV	DNA vector encoding fusion protein comprising elements from six different HIV proteins, administered by intramuscular, intradermal, or transcutaneous routes	Imperial College London/European Commission - CUT'HIVAC Consortium	Phase I
DNA Nat-B Env DNA CON-S Env DNA mosaic Env MVA-CMDR	**Prime:** DNA vector encoding Nat-B, CON-S, or mosaic Env proteins **Boost:** MVA vector encoding Env (E), Gag (A), and Pol (E) proteins	NIAID/ CHAVI/IPPOX/MHRP/HVTN	Phase I
Trimeric gp140	Protein vaccine consisting of a trimeric gp120	CruceII/NIAID/Beth Israel Deaconess Medical Center	Phase I
MVA mosaic	MVA vectors encoding HIV-1 mosaic proteins	CruceII/MHRP/NIAID/Beth Israel Deaconess Medical Center	Phase I
DNA-HIV-PT123 AIDSVAXB/E	DNA vectors encoding HIV-1 clade C Gag, gp140, and Pol-Nef AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	EuroVacc/IAVI/Uganda Medical Research Council/Uganda Virus Research Institute Uganda Research Unit on AIDS/Centre Hospitalier Universitaire Vaudois	Phase I
Oral Ad26	Orally administered replicating adenovirus serotype 26 vector encoding mosaic Env protein	IAVI/University of Rochester/Beth Israel Deaconess Medical Center	Phase I
PENNVAX-GP HIV-1 DNA vaccine IL-12 DNA adjuvant	DNA vector encoding Gag, Pol, and Env proteins + DNA vector encoding IL-12 adjuvant, delivered via intradermal or intramuscular electroporation	NIAID	Phase I
PASSIVE IMMUNIZATION			
VRC01	Monoclonal bNAb administered subcutaneously or intravenously	NIAID	Phase I (adults and HIV-exposed infants)
ANTIBODY GENE TRANSFER			
rAAV1-PG9DP	Recombinant AAV vector encoding the PG9 broadly neutralizing antibody	IAVI/NIAID/Children's Hospital of Philadelphia	Phase I

HIV Vaccines

When HIV was first identified more than three decades ago, it was initially thought that the road to a vaccine might be relatively short and straightforward. Instead, it has proved long and winding, with many sharp, disorienting turns and deceptive cul-de-sacs. But important lessons have been learned en route, and, in 2015, a variety of possible approaches are proceeding toward the hoped-for destination of an effective, licensable product.

Leading the way is the relative juggernaut of the Pox-Protein Public-Private Partnership (P5), which includes the Bill & Melinda Gates Foundation, the HIV Vaccine Trials Network (HVTN), Novartis Vaccines and Diagnostics, Sanofi Pasteur, the South African Medical Research Council, the U.S. Military HIV Research Program, and the U.S. National Institute of Allergy and Infectious Diseases (NIAID)/Division of AIDS. The P5 was established to build on the borderline but significant 31% reduction in the risk of HIV acquisition observed in the RV144 trial, which tested a prime-boost combination of an ALVAC canarypox vector and AIDSVAX, a gp120-based protein vaccine, in over 16,000 Thai individuals.[83] A particular focus is whether it might be possible to duplicate or even improve an apparently higher efficacy of 60% that was evident early on in RV144, at one year of follow-up. After an excruciatingly long period of preparation (partly due to the need to manufacture a new gp120 protein boost to replace AIDSVAX), the work of P5 is now approaching the point where new efficacy trials can be launched.

Recently, two key milestones have been reached: a study of the RV144 regimen completed in South Africa – the site chosen for the follow-up efficacy trials – found that it induced similar immune responses, with evidence of slightly higher response rates than in the Thai study population.[84] And in February of this year, a trial began that will evaluate adapted versions of the RV144 vaccines designed specifically for use in South Africa: an ALVAC vector encoding a gp120 envelope protein from the prevalent clade C virus (in addition to gp41, Gag, and protease from clade B) and an envelope protein boost comprising two gp120s derived from clade C HIV isolates formulated with the MF59 adjuvant.[85] The trial is designated HVTN 100, and, if several key immune response targets are met,[81] it will set the stage for a far larger 5,400-person phase III efficacy trial (HVTN 702) with the potential to lead to licensure if the regimen works well enough. The current hope is to start HVTN 702 in 2016.

P5 is also conducting a program that aims to identify correlates of vaccine-induced protection against HIV acquisition, and a key part of this effort involves a complex phase I/IIa adaptive trial (HVTN 701) that currently has an estimated start date of 2018 and intends to assess the efficacy of multiple prime-boost combinations.[86]

The identification of correlates of protection would provide much-needed guidance to the HIV vaccine field. In their absence, there is uncertainty about whether any of the vaccines in the current pipeline might be effective. None has shown an ability to induce antibody responses capable of potently neutralizing a broad array of HIV isolates from different clades (bNAbs), which is still the ideal goal of vaccination.

An alternative mechanism of HIV prevention is elimination of virus-infected cells before systemic infection takes hold. The task is challenging; recent studies in the SIV/macaque model have shown that the long-lived virus reservoir is established in less than three days.[87] Evidence from RV144 suggests that this may have been achieved by antibody-mediated effector activities such as antibody-mediated cellular cytotoxicity (ADCC) and antibody-mediated cellular phagocytosis (ADCP)[88,89] (processes involving antibodies binding to infected cells and flagging them for destruction by natural killer cells or monocytes). The possible role of non-neutralizing antibody effector mechanisms in the RV144 outcome has spurred intense interest in the topic, and researchers are now exploiting new technologies to identify antibody properties associated with different effector functions.[90,91] This work promises to help identify vaccine candidates most likely to induce potent ADCC and ADCP.

There is evidence from animal models that the presence of effector CD8+ T cells at sites of virus exposure might also be capable of controlling and, in some cases, extinguishing infection. This salutary outcome has been observed in studies of replicating cytomegalovirus (CMV) vector.[92] Although CMV has yet to be adapted for use in humans, several other replicating virus vectors are in clinical trials, and a new addition this year is an orally administered adenovirus serotype 26 (Ad26) vaccine being tested at the University of Rochester, in collaboration with the International AIDS Vaccine Initiative (IAVI) and Beth Israel Deaconess Medical Center (BIDMC).[93] The construct is one of many now incorporating mosaic HIV antigens, which are distilled from multiple viral variants and have shown promise in macaque experiments; interestingly, evidence suggests that antibody effector functions are involved.[94]

IAVI and BIDMC are partners in a larger collaborative endeavor informally known as the mosaic HIV vaccine research program, which aims to conduct a comprehensive assessment of whether the mosaic antigen approach can contribute to protection in humans. The other contributors are Crucell Holland B.V., one of the Janssen Pharmaceutical Companies of Johnson & Johnson, the U.S. Military HIV Research Program (MHRP), the Ragon Institute, and NIAID. The current goal is to test Ad26 and modified vaccinia Ankara (MVA) strain vectors encoding mosaic HIV antigens along with a gp140 envelope protein in various prime-boost combinations. The gp140 is designed to better mimic the natural structure by preserving its trimeric form. Another new vaccine trial that began during the past year is the first evaluation of this trimeric gp140 in humans.[95]

Depending on the outcome of immunogenicity studies in humans and challenge experiments in macaques, the mosaic HIV vaccine research program's aim is to conduct two phase IIb/III efficacy trials in high-risk populations, one in Africa and Asia and the other in the United States, Latin America, and Europe, possibly beginning as early as 2017.[96]

While news of plans for efficacy trials in addition to the P5 program is welcome for the vaccine field, the inclusion of an adenovirus vector might raise some eyebrows. Receipt of an Ad5 vector was associated with a significant increase in the risk of HIV infection in two previous studies,[97] and no definitive explanation for this adverse outcome exists[98] (an issue discussed in the *2014 Pipeline Report*). Alternative-serotype vectors such as Ad26 have been developed based on the idea that the problem was restricted to Ad5, but the evidence is equivocal, and there is a theoretical possibility that it could extend to other adenoviruses. Researchers affiliated with the MHRP have recently shown that Ad5-specific CD4+ T cells are particularly susceptible to HIV infection and argued that responses to alternative vectors should be similarly analyzed in vitro and carefully evaluated in animal models in order to gain a better understanding of whether they might also increase acquisition risk.[99] Offering some preliminary reassurance, results from a phase I trial of the Ad26 vector have demonstrated no significant increases in vector-specific CD4+ T cells in blood or mucosal tissue.[100]

Early safety and immunogenicity results from several other adenovirus vector trials have been published or presented over the past year, including Ad35 and a hybrid of Ad5 and Ad48 (Ad5HVR48.EnvA.01).[101] The overall theme is that the vaccines are safe and immunogenic, but, given the lack of clarity about correlates of protection, further work will be needed to parse which candidates and combinations might be most worthy of further evaluation. Ad35 has been combined with a new replicating Sendai virus vector, with no safety issues emerging; the order of administration was found to significantly influence whether primarily T-cell or antibody responses were induced.[102] In a separate study in which Ad35 was combined with a fusion protein named F4 (developed by GlaxoSmithKline), both T-cell and antibody responses were invoked, and there was some evidence of CD8+ T cell–mediated inhibition of HIV replication as measured by an in vitro assay, albeit not to levels typically observed in HIV controllers.[103]

Elsewhere in the pipeline, the laboratory of Thomas Lehner in the United Kingdom has been working for many years on a novel strategy that aims to inhibit HIV via induction of chemokines and the antiviral restriction factor APOBEC3G. The vaccine links CN54gp140, an envelope protein from a clade C HIV isolate, with a

heat shock protein 70 (Hsp70) adjuvant (heat shock proteins are naturally produced by cells under conditions of stress). Results from a first phase I trial involving nontraumatic intravaginal administration were published late last year, and the researchers report evidence of chemokine-mediated CCR5 downregulation along with induction of APOBEC3G. An in vitro assessment of the ability of participants' peripheral blood mononuclear cells to support HIV replication indicated that vaccination was associated with reduced infectivity.[104]

Another unconventional vaccine approach that has received attention recently involves the use of a probiotic to deliver virus antigens, leading to the development of immune responses that dampen antiviral activity rather than enhance it. The brainchild of Jean-Marie Andrieu, the vaccine has demonstrated a surprisingly high degree of protection against SIV challenges in macaque studies.[105,106,107] The mechanism appears to relate to the inhibition of CD4+ T cell activation, which deprives the virus of susceptible target cells. The researchers have developed a version to test in humans and hope to launch a trial by the end of the year.[108,109]

An ongoing collaboration between researchers in Nairobi, Kenya, and Oxford, United Kingdom, is investigating whether vaccination might be able to enhance protection against HIV transmission to infants through breastfeeding. The group has recently published results demonstrating that administration of an MVA vector encoding clade A HIV antigens was safe and feasible but not immunogenic when given alone.[110] Future studies aim to explore newer prime-boost regimens and the potential for dual immunization against both HIV and tuberculosis.

Passive Immunization

The discovery of a new generation of highly potent bNAbs has opened up the possibility of testing the efficacy of passive immunization as a preventive strategy. The Vaccine Research Center (VRC) at the U.S. National Institutes of Health is developing the bNAb VRC01 for this purpose and is conducting phase I safety and PK studies of subcutaneous and intravenous delivery in both uninfected and HIV-positive adults. Preliminary results suggest that concentrations shown to be effective in macaque studies are achievable in humans with monthly dosing, and no significant safety issues have emerged.[111] The VRC is working toward conducting clinical trials of VRC01 in infants, as an addition to maternal ART to prevent breastfeeding HIV transmission, and in adults at high risk of HIV acquisition. These plans include a preparatory study in a small number of HIV-exposed infants in collaboration with the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network and an assessment of various dosing regimens in adults in collaboration with the HVTN.

The VRC is also pursuing modifications to bNAbs that would allow less frequent dosing,[112,113] and it has initiated manufacturing of two candidates, VRC01-LS and VRC07-523-LS (VRC07 is similar to VRC01 but even more potent and broadly active). Research conducted with antibodies to respiratory syncytial virus indicates that the modifications may allow dosing as infrequently as every six months to one year.[114]

Another bNAb being evaluated for use as passive immunization is 3BNC117. This year saw the publication of highly anticipated first results from a clinical trial that administered 3BNC117 as a single infusion to HIV-positive individuals.[115] At the upper end of the range of doses evaluated, 3BNC117 caused significant declines in viral load that persisted up to 28 days in some cases. However, one participant had high-level resistance to 3BNC117 at baseline, highlighting the fact that even the best bNAbs are unlikely to be able to inhibit all HIV variants when administered as single agents. Researchers intend to explore combinations of bNAbs, and recently Dan Barouch presented encouraging laboratory data showing that just two highly potent bNAbs – PGT121 and PGDM1400 – can together inhibit 98%–99% of a large panel of different HIV variants from across the globe.[116]

Antibody Gene Transfer

An alternative to passive immunization with bNAbs is antibody gene transfer or vectored immunoprophylaxis. AAV vectors, which have been used with some success to supply factor IX in human trials for hemophilia,[117] are employed to deliver the gene encoding a bNAb into muscle tissue, essentially acting as a persistent factory for bNAb production. The approach has shown promise in macaque[118] and humanized mouse[119] models, and a human trial of an AAV vector encoding the bNAb PG9 is ongoing in the United Kingdom.[120] Results are pending, but the investigator Phil Johnson stated in a recent presentation that dose escalation is proceeding according to plan, with the third dosing group now enrolling.[121] Several research groups are interested in pursuing AAV as a vehicle for delivering bNAbs or other HIV inhibitors (such as a recently described and highly potent protein named eCD4-Ig[122]), so the progress of this initial trial is being closely watched.

Conclusion

An astonishing array of antiretroviral-based modalities continue to make their way down the HIV biomedical prevention pipeline, though progress remains slow, with several promising candidates and new technologies still in the same phases of preclinical development reported in the "Preventive Technologies" chapter of the *2014 Pipeline Report*. However, new data continue to emerge at a steady clip – made increasingly accessible through biomedical prevention–focused sessions at longstanding congresses such as CROI and new conferences such as HIV Research for Prevention (HIVR4P) – to help facilitate the development of candidates that are likely to be not only potent and safe but also acceptable (and, indeed, desirable) to vulnerable populations who need them most.

Progress in preventive vaccines, and the related approaches of passive immunization and antibody gene transfer, promises to complement and extend the successes that have been obtained with antiretroviral-based strategies. As long as the research continues to be supported, the tidal wave of new HIV infections promises to be not only stemmed but also reduced to a level that could finally end the epidemic.

Indeed, there appears to be a decline in global funding for HIV prevention research and development, despite an increase in encouraging basic science, preclinical research, and proof-of-concept studies involving antiretroviral-, vaccine-, passive immunotherapy–, and antibody gene transfer–based technologies. According to a recent resource tracking report published by AVAC, funding for HIV prevention R&D declined by US$50 million, or four percent, in 2013 (US$1.26 billion), compared with 2012 (US$1.31 billion). This follows a four-year increase in funding between 2009 (US$1.22 billion) and 2012. The decrease is attributed primarily to a decline in investments by the U.S. public sector – which remains the largest funder of HIV prevention R&D – by US$38 million between 2012 (US$925 million) and 2013 (US$887 million) – along with a 10% decline in investments by European public-sector agencies between 2012 (US$86 million) and 2013 (US$77 million).[123]

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Research Toward a Cure and Immune-Based and Gene Therapies

By Richard Jefferys

Introduction

The rise to prominence of cure research has continued over the past year, with every major scientific conference on HIV now featuring sessions and presentations on the topic. The U.S. National Institute of Allergy and Infectious Diseases (NIAID) sponsors a biannual workshop with the most recent, Strategies for an HIV Cure, taking place in Bethesda in October 2014. The NIAID meeting alternates years with another more longstanding event known as the International HIV Persistence Workshop, which debuted in 2003 and will convene for the seventh time in December 2015. In addition, the International AIDS Society (IAS) sponsors a two-day symposium, Towards an HIV Cure, every year in July.

The proliferation of meetings and workshops reflects the expansion of the research effort and the resultant data, which are presented and discussed at these events. Since the publication of the *2014 Pipeline Report*, many new clinical trials have been initiated (see table 1), and important results from early human studies of candidate HIV latency-reversing agents have been presented and published.

The most significant development has been a disappointment: the child once known as the Mississippi baby, considered possibly cured of HIV infection, experienced a viral-load rebound and had to restart antiretroviral therapy (ART). The news was announced July 10, 2014,[1] and a case report published in the *New England Journal of Medicine* in February of this year.[2] ART had been initiated shortly after the child's birth and then interrupted around 18 months later; the child subsequently went 27 months with no detectable viral load or replication-competent HIV before the rebound occurred. An International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network trial based on the case, P1115, has gone ahead and will attempt to evaluate whether similar or longer periods of remission can be obtained by immediate treatment of newborns infected with HIV because their mothers did not receive appropriate prevention of mother-to-child transmission.

With the return of HIV in the Mississippi child, Timothy Brown once again became the lone individual considered cured (he recently celebrated reaching eight years with this unique status). Gero Hütter, the doctor who identified a stem cell donor homozygous for the CCR5-Δ32 mutation for Brown and performed the transplantation procedures, recently reviewed six other documented cases of people with HIV and cancers who received stem cell transplants from CCR5-Δ32 homozygotes. In a stark and unhappy illustration of the challenges associated with the approach, all six died within a few months, due to either the underlying cancers or complications from the transplantation procedures such as graft-versus-host-disease.[3] In one case, HIV had become undetectable, but ART was not discontinued to evaluate the potential for viral-load rebound, and the individual died from the cancer three months posttransplant.[4] The high mortality has raised some concerns, as recent reports indicate a superior survival rate, of 47%, among HIV-positive individuals receiving stem cell transplants from donors lacking the CCR5-Δ32 mutation.[5,6] Two ongoing trials in the United States continue to attempt to identify CCR5-Δ32 homozygous donors for people with HIV who need stem cell transplants to treat cancers (see table 1), and a similar effort is under way in Europe led by the IrsiCaixa Institute for AIDS Research in Spain.[7]

Clearly, hopes have significantly diminished that additional cases of cures might result in the near term from immediate ART in infants or CCR5-negative stem cell transplants for people with HIV and cancers. While more cases would have been encouraging for the field, they would not necessarily have aided in the design of more broadly relevant approaches. The majority of current clinical trials represent attempts to create stepping stones toward a cure or the intermediate outcome of extended ART-free remission.

On the funding front, a report from the HIV Vaccines and Microbicides Resource Tracking Working Group (in partnership with AVAC and the Towards an HIV Cure initiative) estimates that global investment in HIV cure research was US$102.7 million in 2013, up from US$88.1 million in 2012[8] – still a very small proportion of overall spending on HIV research. More recently, amfAR, the Foundation for AIDS Research, announced a further expansion of its cure research program, to the tune of US$100 million over the next several years,[9] and NIAID has announced a request for funding applications that will lead to the support of three or four Martin Delaney Collaboratories focused on the development of an HIV cure starting in mid-2016 (after the current grants supporting the Collaboratory of AIDS Researchers for Eradication (CARE), Delaney AIDS Research Enterprise, and defeatHIV, the Delaney Cell and Genome Engineering Initiative expire). A little over US$22 million will be allocated in FY 2016, primarily from NIAID with contributions from the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke.[10] Notably, when the director of the U.S. National Institutes of Health (NIH), Francis Collins, asked the Office of AIDS Research Advisory Council to identify the key priorities for future funding, the pursuit of a cure was ranked prominently among them.[11]

For the most part, immune-based and gene therapies have become integrated into the cure research effort. There is now relatively little exploration of approaches that might be added to ART in order to reduce the residual risk of illness that can persist in some individuals, particularly those who experience poor recovery of CD4+ T cells despite effective viral-load suppression (referred to as immunologic nonresponders, or INRs). Immunologic nonresponse to ART and more subtle manifestations of persistent immune dysregulation such as elevated levels of inflammatory biomarkers and low CD4:CD8 ratios have been associated with a significantly increased risk of morbidity and mortality.[12,13] In the absence of immune-based interventions, evidence indicates that the best approach to minimizing risk is to address modifiable lifestyle factors such as smoking, diet, and exercise. Excercise has been reported to have positive immunologic effects including lowering markers of immune senescence.[14,15]

There is one very large clinical endpoint trial of a possible adjunct to ART that has been launched this year. Known as the REPRIEVE trial, it will assess whether the statin drug pitavastatin can reduce the incidence of cardiovascular disease in people on ART; it aims to recruit 6,500 participants.[16] In addition to lipid-lowering effects, some statins have been reported to reduce inflammatory and immune activation biomarkers in HIV-positive individuals.[17,18] Changes in the inflammatory biomarkers RP, Lp-PLA2, and sCD163 will be evaluated in a REPRIEVE substudy.[19]

Table 1. Research Toward a Cure 2015: Current Clinical Trials and Observational Studies

Trial	Additional Description	Trial Registry Identifier(s)*	Manufacturer/Sponsor(s)	Phase
ADOPTIVE IMMUNOTHERAPY				
Early ART in combination with autologous HIV-specific cytotoxic T-lymphocyte (CTL) infusion	T-cell therapy	NCT02231281	Yong-Tao Sun, Tangdu Hospital, Fourth Military Medical University	Phase III
HXTC	HIV-1 antigen–expanded specific T-cell therapy	NCT02208167	University of North Carolina (UNC) at Chapel Hill	Phase I
ANTIBODIES				
3BNC117	Broadly neutralizing monoclonal antibody	NCT02018510	Rockefeller University	Phase I
BMS-936559	Anti-PD-L1 antibody	NCT02028403 (suspended)	U.S. National Institute of Allergy and Infectious Diseases (NIAID)	Phase I
VRC01	Broadly neutralizing monoclonal antibody + ART interruption	NCT02463227 (not yet open for enrollment)	NIAID	Phase I

Trial	Additional Description	Trial Registry Identifier(s)*	Manufacturer/Sponsor(s)	Phase
VRC01	Broadly neutralizing monoclonal antibody	NCT02411539 (not yet open for enrollment)	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
ANTIFIBROTICS				
ACE inhibitors		NCT01535235	University of California, San Francisco/amfAR	Phase IV
losartan	Angiotensin receptor blocker	NCT01852942	University of Minnesota	Phase I
ANTIRETROVIRAL THERAPY IN HIV CONTROLLERS				
emtricitabine + rilpivirine + tenofovir		NCT01777997 (closed to enrollment)	AIDS Clinical Trials Group (ACTG)/ NIAID	Phase IV
COMBINATIONS				
RIVER (Research In Viral Eradication of HIV Reservoirs): ART + ChAdV63.HIVconsv & MVA.HIVconsv vaccines + vorinostat	Therapeutic vaccines + HDAC inhibitor	NCT02336074 (not yet open for enrollment)	Imperial College London	Phase II
SB-728mR-T + cyclophosphamide	Autologous CD4+ T cells gene-modified via messenger RNA to inhibit CCR5 expression + transient chemotherapy	NCT02225665	Sangamo BioSciences	Phase I/II
SB-728-T + cyclophosphamide	Autologous CD4+ T cells gene-modified via adenovirus vector to inhibit CCR5 expression + transient chemotherapy	NCT01543152	Sangamo BioSciences	Phase I/II
Vacc-4x + romidepsin	HDAC inhibitor + peptide-based therapeutic vaccine	NCT02092116	Bionor Immuno AS/Celgene	Phase I/II
CD4-ZETA +/– interleukin-2 (IL-2)	Gene-modified T cells + cytokine	NCT01013415 (closed to enrollment)	University of Pennsylvania	Phase I
SB-728mR-T + cyclophosphamide	Autologous CD4+ T cells gene-modified via messenger RNA to inhibit CCR5 expression + transient chemotherapy	NCT02388594	University of Pennsylvania	Phase I
GENE THERAPIES				
Cal-1: Dual anti-HIV gene transfer construct	Lentiviral vector encoding a short hairpin RNA that inhibits expression of CCR5 + fusion inhibitor (C46)	NCT01734850 NCT02390297 (long-term safety phase)	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

Trial	Additional Description	Trial Registry Identifier(s)*	Manufacturer/Sponsor(s)	Phase
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 (suspended)	Universitätsklinikum Hamburg - Eppendorf	Phase I/II
HIV-resistant gene-modified stem cells and chemotherapy in treating patients with lymphoma and HIV infection	Stem cells gene-modified to delete CCR5 and express an HIV entry inhibitor C46	NCT02343666	Fred Hutchinson Cancer Research Center	Phase I
Gene-modified HIV-protected stem cell transplant in treating patients with HIV-associated lymphoma	Stem cells gene-modified with LVsh5/C46 (Cal-1)	NCT02378922 (not yet open for enrollment)	Fred Hutchinson Cancer Research Center	Phase I
Gene therapy and combination chemotherapy in treating 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)	NCT02337985 (not yet open for enrollment)	City of Hope Medical Center	Not listed
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
LATENCY-REVERSING AGENTS				
MGN1703	Toll-like receptor 9 (TLR-9) agonist	NCT02443935	University of Aarhus	Phase Ib/IIa
poly-ICLC	TLR-3 agonist	NCT02071095	Nina Bhardwaj/Campbell Foundation/Oncovir	Phase I/II
romidepsin	HDAC inhibitor	NCT01933594	ACTG/NIAID/Gilead Sciences	Phase I/II
vorinostat	HDAC inhibitor	NCT01319383	UNC at Chapel Hill/NIAID/Merck	Phase I/II
ALT-803	Recombinant human superagonist interleukin-15 complex	NCT02191098 (not yet open for enrollment)	University of Minnesota – Clinical and Translational Science Institute	Phase I
bryostatin-1	PKC agonist	NCT02269605 (closed to enrollment)	Fundación para la Investigación Biomédica del Hospital Universitario Ramón y Cajal	Phase I
GS-9620	TLR-7 agonist	Not entered in clinicaltrials.gov (closed to enrollment)	Gilead Sciences	Phase I
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	ACTG	N/A
Analytic Treatment Interruption (ATI) to Assess HIV Cure	Antiretroviral treatment interruption	NCT02437526 (enrolling by invitation only)	Mayo Clinic	N/A
CHERUB 003	Prospective cohort study evaluating the effects of chemotherapy on the HIV reservoir	NCT01902693 (closed to enrollment)	Imperial College London/CHERUB	N/A

Trial	Additional Description	Trial Registry Identifier(s)*	Manufacturer/Sponsor(s)	Phase
CODEX (the "Extreme" cohort)	Long-term nonprogressors and HIV controllers	NCT01520844	French National Institute for Health and Medical Research/ French National Agency for Research on AIDS and Viral Hepatitis (INSERM/ANRS)	N/A
EPIC4	Early Pediatric ART Initiation: Canada Child cure Cohort Study	Not listed	Canadian Institutes of Health Research/Canadian Foundation for AIDS Research/International AIDS Society	N/A
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
Quantitative measurement and correlates of the latent HIV reservoir in virally suppressed Ugandans		NCT02154035	NIAID	N/A
Use of leukapheresis to support HIV pathogenesis studies		NCT01161199	University of California, San Francisco	N/A
ULTRASTOP/ERAMUNE-03 (Towards HIV Functional Cure)	Antiretroviral treatment interruption	NCT01876862	Objectif Recherche VACcin Sida/ Fondation Bettencourt Schueller	N/A
mTOR INHIBITORS				
everolimus	Impact of everolimus on HIV persistence following kidney or liver transplant	NCT02429869 (not yet open for enrollment)	University of California, San Francisco	Phase IV
sirolimus	Safety and efficacy of sirolimus for HIV reservoir reduction in individuals on suppressive ART	NCT02440789 (not yet open for enrollment)	ACTG	Phase I/II
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/National Cancer Institute/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				
AGS-004	Personalized therapeutic vaccine using patient-derived dendritic cells and HIV antigens	NCT01069809 (closed to enrollment)	Argos Therapeutics	Phase II
GTU-MultiHIV + LIPO-5	DNA + lipopeptide vaccines	NCT01492985	INSERM/ANRS	Phase II
VAC-3S	Peptide-based vaccine	NCT02041247	InnaVirVax	Phase II

Trial	Additional Description	Trial Registry Identifier(s)*	Manufacturer/Sponsor(s)	Phase
VAC-3S	Peptide-based vaccine	NCT02390466 (not yet open for enrollment)	InnaVirVax	Phase I/IIa
AGS-004	Personalized therapeutic vaccine using patient-derived dendritic cells and HIV antigens	NCT02042248	UNC at Chapel Hill/Argos Therapeutics/U.S. National Institutes of Health	Phase I/II
GTU-MultiHIV B clade	DNA vaccine	NCT02457689	Imperial College London	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
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
D-GPE DNA + M-GPE MVA	DNA and MVA viral vector vaccines	NCT01881581	Centers for Disease Control and Prevention, China	Phase I
HIVAX	Lentiviral vector–based vaccine	NCT01428596	GeneCure Biotechnologies	Phase I
iHIVARNA-01	TriMix + HIV antigen naked messenger RNA	NCT02413645 (not yet open for enrollment)	Institut d'Investigacions Biomèdiques August Pi i Sunyer	Phase I
MAG-pDNA + rVSV$_{IN}$ HIV-1 Gag (DNA + viral vector vaccines)	DNA + vesicular stomatitis virus viral vector vaccines	NCT01859325	NIAID/Profectus Biosciences	Phase I
MVA.HIVconsv	Modified MVA viral vector vaccine	NCT01024842 (closed to enrollment)	University of Oxford/Medical Research Council	Phase I
TRADITIONAL CHINESE MEDICINE				
Triptolide wilfordii		NCT02219672	Peking Union Medical College	Phase III
TREATMENT INTENSIFICATION				
LEOPARD (Latency and Early Neonatal Provision of Antiretroviral Drugs Clinical Trial)	Combination antiretroviral therapy	NCT02431975 (not yet open for enrollment)	Columbia University	Not listed
New Era (treatment with multidrug class HAART)	Combination antiretroviral therapy	NCT00908544 (closed to enrollment)	MUC Research	Not listed
AAHIV (Antiretroviral therapy for Acute HIV infection)	Combination antiretroviral therapy	NCT00796263	South East Asia Research Collaboration with Hawaii	Phase III
EIT (Early Infant HIV Treatment in Botswana)	Combination antiretroviral therapy	NCT02369406	Harvard School of Public Health	Phase II/III
peginterferon alfa-2b		NCT02227277	Wistar Institute	Phase II
peginterferon alfa-2b	Cytokine	NCT01935089	University of Pennsylvania/ Wistar Institute	Phase II
alpha interferon intensification	Cytokine	NCT01295515	NIAID	Phase I/II
IMPAACT P1115 (very early intensive treatment of HIV-infected infants to achieve HIV remission)	Combination antiretroviral therapy	NCT02140255	IMPAACT/NIAID/NICHD	Phase I/II

*For more information about a trial, go to clinicaltrials.gov and enter its trial registry identifier in the search bar.

For a listing including completed trials related to cure research, with links to published and presented results where available, see TAG's "Research Toward a Cure Trials" web page at: http://www.treatmentactiongroup.org/cure/trials.

Concepts of Remission

After the return of viral load in the Mississippi child, some leading researchers – including Nobel laureate Françoise Barré-Sinoussi – are advocating more cautious application of the word *cure* and the term *functional cure* (which has never been particularly well defined) and recommending the use of *remission* instead.[20] The concept is intended to refer to the ability to safely interrupt ART for some period; however, various different forms of ART-free remission have been described, and precise criteria have yet to be proposed.

The 27-month remission that occurred in the Mississippi case shows similarities with two adults in Boston whose HIV reservoirs were significantly diminished after they received stem cell transplants for the treatment of cancers; both were able to interrupt ART without a return of detectable viral load or replication-competent HIV for periods of 12 and 32 weeks, respectively.[21] In all three instances, the cause of the remission appears to have been the very small size of the HIV reservoir (in the Mississippi child, this was due to early ART's curtailing the formation of the reservoir). The outcomes are consistent with mathematical modeling studies suggesting that significant shrinkage of the size of the reservoir can delay viral-load rebound, with very large reductions potentially equating to lifelong remission in the absence of ongoing ART.[22]

But while the three cases support the idea that limiting or reducing the viral reservoir – a key goal of the research effort – can be beneficial, so far no reservoir-reducing strategy has shown notable effects, let alone come close to the estimated 3-log reduction that occurred in the Boston patients as a result of stem cell transplantation. The mathematical models indicate that a 5-log drop or greater would be needed to achieve lifelong remission in the majority of HIV-positive individuals, so the research has some way to go if a cure is to be achieved by this strategy alone.

A key shared aspect of the Mississippi and Boston cases is that all three lacked detectable immune responses against HIV: in the child, this was due to ART's suppressing HIV quickly after birth, before the developing immune system was significantly exposed to the virus; in the adults, it was because the stem cell transplants gave rise to a new donor-derived immune system that did not mount a response to HIV because suppressive ART was maintained throughout the procedures and for a long period afterward. So it's important to appreciate that the periods of remission in these individuals were likely a consequence of reservoir depletion alone (as opposed to immunologic suppression of the virus) with the viral-load rebounds caused by the chance reactivation of a latently infected CD4+ T cell.

A more commonly described, less stringently defined type of remission (sometimes referred to as virological remission or posttreatment control) involves control of HIV viral load to very low but not necessarily completely undetectable levels in the absence of ART. The best known example of this phenomenon is the VISCONTI (Viro-Immunologic Sustained CONtrol after Treatment Interruption) cohort, consisting of 20 individuals treated during early infection who interrupted ART after a period of several years and have since maintained very low or undetectable viral loads for an average of nine years at the time of the last report.[23] There have also been various case reports over the years involving individuals who have maintained low or undetectable viral loads after ART interruption; typically, treatment was initiated during acute or early infection, but rare examples in chronic infection exist.[24,25,26,27,28,29,30]

While a relatively small HIV reservoir has been implicated in some of these cases, HIV-specific and innate immune responses are also present and may be contributing. Therefore, it's possible that enhancing or rejuvenating antiviral immunity could lead to this intermediate type of remission while work continues toward the development of interventions capable of reducing the HIV reservoir to the dramatic extent mathematical models suggest is required to achieve a lifelong cure. Several of the trials listed in table 1 are exploring compounds whose mechanisms of action may have immunologic components, and several trials combining latency-reversing agents with therapeutic vaccines are under way or imminent.

A related thread of research is attempting to identify biomarkers that predict a delay in viral load rebound after ART interruption, which would allow candidate therapeutic approaches to be assessed without necessarily requiring study participants to stop treatment. A number of retrospective analyses presented or published over the past year have reported that levels of HIV DNA showed significant associations with time to viral-load rebound[31] or viral-load set point[32] in past clinical trials involving ART interruption. A forthcoming AIDS Clinical Trials Group (ACTG) study (ACTG A5345) plans to prospectively assess whether HIV reservoir measurements can predict the pace of viral-load recrudescence during a carefully monitored break from ART.

The ongoing efforts to define the parameters and predictors of ART-free remission form a backdrop to the entire cure research portfolio.

HIV Remission and Health

One of the challenges in defining remission is that there is evidence that even very low levels of HIV can have negative health consequences. Elite controllers, who naturally control viral load to low or undetectable levels in the absence of treatment, were at one time thought to experience no HIV-related illnesses. But in recent years it has been discovered that elite controllers can show elevated levels of immune activation and inflammation compared with HIV-negative individuals and are not completely protected from eventual CD4+ T-cell decline and progression to AIDS.[33,34] A recent study reported that elite controllers are at increased risk of hospitalization compared with HIV-positive individuals on ART, particularly due to cardiovascular disease,[35] although the extent to which differences in other risk factors (such as smoking) may have contributed is not entirely clear.[36]

If elite controllers are at increased risk of illness compared with their HIV-negative counterparts or HIV-positive people on ART, it raises an important question: what degree of HIV control can actually be considered synonymous with disease-free remission?

The members of the VISCONTI cohort are reported to be healthy, but no one has attempted to prospectively compare the health of posttreatment controllers with HIV-positive people on ART and HIV-negative individuals (such a study would likely be very difficult to conduct given the small numbers). The issue is further complicated by the spectrum of HIV activity that may or may not be detectable in cases described as examples of remission, posttreatment control, or functional cure; this can range from trace amounts of viral genetic material without evidence of replication-competent virus to readily detectable but very low viral load (e.g., <50 copies/mL). There is reason to hope that the extreme low end of this spectrum would be associated with a lack of negative health consequences, but this has not been formally proved. Until these uncertainties are resolved, it should be borne in mind that the terminology used in cure research is not fully clarified, even though it is now quite common for media stories and company press releases to invoke terms like *functional cure*.

Latency-Reversing Agents

Histone Deacetylase (HDAC) Inhibitors

The research group of Ole Søgaard at the University of Aarhus in Denmark continues to pioneer the study of candidate latency-reversing agents in humans. These compounds aim to activate the dormant HIV in latently infected memory CD4+ T cells, which constitute the major reservoir of virus in individuals on ART.[37] Results from a clinical trial of the HDAC inhibitor panobinostat in HIV-positive individuals showed significant induction of HIV RNA expression,[38] and a genetic analysis by Sarah Palmer indicates that the drug activated a diverse pool of latent viruses.[39] Consistent with previously published laboratory research,[40] induction of HIV RNA expression did not lead to a measurable depletion of the HIV reservoir overall.

Four out of the 15 trial participants experienced a persistent decline in HIV DNA levels, ranging from 67% to 84%, and this correlated with a slightly longer time to viral-load rebound during an analytical ART interruption. An analysis presented as a poster by Martin Tolstrup at the 2014 International AIDS Conference suggested that this outcome may have been linked to innate immunity – particularly enhanced natural killer cell activity[41] – but due to the small subset of participants involved the results can be viewed only as exploratory.

Additional findings from the panobinostat trial were that no activation of HIV or inflammation was detectable in the cerebrospinal fluid;[42] cerebrospinal fluid was analyzed due to concerns that latency-reversing agents might provoke virus-associated damage to the brain. In a separate paper, the researchers reported that the drug significantly reduced biomarkers of inflammation and cardiovascular disease in the blood, leading to the suggestion that it might have role as an anti-inflammatory agent.[43]

Also at the 2014 International AIDS Conference, Søgaard presented preliminary results from an ongoing trial of the HDAC inhibitor romidepsin[44] (also currently under study at the ACTG). The results demonstrated induction of HIV RNA to levels detectable using a clinical viral-load test (>20 copies/mL and up to a little over 100 copies/mL in some cases), which has not been documented with any other latency-reversing agent to date. As in other HDAC inhibitor trials, no overall change in HIV DNA or other reservoir measures was observed.

No serious adverse events were documented in the panobinostat or romidepsin trials (side effects were primarily fatigue and gastrointestinal symptoms), although concerns have been raised about the unknown implications of long-term changes in gene expression associated with the receipt of HDAC inhibitors.[45] No evidence of an inhibitory effect of panobinostat or romidepsin on HIV-specific CD8+ T-cell responses was observed,[46] which a previously published laboratory study had suggested might be a problem.[47]

A second part of the romidepsin trial is now testing whether the addition of the therapeutic HIV vaccine candidate Vacc-4x (consisting of several conserved HIV Gag peptides) can invoke immune responses capable of eliminating latently infected CD4+ T cells that are induced to express HIV.

Other combinations of HDAC inhibitors and therapeutic HIV vaccines are also being explored in trials. Researchers at CARE plan to marry the HDAC inhibitor vorinostat with AGS-004, a dendritic cell–based vaccine that incorporates HIV antigens derived from viral RNA sampled from the intended recipient.[48] In the United Kingdom, the Research In Viral Eradication of HIV Reservoirs (RIVER) trial aims to evaluate an HDAC inhibitor along with chimpanzee adenovirus and modified vaccinia Ankara strain (MVA) vaccine vectors encoding HIV antigens selected based on their conservation among diverse viruses.

Disulfiram

The drug disulfiram, better known by its trade name, Antabuse, is approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcoholism. The potential HIV latency–reversing activity of disulfiram was first identified in a laboratory screen conducted by Robert Siliciano's research group at Johns Hopkins,[49] and a small pilot study was later conducted at the University of California, San Francisco (UCSF).[50] Data from a larger dose-escalation trial recently presented by Steven Deeks of UCSF revealed significant increases in levels of cell-associated HIV RNA, along with a postadministration increase in plasma HIV RNA of around twofold in recipients of the highest dose, 2,000 mg/day.[51] Although there has been some variability in the results, there is interest in continuing to study disulfiram's latency-reversing potential due to its extensive safety record.

Scientists in Spain have completed a small study of disulfiram at a dose of 1,000 mg/day in combination with a therapeutic HIV vaccine, MVA-B (an MVA vector encoding clade B HIV antigens). The vaccine successfully induced HIV Gag-specific T-cell responses and was associated with a very slight delay in viral-load rebound during an analytic ART interruption. Viral-load rebound kinetics were not significantly different among participants receiving disulfiram in addition to MVA-B, and no reduction in HIV DNA levels was observed.[52]

Toll-Like Receptor (TLR) Agonists

TLRs are involved in the recognition of particular patterns common to pathogenic organisms and play a role in the induction of innate and adaptive immunity. Stimulation of TLRs with agonist molecules can have adjuvant and therapeutic effects by modulating the immune response, and several TLR agonists have been reported to activate latent HIV in vitro.[53,54] There is particular interest in the possibility of a dual mechanism of action, as TLR agonists have also been reported to enhance natural killer and CD8+ T-cell activity against HIV.[55]

Two widely publicized presentations at the 2015 Conference on Retroviruses and Opportunistic Infections describe the latency-reversing capacity of GS-9620, a TLR-7 agonist developed by Gilead Sciences. In a study in SIV-infected macaques on ART, GS-9620 caused transient viral-load increases to detectable levels at the highest dose administered. Evidence of increased natural killer cell and CD8+ T-cell activation was also seen, and levels of HIV DNA declined significantly in three of four animals, in both blood and tissues.[56] A separate poster presentation reported that GS-9620 activated latent HIV in CD4+ T cells isolated from HIV-positive individuals on ART.[57] Clinical trials in hepatitis B and C have found GS-9620 to be safe,[58,59] and a phase I exploration of safety and activity in HIV-positive individuals is under way (regrettably, Gilead Sciences has not registered the trial at clinicaltrials.gov).

In addition to its work with HDAC inhibitors and therapeutic vaccination, Søgaard's group has recently launched a trial of a TLR-9 agonist to study its effects on the HIV reservoir. The rationale derives from an exploratory analysis of a trial of a pneumococcal vaccine in HIV-positive individuals on ART in which one arm received a TLR-9 agonist as an adjuvant; levels of HIV DNA among the participants in this arm declined significantly, and this correlated with increases in markers associated with improved CD8+ T-cell function .[60]

An ongoing trial at Rockefeller University is investigating poly-ICLC, a TLR-3 agonist more typically used as a vaccine adjuvant.

Interleukin-15 (IL-15) Superagonist ALT-803

Agents that may have a dual mechanism of action – both reversing HIV latency and enhancing immune responses with the potential to eliminate virus-infected cells – have emerged as a theme this year. Among them is the cytokine IL-15, which has been shown to induce HIV production by latently infected CD4+ T cells[61]

and promote natural killer cell and CD8+ T-cell activity.[62] ALT-803, also known as an IL-15 superagonist, is a modified version of the cytokine with enhanced potency. Recent studies of ALT-803 indicate that it can activate natural killer cells, leading to inhibition of HIV in humanized mice.[63] In laboratory experiments, ALT-803 was found to both stimulate expression of HIV antigens by latently infected CD4+ T cells and enhance their killing by HIV-specific CD8+ T cells.[64] A pilot study of ALT-803 in HIV-positive individuals on ART is due to start soon at the University of Minnesota.

Bryostatin-1/Protein Kinase C (PKC) Agonists

Bryostatin-1 belongs to a class of compounds known as PKC agonists. Laboratory studies have shown that PKC agonists can induce HIV production by latently infected CD4+ T cells[65] and work synergistically with HDAC inhibitors to achieve levels of latency-reversing activity close to those observed with maximal CD4+ T-cell activation.[66,67] Bryostatin-1 has also been reported to interact with TLR-4 and stimulate production of chemokines capable of inhibiting HIV.[68] There are concerns about the potential toxicity of bryostatin-1, which has caused severe myalgias and other grade 3 and 4 adverse events in cancer trials,[69] but a small trial involving low doses is ongoing in Spain. The company supplying the drug, Aphios Corporation, is considering developing a combination latency-reversing agent incorporating bryostatin-1 (or a similar analogue) and an HDAC inhibitor.[70]

Another PKC agonist drawing interest is Ingenol-B, an extract from the sap of the tropical shrub *Euphorbia tirucalli*. Several research laboratories have reported that it has latency-reversing activity,[71,72,73] and there is evidence to suggest that it may be less prone to cause toxicity than other PKC agonists. Clinical trials are in the planning stages.

Broadly Neutralizing Antibodies

New technologies have facilitated the discovery of an increasing number of antibodies capable of broadly neutralizing a diverse array of HIV isolates from across the globe, many with great potency (robust inhibition of HIV is achieved at relatively low antibody concentrations).[74,75,76] Tens of thousands of HIV-specific B cells can now be sampled from HIV-positive individuals and the antibodies they are producing fished from each individual cell and tested for their ability to inhibit viral replication. The broadly neutralizing antibodies (bNAbs) identified with this approach do not necessarily benefit the person they are sampled from, likely due in part to the complex swarm of diverse HIV variants circulating in chronically infected individuals, and the titers of the bNAbs being low compared to the amount of virus present. But the potency and breadth of neutralization of the new generation of bNAbs suggest that they could be beneficial when delivered intravenously or subcutaneously in both preventive and therapeutic contexts (see “Preventive Technologies,” page 57).

For cure researchers, there is particular interest in the potential of bNAbs to promote destruction of HIV-infected cells via antibody-mediated cellular cytotoxicity or antibody-mediated cellular phagocytosis.[77] These effector functions involve the binding of the antibody to HIV antigens being expressed by infected cells, followed by the recruitment of natural killer cells or monocytes to destroy the cell (the recruitment is accomplished by a part of the antibody structure known as the Fc region, which interacts with Fc receptors on the effector cells). A study in humanized mice has provided evidence that this type of antibody-mediated activity can work in concert with latency-reversing agents to diminish the HIV reservoir.[78]

Several potent bNAbs are now being manufactured and tested in clinical trials, and this year saw the publication of results from a phase I evaluation of the bNAb 3BNC117 in HIV-positive individuals.[79] At the highest of the four doses administered (30 mg/kg), a single intravenous infusion of 3BNC117 led to a decline in viral load ranging from 0.8 to 2.5 logs, with four of eight recipients remaining below baseline at the last reported follow-up (day 56 postinfusion). There was evidence of 3BNC117-resistant HIV emerging in some participants, and one individual showed high-level resistance to the antibody at baseline. The investigators are currently analyzing whether any recipients developed immune responses against the 3BNC117 antibody; those results are pending.

The confirmation that bNAbs are active against HIV in humans presages a significant expansion of research in this area. VRC01, a bNAb developed by the NIH Vaccine Research Center (VRC), is already undergoing testing (delivered intravenously or subcutaneously)[80] in both HIV-positive and HIV-negative individuals, and several new clinical trials are imminent; these include an assessment of effects on the HIV reservoir and on viral-load rebound after ART interruption. The U.S. Military HIV Research Program will soon launch a study of VRC01 in Thai individuals with acute HIV infection.[81] The VRC has begun manufacture of a longer-acting formulation of VRC01 (VRC01-LS) and an additional long-acting bNAb, VRC07-523-LS.

The research group of Dan Barouch at the Beth Israel Deaconess Medical Center is on the verge of initiating trials of the bNAb PGT121 after obtaining promising results in macaque experiments.[82] If all goes well, future plans include combination studies with other bNAbs and latency-reversing agents.[83]

The researchers responsible for the 3BNC117 trial, led by Sarah Schlesinger at Rockefeller University, are working on several protocols that aim to test the effects of 3BNC117 on the HIV reservoir (either alone or in combination with a latency-reversing agent), the impact on viral rebound after ART interruption, and efficacy in combination with the bNAb 10-1074.[84]

Adoptive Immunotherapy

An alternative approach to therapeutically exploiting immune responses against HIV is to administer CD8+ T cells targeting the virus. The CD8+ T cells are extracted from the intended recipient, stimulated with HIV antigens and expanded in the laboratory, and then reinfused. David Margolis and colleagues from CARE and the University of North Carolina at Chapel Hill are pursuing this strategy – which they have named HIV-1 Antigen Expanded Specific T Cell Therapy (HXTC)[85] – as a means to target the HIV reservoir, and an initial phase I trial investigating safety and efficacy has begun. In laboratory studies, HIV-specific CD8+ T cells generated by their method were able to kill latently infected CD4+ T cells exposed to the latency-reversing HDAC inhibitor vorinostat.[86] Infusions of autologous HIV-specific CD8+ T cells are also being studied in an ongoing trial led by Yong-Tao Sun of the Tangdu Hospital, Fourth Military Medical University in Xi'an, China.

Mammalian Target of Rapamycin (mTOR) Inhibitors

Drugs that inhibit the cellular protein mTOR are under investigation in two trials. The effects of mTOR inhibitors are complex, involving both immune-suppressive and immune-enhancing activity. In a retrospective study of HIV-positive individuals who had undergone kidney transplantation, receipt of the mTOR inhibitor sirolimus was associated with significantly reduced levels of HIV DNA.[87] The ACTG is soon to launch a pilot study to prospectively measure the impact of the drug on the HIV reservoir.

Researchers at UCSF plan to conduct a trial that will add six months of everolimus, a derivative of sirolimus, to the regimens of HIV-positive individuals who have received kidney or liver transplants. The effect on the HIV reservoir will be assessed at several times during and after receipt of the drug.

Gene Therapies

A development in gene therapy that made the news earlier this year was the approval by the FDA of a clinical trial involving genetic modification of stem cells. The project involves collaboration between researchers from City of Hope Medical Center in Los Angeles, the Keck School of Medicine at the University of Southern California, and Sangamo BioSciences, with support from the California Institute for Regenerative Medicine (CIRM). Stem cells will be extracted from individuals, treated with Sangamo's zinc finger nuclease technology to disrupt the CCR5 gene, and then reinfused with the aim of generating CCR5-negative immune cells resistant to HIV. According to a press release from CIRM, the initial study population will be HIV-positive individuals responding poorly to ART.[88] Although some of the headlines described the approach as a "functional cure"[89] or "potential cure,"[90] this is in fact only an exploratory study, and it is wildly premature to suggest that it could be curative; previous trials involving genetic modification of stem cells have generated only low levels of gene-modified CD4+ T cells.[91]

The Fred Hutchinson Cancer Research Center has listed two new gene therapy trials for HIV-positive individuals requiring stem cell transplants for lymphoma. One protocol will genetically modify stem cells with a vector that disrupts CCR5 and encodes the HIV fusion inhibitor protein C46. The vector also encodes a gene (P140K) that enables the engraftment of gene-modified cells to be promoted by the administration of a combination of drugs, O6-benzylguanine and carmustine.[92] Analytic ART interruptions may be performed if sufficient levels of gene-modified cells are achieved. The other trial will alter stem cells with Cal-1, a lentiviral vector developed by Calimmune that encodes a short hairpin RNA that inhibits expression of CCR5 and C46.[93]

Research continues into the use of the Sangamo BioSciences technology to genetically modify CD4+ T cells ex vivo. The CD4+ T cells are extracted from HIV-positive individuals, exposed to the zinc finger nuclease to disrupt the CCR5 gene, then expanded and reinfused. In studies published and presented to date,[94,95] an adenovirus vector was used to deliver the zinc finger nuclease into the CD4+ T cells during the process. The company is now testing a different and potentially more efficient approach in which messenger RNA encoding the zinc finger nuclease is used instead of an adenovirus vector. Over the past year, two clinical trials have opened that will deliver CD4+ T cells modified with this method; both are using transient administration of cyclophosphamide prior to the infusion to enhance the engraftment of the altered cells.

Pediatric Cure Research

In addition to the IMPAACT P1115 clinical trial mentioned in the introduction, there are three other new studies investigating the effect of ART on the HIV reservoir in the context of mother-to-child transmission. The Early Pediatric Initiation: Canadian Child Cure Cohort Study (EPIC4) is an observational cohort study being conducted by Hugo Soudeyns and colleagues under the aegis of the recently established Canadian HIV Cure Enterprise. The aim is to study the HIV reservoir and biomarkers of disease pathogenesis in children and adults who acquired infection at birth and have had varied treatment histories.

The Latency and Early Neonatal Provision of Antiretroviral Drugs (LEOPARD) clinical trial is being led by Louise Kuhn at Columbia University and plans to investigate ART initiated within 48 hours of birth in 60 vertically infected infants in South Africa. The Harvard School of Public Health is sponsoring Early Infant HIV Treatment (EIT) in Botswana, which will assess early ART in two cohorts of infants, one infected antepartum (started on ART within seven days of birth) and the other peripartum (started on ART within 57 days of birth).

Therapeutic Vaccines

New therapeutic vaccines undergoing evaluation include iHIVARNA-01, which uses messenger RNA to deliver HIV antigens along with TriMix, an adjuvant cocktail consisting of three proteins involved in the activation of antigen-presenting cells: CD40L, CD70, and TLR4. The first clinical trial is being launched as part of a collaborative effort involving multiple European institutions coordinated by Felipe García of Barcelona's Institut d'Investigacions Biomèdiques August Pi i Sunyer, with funding support from the European Commission.[96]

Researchers at Imperial College London have initiated a new trial of FIT Biotech's GTU-MultiHIV B clade naked DNA vaccine in HIV-positive individuals on ART. Two different routes of administration will be compared: transcutaneous, or intramuscular with electroporation (which delivers a brief electrical pulse to enhance cellular uptake of the DNA).

Recent published results include those from a completed trial of Barbara Ensoli's HIV Tat protein vaccine, which has been the subject of some controversy over the years, with questions having been raised about the appropriateness of Italian government funding for the research.[97] Ensoli and colleagues' paper, published in the open-access journal *Retrovirology*, reports that the vaccine induced Tat-specific antibody responses and that recipients showed a lowering of HIV DNA levels.[98] However, the trial did not include a placebo control group; instead, comparisons were made with a separate parallel cohort, and this makes the data difficult to interpret. Results from a randomized clinical trial conducted in South Africa are pending.

At the HIV Research 4 Prevention conference in Cape Town in October 2014, Harriet Robinson from GeoVax presented results from a small therapeutic trial of the company's DNA/MVA prime-boost HIV vaccine approach. A total of nine individuals who had started ART within 18 months of seroconversion received the DNA/MVA regimen and underwent a 12-week analytic ART interruption. HIV-specific CD8+ T cells were increased in the majority of participants, but viral-load rebound occurred in all individuals after ART cessation. The levels of HIV viral load were somewhat lower at the end of the ART interruption compared with the pre-ART baseline in five participants, but there was no suggestion of vaccination leading to durable control. A clinical trial is now being planned that will combine the DNA/MVA vaccine with a latency-reversing agent.[99]

Table 2. Immune-Based Therapy Pipeline 2015

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
interleukin-7 (IL-7)	Cytokine	French National Agency for Research on AIDS and Viral Hepatitis (ANRS)/Cognate Biosciences	Phase II
losartan	Angiotensin II receptor antagonist, anti-inflammatory	Minneapolis Medical Research Foundation	Phase II
lubiprostone	Apical lumen ClC-2 chloride channel activator	Ruth M. Rothstein CORE Center/Chicago Developmental Center for AIDS Research	Phase II
methotrexate (low-dose)	Anti-inflammatory	NIAID	Phase II
metformin	Biguanide antidiabetic	University of Hawaii/National Institute of General Medical Sciences	Phase II
niacin	Vitamin B3	McGill University Health Center/Canadian Institutes of Health Research (CIHR) Canadian HIV Trials Network	Phase II
VSL#3	Probiotic	Virginia Commonwealth University/Bill & Melinda Gates Foundation University Health Network, Toronto/CIHR Canadian HIV Trials Network	Phase II
dipyridamole	Phosphodiesterase type 5 inhibitor, anti-inflammatory	Sharon Riddler, University of Pittsburgh/NIAID	Phase I/II

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
Mesenchymal stem cells	Allogenic adult mesenchymal stem cells from adipose tissue	Iniciativa Andaluza en Terapias Avanzadas – Fundación Pública Andaluza Progreso y Salud	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	Adult stem cells originating from the mesenchymal and connective tissues	Beijing 302 Hospital	Phase I//II
vorapaxar	Thrombin receptor (PAR-1) antagonist	Kirby Institute/NIAID/University of Minnesota – Clinical and Translational Science Institute/University of Melbourne/Merck	Phase I/II
aprepitant	Neurokinin 1 receptor antagonist	University of Pennsylvania	Phase I
HLA-B*57 cell transfer	Cell infusion	NIH Clinical Center	Phase I
hydroxychloroquine	Antimalarial, antirheumatic, anti-inflammatory	St Stephens AIDS Trust	Phase I

As outlined in the introduction to this chapter, very little is trickling through the immune-based therapy pipeline. A study of the antifibrotic drug pirfenidone in SIV-infected macaques offered support for the idea that repairing lymph node fibrosis, a type of scarring damage that occurs in HIV infection, might promote CD4+ T-cell reconstitution.[100] The immunologic effects of a similar drug, losartan, are being tested in an ongoing clinical trial for HIV-positive individuals on ART at the University of Minnesota.[101]

In a small trial conducted in China, therapeutic administration of umbilical cord–derived mesenchymal stem cells was reported to increase CD4+ T cells and decrease markers of immune activation and inflammation in INRs.[102] An additional trial in INRs is now being launched in Spain; it differs somewhat from the research in China because the mesenchymal stem cells are sourced from adipose (fatty) tissue rather than umbilical cords.[103]

Another relatively unconventional therapy is *Tripterygium wilfordii* Hook F, an extract from a vine used in traditional Chinese medicine. A paper published earlier this year reported that administration to INRs in a small pilot study was associated with an increase in CD4+ T-cell counts;[104] a larger randomized trial that aims to enroll 60 people is under way.[105] An extract of *Tripterygium wilfordii* is also being studied in China for its effects on the HIV reservoir (see table 1).

Interventions with potential anti-inflammatory effects continue to generate interest. A trial with sites in Australia and the United States will test the Merck drug vorapaxar for its effects on D-dimer (a coagulation biomarker that has been associated with mortality in HIV infection)[106] and markers of immune activation.[107] Aprepitant (brand name Emend) is an FDA-approved antiemetic that has been reported to have anti-inflammatory properties in HIV-positive individuals during a short two-week course of treatment.[108] A follow-up trial is now evaluating whether ritonavir-containing ART regimens can increase aprepitant levels and enhance the drug's impact on inflammatory biomarkers over four weeks of administration.[109]

Results from a double-blind, randomized, placebo-controlled trial of the probiotic *Saccharomyces boulardii* were published in March 2015.[110] A total of 44 HIV-positive individuals on ART were enrolled, and significant declines in lipopolysaccharide-binding protein (LBP) and IL-6 were documented in the probiotic recipients. LBP is a marker of microbial translocation (leakage of normally beneficial bacteria from the gut into the systemic circulation), and IL-6 is an inflammatory biomarker that has been associated with the risk of death in HIV-positive people.[111] Three new studies of the probiotic VSL#3 are being undertaken: one sponsored by Virginia Commonwealth University and the Bill & Melinda Gates Foundation that is recruiting Malian women not yet on ART[112] and two by the University Health Network, Toronto, and the Canadian HIV Trials Network – one involving individuals starting ART[113] and the other INRs with CD4+ T-cell counts less than 350/mm^3 despite two years or more of ART.[114]

Hopes that the anti-inflammatory properties of chloroquine might be of benefit to INRs appear to be fading. Results from two clinical trials have become available: researchers in Canada added chloroquine to ART in INRs and found no significant changes in T-cell counts or markers of immune activation and inflammation except for an increase in alpha interferon.[115] An ACTG study of chloroquine in HIV-positive individuals either on or off ART documented no significant differences in immune activation or CD4+ T-cell counts; these results are unpublished but available at clinicaltrials.gov.[116]

Conclusion

The expansion of research toward an HIV cure has continued over the past year. The growing number of clinical trials can be viewed as the tip of the iceberg; below the waterline lies formative basic research and work in animal models aiming to fully delineate the HIV reservoir and refine how to measure and, ultimately, eliminate it. Prominent among the approaches being translated from the basic to clinical realms this year are those with a potential dual mechanism of action: reversing HIV latency and stimulating immune responses against virus-infected cells.

The growing number of cure-related projects and collaborations globally is encouraging, but the decline in funding for the NIH – the world's largest funder of scientific research – is a major concern that must be addressed. As the field increasingly draws media attention, a broader dialogue is needed in order to reach consensus about how the goals of cure research and the terminology are characterized and communicated; the concept of HIV remission is increasingly invoked but is not yet clearly defined.

While the cure research pipeline is swelling, prospects for immune-based adjuncts to ART – interventions for which there remains a need – have dimmed in recent years. This is not due to lack of interest from scientists and clinicians, who are still pursuing small-scale studies of a range of possible therapies, but there is little sign of the industry support that might thrust an approach with promise through the pipeline. On a more hopeful note, although only tangentially related to immune-based therapy, the REPRIEVE trial of statin treatment may offer insight into the feasibility of conducting large-scale clinical evaluations of add-ons to ART.

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New Drugs, New Strategies: Conquering Hepatitis C with Direct-Acting Antivirals

By Tracy Swan

> *Hepatitis C has to be one of the most grossly miscalculated diseases by governments on the planet.*
>
> —Michel Kazatchkine, UN secretary general's special envoy on HIV/AIDS in Eastern Europe and Central Asia and commissioner, Global Commission on Drug Policy

The evolution of hepatitis C virus (HCV) treatment has been swift, dazzling, and unprecedented. In only five years, proof of concept for oral, interferon-free treatment has been established, nine direct-acting antivirals (DAAs) have been approved, treatment duration has been shortened to 12 weeks, and cure rates have been nearly 100% in clinical trials.[1,2,3,4]

Scaling up access to these wonder drugs – and primary prevention – could eliminate HCV, even without a vaccine. Unfortunately, sky-high DAA prices have created a paradox: the more treatment improves, the fewer people have access to it.

A public health approach will be needed to select, procure, and deliver HCV treatment. It is time to pick a first-line regimen, consider options for second-line treatment, and turn up the pressure for universal access to HCV treatment.

HCV Treatment Rationing

> *What is a cynic? A man who knows the price of everything and the value of nothing.*
>
> —Oscar Wilde

Worldwide, 185 million people have been infected with hepatitis C; 73% of them live in middle-income countries (MICs).[5] Pharmaceutical companies see MICs as emerging markets, even though they are home to the "bottom billion" – 73% of the world's poorest people.[6] MIC governments cannot afford DAAs for everyone who needs them.

The price of DAAs in the United States should not be the benchmark anywhere – even in the United States. In high-income countries (HICs), payers have been withholding treatment for hepatitis C, citing sofosbuvir's scandalous launch price (US$1,000 per pill). People who drink alcohol or who use and inject drugs are often ineligible for treatment.

HCV guidelines have been deliberately misinterpreted to justify withholding treatment. DAAs are given only to people with advanced liver disease, to stave off liver cancer, liver failure, transplantation, and death. Limiting HCV treatment access to people with advanced liver damage will stem liver-related mortality, but not epidemics.

HCV Disease Burden and Treatment Access in Egypt

Egypt has the world's highest HCV prevalence: more than 7%.[7,8] In 2006, the country instituted a national hepatitis C program. Since 2008, it has provided treatment for nearly 200,000 people. In 2014, Egypt's government negotiated with Gilead and Janssen to obtain volume-based discounts on their DAAs. Companies can charge higher prices on the private market, where uninsured Egyptians buy their own medicine. In Egypt, 85% of drugs are paid for out of pocket.[9]

Most Egyptians cannot afford HCV treatment. It is a middle-income country where the per capita gross national income (GNI) is US$3,140 – but more than 25% of Egyptians live on less than US$600 a year.[10,11] On the private market, a month of sofosbuvir (Sovaldi) costs EGP2,670 (US$350); simeprevir costs EGP3,166 (US$414).[12,13,14] Government prices are much lower: sofosbuvir costs EGP1,400 (US$184) per month; simeprevir costs EGP1,900 (US$248).[12,13]

The government provides free treatment to people who are unable to afford it, but it cannot do so for millions of people. In 2015, Egypt plans to treat 100,000 people through the national program.[15,16]

Rationing HCV treatment is a stopgap, not a solution – for several reasons:

- If HCV treatment is withheld for too long, it is less effective, and adverse events are worsened.[17,18]
- People with HCV-related cirrhosis remain at risk for liver cancer – *even after being cured* – and must undergo lifelong monitoring. Earlier treatment removes this risk.[19,20]
- HCV lowers quality of life and might cause or worsen many systemic health problems, even in the absence of serious liver disease.[21,22,23,24,25,26,27,28]
- HCV increases health care costs and hospitalization rates, even in people with mild-to-moderate liver disease.[29,30,31,32]
- Chronic HCV infection is associated with a higher incidence of non-liver-related comorbidities (alcohol and substance use disorders, mental illness, chronic kidney disease, obesity, metabolic disorders, pneumonia, and HIV) in people who are 45 to 64 years old.[33]
- People with HCV are dying two decades earlier from non-liver-related causes (including cardiovascular disease and respiratory failure) than people without HCV.[34]
- Many state-funded programs in the United States withhold HCV treatment from people who use alcohol. Withholding treatment based on alcohol use or dependence is harmful because alcohol accelerates HCV liver damage.[34]
    - There is no evidence that alcohol use during DAA treatment impairs efficacy (or safety).
- People who inject drugs are often ineligible for HCV treatment, although they are the highest-prevalence population. Worldwide, HCV prevalence among people who inject drugs is estimated at 67%; anywhere from 6 million to 15 million of them have chronic HCV.[35]
    - Likelihood of HCV reinfection is often a rationale for withholding treatment, although actual reinfection rates are low.[36]

  - People who inject drugs are often ineligible for HCV treatment because of concerns about poor adherence and treatment outcomes. But cure rates in injection drug users are similar to those in nonusers.[37,38]

- Withholding treatment allows HCV to keep spreading, especially among people who inject drugs (since access to injection equipment, methadone, and buprenorphine are woefully inadequate).
- Larger volume and competition between originators and generic drug producers can be leveraged to reduce prices. DAA prices have rapidly dropped by over 40% in some countries.[39,40,41,42] Still, these prices are unsustainable, even for HICs.

Competition, negotiations, and volume-based discounts have begun to bring down originator DAA prices in HICs. Gilead is expected to drop U.S. DAA prices by 46% or more in 2015.[41] Financial analysts estimate that DAA prices will drop to US$45,000 per treatment course in the United States and US$35,000 in HICs elsewhere.[41]

In France and Germany, sofosbuvir alone costs €488 per pill (US$550), or €41,000 (US$46,248) for a 12-week treatment course.[39, 42] In Spain, sofosbuvir costs €297 (US$335) per pill, or €25,000 (US$28,200) for a 12-week treatment course.[40] No information about E.U. prices for simeprevir and daclatasvir (DAAs often used with sofosbuvir) is publicly available.

In 2012, worldwide sales of hepatitis C treatment reached US$4.4 billion and were projected to reach US$10.8 billion by 2022.[43] In just one year, sofosbuvir sales have reached US$10.8 billion.[44] Lack of access to these lifesaving medicines has sparked outrage. Since sofosbuvir was approved, patent challenges, government inquiries, lawsuits, sit-in protests at hospitals, and massive demonstrations have sprung up worldwide.

The right to health *and* clinical evidence should inform access to HCV treatment. Withholding treatment for a curable infectious disease is not justifiable, particularly for one that is often chronic, known to worsen overall health, and potentially life-threatening.

HCV Treatment Strategies: Less Knowledge, More Options

> *We can't make perfectovir the enemy of goodovir.*
>
> —Jennifer Cohn, medical director, Médicines Sans Frontières/Doctors Without Borders Access Campaign

Three decades of antiretroviral drug development for HIV have been augmented by research from publicly funded networks, public-private partnerships, postmarketing trials, registries, and other sources. This robust evidence base informs treatment strategies and guidelines. But HCV DAAs are coming in a very short time frame; there are many choices – but far less knowledge about them. Although real-life data are emerging from registries, compassionate use/early access programs, and postmarketing studies, most of what we know about HCV DAAs comes from registration trials in HICs.

For now, optimizing DAA treatment means selecting the best available regimen and devising a follow-up strategy for new DAAs – or treatment failure (see figure 1).

Goodovir: Sofosbuvir and Daclatasvir

HCV "perfectovir" does not exist – yet.[45] But hepatitis C treatment is already "goodovir" – and it is not likely to improve enough to justify waiting for perfectovir.

Sofosbuvir and daclatasvir together constitute a once-daily, multigenotypic regimen. These DAAs have been effective, safe, and tolerable for thousands of people (including in liver transplant candidates and recipients or HIV/HCV coinfection) (see table 1).[46,47,48]

There is no reason to delay HCV treatment scale-up. A first-line regimen of sofosbuvir and daclatasvir (possibly plus ribavirin [RBV] for people with cirrhosis) will simplify procurement and delivery of HCV treatment. It can be profitably mass-produced for less than US$175.[49]

Table 1. Goodovir and the Future Perfectovir[1,2,3,4,46,47,48,50,51,52,53,54,55,56,57,58,59,60,61,62]

REGIMEN, STATUS, MANUFACTURER	UNIVERSAL		SIMPLE		EFFECTIVE (SVR >90%)	SAFE, TOLERABLE	COMMENTS
	Pangenotypic	Used in HIV	QD	Fixed Duration			
sofosbuvir/daclatasvir (400 mg/60 mg) QD Approved Gilead/BMS	YES (laboratory data only for G5 and G6)	YES	YES	Possibly, with RBV in cirrhosis (especially G3)	YES, except in G3/cirrhosis (without RBV)	YES	RBV may be needed to boost cure rate in cirrhosis (especially for genotype 3)
sofosbuvir/ledipasvir FDC (400 mg/90 mg) QD Approved Gilead	NO (no data in G2)	YES	YES	NO	YES, except in G2 and TX-experienced G3/ cirrhosis	YES	Longer treatment needed in cirrhosis; RBV needed for G3
grazoprevir/elbasvir FDC (100 mg/50 mg) QD Phase III Merck	NO (unless sofosbuvir is added)	YES	YES	NO	NO; less effective in G2; high failure rate in G3; indication sought for G1, G4, and G6	YES	Adding sofosbuvir significantly increased efficacy in G3
sofosbuvir/GS-5816 FDC (400 mg/100 mg) QD Phase III Gilead	YES	NO	YES	?	Depends on duration of treatment, genotype, cirrhosis	YES	Phase II data only
sofosbuvir/GS-5816/FDC + GS-9857 Phase II Gilead	YES	NO	YES	Under study	?	YES	Phase II data only
ABT-530 + ABT-493 Phase II AbbVie	?	NO	?	?	?	?	?
grazoprevir + MK-3682 with elbasvir or MK-8408 Phase II Merck	?	NO	?	?	?	?	?

BMS: Bristol-Myers Squibb
FDC: fixed-dose combination
G: genotype (as in G1, G2, G3, G4, G5, G6)
RBV: ribavirin
SVR: sustained virologic response; undetectable HCV RNA 12 or 24 weeks after finishing treatment, equivalent to cure
TX: treatment
QD: once daily

HCV Drug Resistance

Resistance-associated variants (RAVs) occur naturally in people who have never been treated for hepatitis C. During DAA treatment, RAVs can persist or emerge. In clinical trials, most people with pretreatment RAVs were cured – but RAVs are found in most people who were not cured. The prevalence, longevity, and impact of RAVs differ. Some RAVs have greater impact on drug potency than others.

Baseline resistance testing is not done outside of HCV clinical trials since it is expensive and not always predictive of treatment outcomes.

NS5A resistance

The barrier to resistance varies by class and individual DAA. NS5A inhibitors, although potent, have a low resistance barrier. Many people with pretreatment NS5A RAVs have been cured by an NS5A-containing regimen – but people who are not cured are likely to have NS5A RAVs. In the C-EDGE, ION-1, ION-2, and ION-3 trials of NS5A-containing regimens, most people who were not cured had NS5A RAVS before and after treatment.[1,2,3,53,62] In these trials, treatment failure occurred only in people with an HCV RNA >800,000 IU/mL, suggesting that NS5A RAVs are more likely with a high viral load.

Treatment-emergent NS5A RAVs are persistent for 96–170 weeks after treatment failure.[63,64,65,66] Second-generation NS5A inhibitors might be able to overcome resistance.[67]

NS3 resistance (protease inhibitors)

With HCV protease inhibitors, treatment-emergent RAVs tend to wane within months.[63] People who were not cured by a protease inhibitor–based regimen can be successfully re-treated with DAAs from different classes or with a regimen including a second-generation HCV protease inhibitor with a different resistance profile.[2,68,69]

NS5B resistance (sofosbuvir)

Sofosbuvir has a high resistance barrier and can be recycled in re-treatment regimens. In one trial, 98% (44/45) of sofosbuvir-experienced people were cured by a sofosbuvir-based re-treatment regimen.[70] Although rare, sofosbuvir treatment failure with baseline or emergent RAVs has been documented (especially in genotype 1b).[71,72,73,74]

HCV Treatment in HIV/HCV Coinfection

With DAAs, cure rates do not differ by HIV status, although drug-drug interactions between antiretroviral therapy and HCV treatment need to be avoided or managed.

New HCV Treatment Strategies

Approximately 90% of people are cured by sofosbuvir and daclatasvir (with or without ribavirin); the remaining 10% will need a second-line regimen. There is still a robust HCV pipeline to pluck for second-line DAAs.

Although HCV treatment is moving toward pangenotypic regimens, current strategies are still based on genotype (and sometimes subtype), treatment history, and extent of liver damage. Re-treatment options are limited, especially in genotypes 2 and 3. If pipeline DAAs live up to expectations, it will be possible to select interferon-free first- and second-line regimens.

Figure 1. Current and Proposed Interferon-Free HCV DAA Treatment Strategies

Current first-line strategies for HCV genotype 1

1. **Nucleotide + NS5A inhibitor, with or without RBV**
2. **Protease inhibitor + NS5A inhibitor + non-nucleoside inhibitor, with or without RBV (**complexity, subgenotyping, drug interactions, and RBV use may limit this approach)
3. **Nucleotide + protease inhibitor** (also HCV genotype 4; high DAA prices may limit use of this combination)

Current first-line strategies for HCV non-1 genotypes

1. **Nucleotide + RBV** (suboptimal efficacy in G3/cirrhosis)
2. **Nucleotide + NS5A inhibitor, with or without RBV** (RBV may increase efficacy in G3/cirrhosis)
3. **For G4, protease inhibitor + NS5A inhibitor, with or without RBV**

Next-generation, first-line strategies for all HCV genotypes

1. **Nucleotide + NS5A inhibitor, with or without RBV (NS5A resistance may limit efficacy)**
2. **12 weeks (or less) of a pangenotypic, triple-class regimen (NS5A inhibitor + protease inhibitor + nucleotide polymerase inhibitor). The drawback: this strategy limits options for second-line treatment unless second-generation NS5A and protease inhibitors are effective against RAVs**

Future retreatment strategies for all HCV genotypes

1. **Pangenotypic protease inhibitor (preferably active against RAVs) + nucleotide (for people with NS5A RAVs)**
2. **Pangenotypic protease inhibitor + pangenotypic NS5A inhibitor; both must be effective against NS3 and NS5A RAVs; these could be paired with a nucleotide**

DAAs and Diagnostic Simplification

Costly, complex diagnostic and monitoring requirements are also barriers to HCV treatment, particularly in resource-limited settings. DAAs and innovative diagnostics will make it simpler to identify people with chronic HCV, treat them, and cure them (see figure 2).

- Pre- and posttreatment HCV core-antigen tests could replace anti-HCV and HCV RNA tests.[75]
- Safety monitoring can be less intensive, since adverse event rates are lower and duration of treatment is shorter with DAAs versus interferon.[49]
    - Routine blood tests can be used for pretreatment assessment, identifying people with advanced liver damage (such as APRI or FIB-4), and safety monitoring during treatment.[76]
- Pangenotypic regimens will eliminate the need for pretreatment HCV genotyping and subtyping.

Figure 2. HCV Diagnostics, Assessment for Treatment, and Efficacy Monitoring:* High-Income Country Recommendations versus a Streamlined Process for Resource-Limited Settings[77,78]

High-Income Country Recommendations

HCV antibody testing (to screen)

HCV RNA (to diagnose; with some regimens, may determine duration of treatment and, possibly, whether to add another DAA)

Genotyping/subtyping (to select regimen and duration)

Assess liver damage (to inform duration of treatment)

Assess overall health* (for safety)

HCV RNA testing during and after treatment (to monitor treatment adherence, efficacy, and outcome)

- following E.U. guidelines: at baseline, weeks 2 and 4, EOT, and 12 or 24 weeks after EOT
- following U.S. guidelines: at week 4 and 12 weeks after EOT

Streamlined Process for Resource-Limited Settings

Core antigen (to diagnose HCV)

Assess overall health* and liver damage with routine blood tests (to inform regimen selection and safety monitoring)

Select pangenotypic DAA regimen with fixed duration of treatment (and potential for re-treatment, with longer duration or second-line regimen)

Monitor according to DAA safety profile and patient health

Adherence education, support, counseling

Core-antigen testing 12 or 24 weeks after EOT (to check treatment outcome)

*Additional pretreatment testing is recommended (including pregnancy testing; complete blood count; international normalized ratio; renal function; and levels of albumin, total and direct bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase).
EOT: end of treatment

HCV Drug Development and Pipeline Strategies

HIV treatment strategies are based on data from industry-sponsored clinical trials, cohort studies, government-funded research networks, public-private partnerships, and investigator-initiated trials. For decades, drugs from different companies have been combined in trials, clinical practice, and fixed-dose combinations (FDCs) from generic and originator companies.

Pharmaceutical companies mastermind DAA development. Clinical collaborations are rare. Incestuous DAA combinations are usually co-formulated to prevent use with a competitor's drug. Other market-driven strategies have delayed or prevented research into and development of optimal DAA combinations.

HCV drug development continues at breakneck speed. DAAs in early development promise to be pangenotypic and active against common RAVs. There is a trend to shorten treatment with multiclass DAA regimens. Several companies are developing – or buying – nucleotide polymerase inhibitors. In the meantime, they are doing "proxy" trials, using sofosbuvir as a placeholder for their own DAAs.

Table 2. Shortening Treatment[58,61,69,79,80,81]

TRIAL, POPULATION, AND MANUFACTURER	PHASE	REGIMEN, POPULATION, AND DURATION			SVR	COMMENTS
"Proxy" Study G1, TX-naive (N = 30) (6 in observation group) Achillion	II	ACH-3102 50 mg + sofosbuvir 400 mg QD		6 weeks	100% (12/12)	Achillion used sofosbuvir as a placeholder for its own nucleotide polymerase inhibitor, ACH-3422 (currently in phase I)
				8 weeks	100% (12/12)	
ELECTRON-2 G3, TX-naive (N = 104) Gilead	II	sofosbuvir 400 mg + GS-5186 25 mg or 100 mg +/– weight-based RBV QD	+ 25 mg	8 weeks	100% (27/27)	This regimen has been studied in other populations. Gilead selected the 100 mg dose of GS-5816 for co-formulation with sofosbuvir; the FDC is currently in phase III
			+ 25 mg & RBV		88% (21/24)	
			+ 100 mg		96% (26/27)	
			+ 100 mg & RBV		100% (26/26)	
G1 and G2 TX-naive noncirrhotic (N = 223) Gilead	II; part B	sofosbuvir 400 mg + GS-5186 25 mg or 100 mg +/– weight-based RBV QD	G1 + 25 mg	8 weeks	77% (20/26)	Longer duration of treatment with this regimen may increase efficacy
			G1 + 25 mg & RBV		88% (22/25)	
			G1 + 100 mg		88% (23/26)	
			G1 + 100 mg & RBV		88% (23/26)	
			G2 + 25 mg		77% (20/26)	
			G2 + 25 mg & RBV		88% (22/25)	
			G2 + 100 mg		88% (23/26)	
			G2 + 100 mg & RBV		88% (23/26)	
G1, TX-naive or DAA-experienced, with or without cirrhosis (N = 75) Gilead	II	sofosbuvir/GS-5186 400 mg/100 mg FDC + GS-9857 100 mg QD	TX-naive	4 weeks	27% (4/15)	Longer treatment and RBV might be needed in cirrhosis, especially in people who are treatment-experienced
			TX-naive	6 weeks	93% (14/15)	
			TX-naive + cirrhosis		87% (13/15)	
			DAA-experienced		68% (17/25)	
			DAA-experienced + cirrhosis		60% (3/5)	
C-SWIFT G1 and G3, TX-naive Noncirrhotic and cirrhotic (N = 143) Merck	II	grazoprevir/elbasvir 100 mg/50 mg FDC + sofosbuvir 400 mg QD	G1	4 weeks	33% (10/30)*	Merck is using sofosbuvir as a placeholder for MK-3682 (currently in phase II) This regimen was less effective for HCV RNA >2,000,000 IU/mL (85% vs. 100%)
			G1	6 weeks	87% (26/30)	
			G1 + cirrhosis	6 weeks	80% (16/20)	
			G1 + cirrhosis	8 weeks	94% (17/18)*	
			G3	8 weeks	93% (14/15)	
			G3	12 weeks	100% (14/14)	
			G3 + cirrhosis	12 weeks	91% (10/12)	
SYNERGY G1, TX-naive (N = 60) NIH	IIa	sofosbuvir/ledipasvir 400 mg/90 mg FDC QD		12 weeks	100% (20/20)	SYNERGY led the way for trials of shorter, multiclass regimens Gilead has not used GS-9669 or GS-9451 in other trials
		sofosbuvir/ledipasvir 400 mg/90 mg FDC + GS-9669 500 mg QD		6 weeks	95% (19/20)	
		sofosbuvir/ledipasvir 400 mg/90 mg FDC + GS-9451 80 mg QD		6 weeks	100% (20/20)	

*modified intent-to-treat analysis; 5 people excluded for nonvirological failure

ACH-3102 (NS5A inhibitor); elbasvir (NS5A inhibitor); grazoprevir (protease inhibitor); GS-5186 (NS5A inhibitor); GS-9451 (protease inhibitor); GS-9669 (non-nucleoside polymerase inhibitor); GS-9857 (protease inhibitor); ledipasvir (NS5A inhibitor); sofosbuvir (nucleotide polymerase inhibitor)

FDC: fixed-dose combination
G: genotype
QD: once daily
SVR: sustained virological response
TX: treatment

Company-Specific Strategies for DAA Development

AbbVie

AbbVie is developing ABT-530 (an NS5A inhibitor) and ABT-493 (a protease inhibitor). In preclinical studies, ABT-530 was active against many NS5A RAVs and pangenotypic; ABT-493 was active against HCV genotypes 1, 2, 3 (especially 3a), 4, and 6 – and common NS3 RAVs.[82,83] These drugs are being studied with or without RBV in phase II trials of all HCV genotypes. An April 8 press release announced a 99% sustained virological response four weeks after treatment (SVR-4) from a phase II trial combining these DAAs.[84]

If AbbVie's pipeline DAAs live up to their pangenotypic, resistance-proof promise, they could be part of second-line treatment. ABT-493 could be paired with sofosbuvir for a pangenotypic re-treatment regimen; if ABT-530 is effective against RAVs, it could be used with sofosbuvir or ABT-493.

Bristol-Myers Squibb (BMS)

Data from thousands of people have supported the safety, tolerability, and efficacy of daclatasvir. Hopefully, it will be available – and affordable – worldwide; it is urgently needed for a pangenotypic first-line regimen.

Daclatasvir's approval – and BMS's overall HCV drug development program – has been stymied by bad luck, inopportune timing, and bold decisions that should have been cautious (and vice versa). The future of the BMS HCV program and its twice-daily, RBV-free TRIO regimen is uncertain. Although SVR in genotype 1b is 98%, TRIO is less effective for genotype 1a than other RBV-free treatment options (SVR: 89% in noncirrhotic; 88% in cirrhotic).[85,86]

Gilead

Gilead's drug development program has been swift, flexible, efficient – and ruthless. The company is seeking to shorten treatment with once-daily, multiclass, pangenotypic FDCs. Gilead's FDC of sofosbuvir and GS-5816 (an NS5A inhibitor) is in phase III. It remains to be seen whether GS-5816 has advantages over daclatasvir (aside from being owned by Gilead). The company is also developing a triple-class combination with the sofosbuvir/GS-5816 FDC and GS-9857 (a protease inhibitor), currently in phase II.

Sofosbuvir has been the backbone of short-course regimens (with grazoprevir/elbasvir; Achillion's NS5A inhibitor, ACH-3102; and Gilead's own drugs, ledipasvir, GS-9669 [a non-nucleoside polymerase inhibitor], or GS-9451 [a protease inhibitor]) (see table 2). Coming up with a short, cure-all regimen has proved to be tricky: six weeks of Gilead's triple-class regimen cured 93% (14/15) of treatment-naive people with HCV genotype 1, but only 68% (17/25) of DAA-experienced people.[69]

Janssen

At the end of 2013, results from the phase II COSMOS trial were used to recommend off-label use of simeprevir with sofosbuvir for genotype 1.[87] Since then, simeprevir has been used in HIV/HCV, cirrhosis, after liver or kidney transplantation, in HCV genotype 4, and with daclatasvir.[88,89,90,91,92,93,94,95]

Janssen will continue to develop DAAs, with a focus on nucleotides. The company has an NS5A inhibitor, JNJ-56914845, in phase II. In November 2014, it purchased Alios BioPharma and acquired two nucleotides: AL-335 (currently in phase I) and AL-516 (currently in preclinical development). In May 2015, Janssen announced a licensing agreement with Achillion, which is developing ACH-3102 (an NA5A inhibitor in phase II) and ACH-3422 (a nucleotide in phase I). Medivir, a past development partner of Janssen's, has a nucleotide (MIV-802) in preclinical development.

Merck

Merck's nautically themed development program for the grazoprevir/elbasvir FDC was bedeviled by dosing problems with grazoprevir and loss of "breakthrough therapy" designation from the U.S. Food and Drug Administration (although Merck subsequently regained it).

It was nearly impossible to figure out the combined impact of host and viral factors, regimen, and duration on SVR in Merck's phase II, multiarm C-WORTHY trial. In phase III trials, a fuller picture of the strengths and vulnerabilities of the FDC emerged. Cure rates in genotype 1b and genotype 4 have been >90%, regardless of HIV status, treatment experience, or cirrhosis.[53,59,62,68] In the oddly named C-SURFER trial, 12 weeks of grazoprevir/elbasvir cured 94% (115/122) of people with HCV genotype 1 and end-stage renal disease, a population with few options and urgent need for HCV treatment.[96] The FDC was less effective against genotype 1a – especially for people with baseline NS5A RAVs known to lower elbasvir potency more than fivefold.[53,62,68] In the C-EDGE treatment-naive trial, overall SVR in HCV genotype 1a was 92% (144/157). It dropped to 58% (11/19) among people with baseline NS5A RAVs and was even lower in people with RAVs associated with lower elbasvir potency (22%; 2/9).[62] In the C-EDGE treatment-experienced trial, SVR dropped from >90% in genotype 1a to 52% (11/21) in people with baseline NS5A RAVs that lower the potency of elbasvir more than fivefold.[53]

On May 28, Merck announced submission of a new drug application for the FDC in genotypes 1, 4, and 6 (the FDC underperformed in genotypes 2, 3, and 5).[51,97,98]

Merck has a strategy beyond launching the FDC: to shorten treatment, with a multiclass regimen. In C-SWIFT, sofosbuvir was added to the FDC for four to 12 weeks of treatment. SVR topped 90% in people with genotype 1 and cirrhosis after only eight weeks of treatment; in people with genotype 3 and cirrhosis, SVR was >90% after 12 weeks of treatment (see table 2).[58]

Merck has DAAs to advance this strategy: MK-8408, a second-generation NS5A that was pangenotypic and active against drug resistance in laboratory studies, and MK-3682, a nucleotide polymerase inhibitor Merck acquired with its 2014 purchase of Idenix.[99] Based on proof of concept from phase I and C-SWIFT, Merck's trials are combining grazoprevir and MK-3682 with elbasvir or MK-8408 for six to eight weeks in ongoing phase II studies in HCV and HIV/HCV, genotypes 1, 2, 3, 4, and 6.[58,100]

Company-Specific Access Strategies for Low- and Middle-Income Countries

World CAB Meeting

In February 2014, the first WORLD CAB meeting was held in Bangkok, Thailand, where activists from low- and middle-income countries (LMICs) met with representatives from AbbVie, BMS, Gilead, Janssen, Merck, and Roche to discuss HCV treatment access. During the meeting, company representatives insisted that access in LMICs would not be possible without a global funding mechanism (such as the U.S. President's Emergency Plan for AIDS Relief or the Global Fund to Fight AIDS, Tuberculosis and Malaria) and that governments needed to "show commitment by scaling up HCV treatment programs before obtaining price reduction."[101]

AbbVie

AbbVie has not disclosed access plans for LMICs. According to a statement on its website from Richard A. Gonzalez, AbbVie's chairman and CEO, the company is "committed to improving lives, and we pledge to go about it in a transparent and sustainable way."[102]

A corporate responsibility brochure describes AbbVie's philanthropic initiatives, including a US$100 million investment in "state-of-the art manufacturing facilities to ensure patients receive a consistent supply of our HIV products"; the "Week of Possibilities" (an adult volunteer program to "transform educational spaces" and "support patients"); and AbbVie Foundation grants for pediatric AIDS, Buruli ulcer detection programs, and disaster relief, but it says nothing about hepatitis C.[103]

BMS

In November 2014, BMS announced its plans for a "Hepatitis C (HCV) Developing World Strategy." The company plans to offer tiered pricing and grant voluntary licenses (VLs) to 90 LMICs – including places where the drug is not patented.[104] Médicines Sans Frontières/Doctors Without Borders (MSF) has described the BMS plan as "a restrictive commercial strategy for sales of its new direct-acting antiviral (DAA) hepatitis C drug daclatasvir in developing countries."[105]

Notably, BMS has not offered VLs to high-burden MICs such as China, Brazil, Egypt, Thailand, and Ukraine. In fact, 50 million people with HCV live in countries where BMS is not offering VLs.[5] Although the country has "initiated discussions with government health authorities and other stakeholders," there is no additional information on plans to license, register, and price daclatasvir.

Gilead

Gilead has not offered VLs to certain high-burden MICs where there are over 50 million people with HCV.[5,106] This means that generic DAAs cannot be sold in these countries. Gilead has blocked other pathways by limiting access to the raw ingredients for its drugs. Gilead's licensees must purchase them from certain suppliers, who are not allowed to sell them to unlicensed generic drug producers. Gilead's extortionate pricing in HICs, unwillingness to provide HCV treatment access to millions of people in MICs, and unethical antidiversion measures (which would not be necessary if its drugs were affordable) are unacceptable.

Janssen

Janssen's website features a global public health section that does not mention hepatitis C.[107] Johnson & Johnson's "Strategic Framework" does not mention HCV. Another part of the company's website ("Pricing Strategies and Programs") describes "strategic, innovative and equitable pricing strategies for a wide variety of diseases" and the access strategy of "a tiered pricing model based on a combination of a country's economic conditions and public health situation."[108,109]

Merck

Merck's website does not provide any HCV-specific access information.

The company's "Statement of Guiding Principles" cites Merck's commitments to research and development, manufacturing and supply, registration, and community investment. Expectations are managed: "While we cannot address complex public health challenges on our own, we will engage in community investment to address the barriers to access where we believe we can make the strongest contributions."[110]

The Medicines Patent Pool and HCV

The Medicines Patent Pool (MPP) is considering expanding its mandate to include negotiating VLs for tuberculosis and hepatitis C. But the MPP has not announced a strategy, goal, or vision for increasing access to DAAs.

MSF has released a statement of support for the MPP's entry into HCV, contingent on consideration of "key issues."[111]

Activists have expressed deep concerns about the MPP entering the "HCV space":

- The MPP's VLs for HIV treatment have excluded most MICs, where access to HCV treatment is needed most. The MPP has not disclosed plans to increase access to HCV treatment in MICs, including countries that have been excluded from the Gilead HCV licensing agreements.
    - Unless the MPP can significantly broaden the geographic scope of the HCV VLs, it will have limited impact on access to HCV treatment.
- The MPP does not directly support other means to increasing access, including patent oppositions and TRIPS flexibilities (allowing countries to produce affordable medicines through a compulsory license, or to import medicines from countries where prices are lower). In fact, some MPP licenses may actually undermine legal TRIPS flexibilities.[112]
    - The MPP's existing HIV licensing agreements with Gilead have the same clauses as Gilead's own HCV licenses; this lowers confidence that the MPP will be able to improve the terms of existing HCV VLs.[110]
    - The MPP's entry into HCV may discourage other community-led approaches, such as pushing governments to issue compulsory licenses. Brazil's compulsory license for efavirenz saved US$100 million, which the country used to provide universal HIV treatment.[113]
- The MPP VLs will attract more generic drug producers. This will limit the remaining sources from which excluded countries can obtain generic DAAs and their raw ingredients.[110]
- The MPP has not made a public statement about the antidiversion measures initially included in Gilead's HCV VLs. These included requiring proof of identity, residence, and citizenship; issuing a one-month

supply of medicine in a smartphone-enabled, coded pill bottle that tracks patients by name, address, and adherence; and refusing to refill medication until empty pill bottles were returned to the local distributor. MSF has issued a briefing document that calls on Gilead to remove these measures.[114]

- VLs are not needed in countries where drugs are not patented. If the MPP offers them, ongoing patent oppositions in LMICs may be undermined.
    - DAAs are covered under patents for years to come: daclatasvir until 2027, sofosbuvir until 2029.[115] Each year, 700,000 people die from HCV-related liver disease.[116] Delaying access to DAAs in LMICs until patent expiry will cost millions of lives.

The same strategies that have led to dramatic price reductions for HIV treatment must be used to provide a cure for millions of people with hepatitis C in LMICs. Generic DAAs can be profitably – and affordably – mass-produced for less than US$200 per treatment course.[49,117]

Conclusion

Curing hepatitis C with safe and effective oral drugs is now possible. The challenge is to secure universal access to HCV treatment and deliver DAAs to the millions of people who need them.

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CROI: Conference on Retroviruses and Opportunistic Infections
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The Tuberculosis Treatment Pipeline: Moving Beyond "Making the Most of What We've Got"

by Erica Lessem

For decades, those living with tuberculosis (TB) and their providers have operated in conditions of scarcity and neglect: inadequate funding for programs and research, aging infrastructure and outdated technologies, limited scientific understanding, knowledge gaps on existing treatments, low public attention, and absent political will.

The limited response to TB born of these conditions remains entrenched, even with two new drugs conditionally approved by stringent regulatory authorities,[1,2] a new global strategy to end TB from the World Health Organization (WHO) that envisions a world free of TB (with a 95% reduction in TB deaths and 90% reduction in TB incidence by 2035 compared with 2015 levels),[3] and a relative increase in resources for TB drug development since 2006.[4] (Though funding for TB research and development [R&D] is still grossly insufficient, investments in TB drug research, which amounted to US$255 million in 2013, have reached just one-third of the annual target set by the *Global Plan to Stop TB, 2011–2015*.[5])

To their credit, TB treatment researchers are making the most of what they have, cobbling together combinations and treatment strategies to better use existing medicines and the few new and experimental drugs available, as well as exploring adjunct, host-directed therapies to improve treatment. For the first time since 2009, a new drug candidate recently entered phase I (see table 1).[6] Studies are at last under way or coming together to test new drugs in smarter combinations to determine the safety of coadministration and optimal regimens for multidrug-resistant TB (MDR-TB). Innovative trial designs are attempting to shorten treatment for drug-sensitive TB (DS-TB), and improved preventive therapy for TB, including for MDR-TB, is progressing.

But for the most part, these research efforts won't bear fruit for years. Drug sponsors are slow or unwilling to collaborate, pharmaceutical investment is minimal, and TB treatment trials remain lengthy. This work should have advanced long ago – but better late than never.

Table 1. Drugs in Development for Tuberculosis

Drug	Class	Sponsor(s)	Phase
delamanid	nitroimidazole	Otsuka, NIAID, UNITAID	III
pretomanid	nitroimidazole	TB Alliance	III
bedaquiline	diarylquinoline	Janssen, TB Alliance, NIAID, SAMRC, the Union, UNITAID, USAID	IIb/III
AZD5847	oxazolidinone	AstraZeneca, NIAID	IIa
sutezolid	oxazolidinone	Sequella	IIa
TBA-354	nitroimidazole	TB Alliance	I

NIAID: National Institute of Allergy and Infectious Diseases (United States)
SAMRC: South African Medical Research Council
The Union: International Union Against Tuberculosis and Lung Disease

In the meantime, TB programs, donors, multilateral agencies and nongovernmental organizations providing technical assistance, and pharmaceutical companies have been halting and unambitious in rolling out available strategies and new technologies. Nearly half a million people develop MDR-TB a year, yet less than

one in three is diagnosed, and only one in five starts treatment.[7] According to estimates based on WHO guidelines, bedaquiline or delamanid is clinically appropriate for a third of those who develop MDR-TB (160,000 people per year).[8] Yet despite bedaquiline's being approved for two-and-a-half years, fewer than 1,000 people worldwide have received it outside of a clinical trial.[9] A bedaquiline donation program that opened in April 2015 could improve access if implemented properly, though drug donations are by definition a limited and unsustainable approach.[10] Access to delamanid has been far worse, with fewer than 200 patients receiving it outside of studies, even though it was approved over a year ago.[11] TB drug research and programming alike need an infusion of urgency, coordination, and funding.

Regulatory Spotlight

Regulatory hurdles are one of the major barriers to obtaining medicines for people with TB and the providers who treat them; they can also delay research. In the United States, where the FDA is relatively well equipped to review trial proposals and new drug applications in a timely and rigorous fashion, a lack of flexibility and high fees have discouraged registrations of generic drugs, contributing to drug shortages by leaving the market dependent on a limited number of suppliers. Globally, regulatory inefficiencies plague most regions, countries, and disease areas. China offers an extreme example, with over 18,500 drugs in line for approval at the end of 2014 and wait times of six to eight years.[29] Reviewing research proposals can take years, delaying trial starts and at times derailing studies completely. These general delays, due largely to weak regulatory infrastructure, tend to be exacerbated in TB, where decades without new drugs for approval have left regulators with no experience in evaluating new TB drugs. Submitting applications to multiple national regulatory authorities, with long wait times and varying requirements for data presentation and language of submission, is onerous and resource-intensive. Efforts toward regional harmonization, such as in the East African Community, are welcome.[30]

In spite of these concerns, drug sponsors can and must do more to ensure access to TB drugs. If companies do not file for drug approval in a country, there is no consistent, universal mechanism for access. Work-arounds such as pre-approval access or import waivers are limited in scope, cumbersome, inefficient, and unsustainable. Otsuka has filed for registration of delamanid only in Europe, Japan, and South Korea, where very few patients with MDR-TB live. It still has not registered the drug in any of the high–MDR-TB burden countries that housed its clinical trials (Moldova, Peru, the Philippines, and South Africa), despite sustained international advocacy campaigns to do so. Otsuka notes that additional applications are pending in China, the Philippines, Indonesia, and the United States.[31] Janssen, in contrast, along with Pharmstandard (the Russian company to which Janssen licensed bedaquiline for marketing in the former Soviet republics known as the Commonwealth of Independent States) has made progress in registering bedaquiline in far more countries with high burdens of MDR-TB (see table 3). Manufacturers of older and off-label drugs used to treat TB such as rifapentine, linezolid, and clofazimine must do more to widely register their drugs and seek an indication for TB.[32]

At the same time, the WHO, UNITAID, the Global Fund, the Stop TB Partnership's Global Drug Facility (GDF), and others can support these efforts by providing technical support to regulatory authorities, ministries of health, and TB programs. The WHO can also include clofazimine on the Model List of Essential Medicines, as it recently did for bedaquiline, delamanid, and linezolid after advocates, drug sponsors, Médecins Sans Frontières/Doctors Without Borders, and the Global TB Program of the WHO itself called for their inclusion.[33,34]

TB Infection

Table 2. Tuberculosis Infection Clinical Trials

Study/Regimen	Status	Population	Sponsor(s)
A5279 Self-administered daily rifapentine + isoniazid for 1 month (vs. isoniazid daily for 9 months) NCT01404312*	Fully enrolled	People with HIV with positive skin test/IGRA or living in high-TB-prevalence regions	ACTG
A5300/Phoenix 6 months daily levofloxacin (vs. isoniazid)	Protocol development	Household contacts (adults, adolescents, and children ≥2 years) of individuals with MDR-TB	ACTG, IMPAACT
iAdhere (S33) Self-administered once-weekly rifapentine + isoniazid for 12 weeks (with and without electronic reminders) NCT01582711*	Completed	Adults with TB infection	TBTC
4R vs. 9H 4 months daily rifampin (self-administered) NCT00931736*	Fully enrolled	Adults with positive skin test or QuantiFERON-TB blood test, including people with HIV not on ARVs whose efficacy is reduced by rifampin	McGill University, CIHR
V QUIN 6 months daily levofloxacin (vs. placebo)	Protocol development	Household contacts (adults, adolescents, and children down to 3 kg) of individuals with MDR-TB	NHMRC, Vietnam National Treatment Program
I2001 12 weeks of supervised weekly rifapentine + isoniazid	Beginning enrollment Q3 2015	Pregnant women at high risk of TB	IMPAACT

*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
ARVs: antiretrovirals
CIHR: Canadian Institutes of Health Research
IGRA: interferon gamma release assay – QuantiFERON-TB Gold In-Tube (QFT) or T-SPOT TB test
NHMRC: National Health and Medical Research Council (Australia)
IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Group
TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention

Preventing TB requires infection control to avert transmission and preventive therapy for subclinical TB infection (often referred to as latent TB infection, or LTBI, as it is asymptomatic and is not transmissible), as an improved vaccine is years away (see "Tuberculosis Vaccines Pipeline," p. 163). Modeling demonstrates that rapidly reducing TB incidence and death on the path to elimination depends on treating both active TB disease and TB infection.[12] With an estimated one-third of the world's population infected with TB, we need a much better understanding of who is most at risk of progression from TB infection to active TB disease to target prevention efforts.

Meanwhile, efforts advance to refine prevention strategies. In 2014, the WHO issued refreshingly clear and concise guidelines on testing for and treating TB infection.[13] The guidelines recommend as equivalent six months of daily isoniazid, nine months of daily isoniazid, and three months of weekly rifapentine plus isoniazid. Two additional regimens received a majority vote for WHO recommendation but did not receive consensus from the panel: three to four months of isoniazid plus rifampin daily and three to fourth months of

rifampin alone daily. This last regimen is already recommended by the U.S. Centers for Disease Control and Prevention (CDC) in patients who cannot tolerate isoniazid or have been exposed to isoniazid-resistant TB.[14] A phase III clinical trial comparing four months of daily self-administered rifampin with nine months of daily self-administered isoniazid in adults has completed enrollment; results are expected in 2016.[15]

In the United States, the regimen of 12 once-weekly doses of rifapentine plus isoniazid, also known as 3HP, is being rolled out after having been demonstrated to be noninferior to the standard nine months of isoniazid alone when given as directly observed therapy.[16,17] In 2014, the U.S. Food and Drug Administration (FDA) approved rifapentine's indication for treatment for TB infection when given with isoniazid to people ages two years and over.[18] Research is examining the role of a historic price reduction in increasing access to this regimen in the United States.[19]

Tuberculosis Trials Consortium (TBTC) Study 33, the iAdhere trial, sponsored by the CDC, found that adherence to self-administered 3HP, with or without text-messaging reminders, was not equivalent to supervised treatment (noninferiority was not demonstrated). But among the large subset of participants enrolled in the United States, self-administered treatment was noninferior.[20] Treatment completion among U.S. participants was 85.4% (95% CI: 80.4%–89.4%) under directly observed therapy and 77.9% (95% CI: 77.2%–82.6%) under self-administered therapy, which was deemed noninferior. In the United States, treatment completion was only 76.7% (95% CI: 70.9%–81.7%) under self-administered therapy with electronic reminders, which did not achieve noninferiority. Overall treatment completion (including sites in China, South Africa, and Spain[21]) was 87.2% (95% CI: 83.1%–90.5%) under directly observed therapy, 74.0% (95% CI: 68.9%–78.6%) by self-administered therapy, and 76.4% (95% CI: 71.3%–80.8%) by self-administered therapy with electronic reminders, failing to meet noninferiority margins.

This divide in results between the United States (a low-incidence, high-income country) and high-incidence countries such as China and South Africa mirrors a broader split in the approach to preventive therapy for TB. While shortened regimens such as 3HP may confer advantages in some settings, it is unclear if shorter treatment is an advantage in settings with high rates of transmission such as mines in South Africa, as the protective effects of preventive therapy last only for the duration of treatment.[22] Rifamycin-based shorter or intermittent treatment may also not be particularly desirable in people already on daily antiretroviral therapy (ART), especially when direct observation for the TB treatment is required and rifampin and rifapentine interact with some ART components, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs).[23]

The WHO guidelines further this divide in strategies for treating TB infection. These guidelines differ in recommendations for high- and upper-middle income countries with lower TB incidence (<100/100,000) and for resource-limited or other middle-income countries. According to the guidelines, the former should systematically test for and treat TB infection in people living with HIV, adult and child contacts of individuals with pulmonary TB, and patients on tumor necrosis factor alpha (TNFα) treatment, on dialysis preparing for organ transplantation, or with silicosis. Resource-limited countries should systematically test for and treat TB infection in people living with HIV and in children under five years old, in whom active TB has been ruled out, who are close contacts of people with TB.

The recently completed Temprano study, conducted in Côte d'Ivoire, had two exciting findings regarding TB prevention in people with HIV. First, among those whose CD4 counts were higher than the original WHO cut-off point of 500 cells/mm^3,[24] starting ART immediately reduced the risk of death and serious HIV-related illness, including TB, by 44% (2.8 vs. 4.9 severe events per 100 person-years; P = .0002). Second, six months of isoniazid preventive therapy independently reduced the risk of severe HIV morbidity by 35% (3.0 vs. 4.7 severe events per 100 person years; P = .005) with no overall increased risk of other adverse events.[25] These results warrant an update to the WHO guidelines: they should emphasize the importance of earlier ART initiation and treatment of TB infection in those with HIV as long as active TB disease is ruled out (even in the absence of testing for TB infection).

Evidence-based strategies for preventing infection with MDR-TB from progressing to active disease are urgently needed. The long-awaited A5300 or Phoenix study is moving slowly through midstage protocol development and approval within the AIDS Clinical Trials Group (ACTG) and International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT). The study will evaluate the efficacy of levofloxacin compared with isoniazid in preventing TB disease in adults, adolescents, and children in households with a case of active MDR-TB. A related protocol, TB CHAMP (see "Momentum in the Pediatric Tuberculosis Treatment Pipeline," page 137), will compare levofloxacin versus placebo in children five years and younger.[26] A third study, V QUIN, will look at six months of levofloxacin versus placebo in Vietnamese adult, adolescent, and child household contacts of individuals with MDR-TB; enrollment is expected to start in the second half of 2015.[27,28] These will be the first three large-scale clinical trials to build a much-needed evidence-based approach for managing TB infection in those with close contact with someone with MDR-TB. If currently ongoing adult and pediatric trials continue to support delamanid's safety, the ACTG and IMPAACT should work with Otsuka to conduct a similar study using delamanid-based preventive regimens.

Table 3. Research and Access for Late-Stage New Compounds

	Bedaquiline	Delamanid	Pretomanid
RESEARCH			
Pediatrics (see "Momentum in the Pediatric Tuberculosis Treatment Pipeline," p. 137)	Trial not yet started	Trial started June 2013; results expected 2017	Trial not yet started (further preclinical toxicology work pending)
Phase III trial	Trial not yet started (two arms to be added to STREAM trial July 2015)	Enrollment completed November 2013; results expected 2017	STAND trial initiated February 2015; results expected 2018
ACCESS			
Compassionate use program	Started Q1 2011 660 patients enrolled (as of June 5, 2015)	Started Q1 2014 >23 patients enrolled (as of June 4, 2015)	None
Expanded access trials	Started 2011 in Lithuania, Russia (application in China denied)	None	None
Approvals	United States (2012), Russia (2013), European Union (2014), South Africa (2014), South Korea (2014), the Philippines (2014), Peru (2014), India (2015)	Europe (2014), Korea (2014), Japan (2014)	None (not pursuing accelerated approval; waiting for phase III trial completion)
Additional registrations (decision pending)	Armenia, Azerbaijan, Bangladesh, China, Colombia, Georgia, Indonesia, Kazakhstan, Kyrgyzstan, Taiwan, Thailand, Turkmenistan, Uzbekistan, Vietnam	None	None
World Health Organization Essential Medicines List inclusion	Included (April 2015)	Included (April 2015)	N/A
Pricing	Tiered pricing by country income level (per-pill price: high US$159.57; middle US$15.96; low US$4.79); 30,000 treatment courses donated for free	Tiered pricing by country income level (per-pill price US$78 in the United Kingdom and US$111 in Japan; low- and middle-income country details unannounced)	N/A (note: nonprofit TB Alliance has affordability commitment)

N/A: not applicable

Active TB Disease

For the first time in six years, a new drug candidate for TB has entered phase I clinical trials.[35] TBA-354, the newest nitroimidazole under study, is in the same class of drugs as delamanid and pretomanid (formerly PA-824).

Little progress has been made on other early-stage candidates. For example, there is still no evidence to suggest that SQ109 has clinical activity in persons with TB disease. In preliminary results presented at the 2015 Conference on Retroviruses and Opportunistic Infections (CROI), the PanACEA MAMS-TB-01 trial indicated no benefit in time to stable culture conversion over 12 weeks of including SQ109 rather than ethambutol in standard therapy for drug-sensitive TB (median 63 vs. 62 days; adjusted hazard ratio 0.82; 95% CI: 0.55–1.24; P = .35). Even when SQ109 was given with double the standard dose of rifampin, there was no apparent advantage in time to culture conversion over standard therapy (median 66 vs. 62 days; adjusted hazard ratio 0.73; 95% CI: 0.48–1.13; P = .16). Final clinical outcomes from this study are still pending.[36]

The resulting small number of plausible new compounds (six) and narrow diversity of new drug classes (two, as linezolid from the oxazolidinones is already on the market) for TB treatment remain a serious concern (see table 1).

For most of these products, progress remains glacially slow. Since Pfizer's abandonment of TB R&D and its decision to license sutezolid (an oxazolidinone potentially less toxic and more potent than linezolid) to the small, underfunded company Sequella, the drug's development has completely stalled.[37] The Johns Hopkins University, which owns some of the intellectual property rights to sutezolid, is in a unique position to ensure that the drug is developed and marketed responsibly. Johns Hopkins should make the transfer of intellectual property rights conditional on Sequella's meeting firm deadlines for conducting studies and ensuring specific and strong provisions for collaborative research, fair pricing, and availability pre- and postapproval for people with TB and TB programs.[38]

AZD5847, another oxazolidinone, has languished. AstraZeneca, its sponsor, has exited the TB field, and results from a phase IIa U.S. National Institutes of Health–sponsored trial completed in 2013 remain unpresented.[39] We urgently need new candidates to come through preclinical development, yet companies like Vertex have been sitting on promising compounds such as VXc-486 without advancing them or allowing others to do so.[40]

With so few options, researchers are focusing on repurposing what's available, for both drug-sensitive and drug-resistant TB (DR-TB). Efforts are also picking up to evaluate the utility and safety of host-directed therapy.[41]

DS-TB

The quest for shorter treatments for DS-TB continues, with a commitment to optimizing the use of older treatments and some creative thinking on how to use new ones.

Better use of rifamycins, whose potent anti-TB activity and likely current underdosing offer promise, could potentially be one avenue for shortening DS-TB treatment. TBTC Study 31/ACTG A5349, a phase III trial that will test whether a higher dose of 1,200 mg daily rifapentine with or without moxifloxacin can shorten DS-TB treatment to four months in people with and without HIV, will begin enrollment in mid-2015. HIRIF, a two-month phase IIb trial comparing rifampin at 10 (standard), 15, and 20 mg/kg daily on top of the standard regimen, has completed enrollment in Lima, Peru; top-line results are expected by the end of 2015.[42] A two-week study found that more than tripling the standard dose of rifampin to 35 mg/kg was safe and well tolerated, at least over this short period, and was associated with higher rates of early bacterial killing.[43]

A higher dose of rifampin (40 mg/kg) from this study is currently under analysis, and, if it is shown safe, even higher doses may be examined.[44]

The potential efficacy benefits and safety of higher doses of rifampin appear promising so far in a longer study. The above-mentioned PanACEA MAMS-TB-01 trial found that three months of dosing with 35 mg/kg of rifampin, in addition to standard isoniazid, ethambutol, and pyrazinamide, improved time to stable culture conversion over 12 weeks on liquid (though not on solid) media over the standard DS-TB treatment (median 48 vs. 62 days; adjusted hazard ratio 1.75; 95% CI: 1.21–2.55; P = .003). The experimental culture conversion rate was the highest ever reported in a TB trial. Another experimental arm containing 20 mg/kg of rifampin, along with moxifloxacin, showed statistically nonsignificant improvements in time to stable culture on liquid (again, not on solid) media over 12 weeks (hazard ratio 1.42; 95% CI: 0.98–2.05). All arms appeared safe and well tolerated, though a slightly higher percentage of patients (14% vs. 10%) experienced grade 3 adverse events in the higher-dose rifampin-containing arms than in the control arm, with potentially higher rates of hepatic adverse events that resulted in a change of treatment in the 35 mg/kg rifampin arm.[45] Final analysis of the study is under way.

These approaches to optimize rifamycins, with or without the addition of moxifloxacin, are among the most straightforward options for potentially shortening DS-TB treatment using existing drugs.

A study in India showed that four-month therapy adding moxifloxacin to first-line treatment (either with daily or intermittent therapy in the continuation phase) was equally effective to the local standard of care (which consists of the standard first-line drugs given for six months of treatment, but only thrice weekly).[46] The moxifloxacin-containing arms all performed better than the control in terms of favorable outcomes at the end of treatment (92% vs. 81%; P < .03). Twelve months following treatment, the three four-month regimens tested had TB recurrence rates (5.2%, 6.6%, and 4.6%, respectively) similar to the control (4.6%) (P-values were all much greater than .05). Moderate and severe adverse events were slightly higher in the experimental arms (6–9% versus 4%). Whether these regimens would perform equally well when compared with a control of daily dosing is unclear, however.

REMoxTB failed to show that a four-month regimen substituting moxifloxacin for either ethambutol or isoniazid is noninferior to the current standard of care, with 7.8% (95% CI: 2.7–13.0) and 9.0% (95% CI: 3.8–14.2) fewer participants with favorable outcomes, respectively.[47] Similarly, as previously reported, the OFLOTUB study failed to show any benefit for using gatifloxacin in a treatment-shortening regimen.[48] Though disappointing, these definitive results add to an evidence base clearly indicating that exchanging one standard first-line TB drug for a fluoroquinolone is not enough to meaningfully reduce treatment duration without a much greater risk of relapse than the six-month standard of care. However, these results provide support for another approach to thinking through shortening treatment for TB.

For DS-TB, a curative regimen with a shorter duration would increase success rates in practice and reduce the emergence of new resistant organisms. While REMox and OFLOTUB four-month regimens did not demonstrate noninferiority against the six-month standard of care, they worked in a large majority of patients (in REMox, 77% and 76% vs. 85%). It is arguable that we are overtreating a majority of those with DS-TB to avoid relapses in a minority. However, we do not know how to identify which individuals will be cured in a shorter-than-standard time, despite the results noted.

A clinical trial is now in design to test treatment-shortening options that seek to produce relapse-free cure in most patients, accepting that in a clinical trial there may be more relapses than with the current standard of care. TRUNCATE-TB will use an adaptive design to test several two-month DS-TB regimens including new and repurposed drugs (including high-dose rifampin, linezolid, clofazimine, delamanid, and bedaquiline); it will also attempt to identify who may be at increased risk of relapse.[49] The study plans to start enrolling at the end of 2015. To be successful, this approach requires reliable prediction of those who will benefit from

the shortened regimens and the appropriate selection of patients, care, and follow-up, which programs are already responsible for but are often failing to deliver. Research to understand preferences about the risks and benefits of shortened treatment is also necessary prior to uptake; some patients may prefer a longer treatment if it makes a second round of treatment less likely. Although TRUNCATE-TB's approach will be risky until we can reliably identify who can benefit from it, it reflects the sort of exciting and highly innovative thinking that is urgently needed to break TB treatment and research out of its calcification. Sponsors should make drugs available to TRUNCATE-TB for this effort.

The APT study, sponsored by Johns Hopkins and funded by the FDA's Orphan Products Grants Program, will also examine the role of a new drug, in this case pretomanid, in DS-TB treatment. This phase II trial will add pretomanid to isoniazid, rifampin, and pyrazinamide for eight weeks to assess time to sputum culture conversion and safety.[50]

The ACTG is developing a protocol to study clofazimine in DS-TB, based on preclinical work from the Johns Hopkins University. The current proposal is to test the addition of clofazimine at 100 or 50 mg daily for 12 weeks to the standard of care versus the standard as a control.[51]

Studies for DS-TB and Some Forms of DR-TB

Two new trials from the TB Alliance are also looking at using new drugs to treat DS-TB, in addition to some forms of DR-TB, by treating patients based on the drugs to which their TB is susceptible rather than resistant. The phase III STAND-TB trial, designed to evaluate four- and six-month regimens of pretomanid, moxifloxacin, and pyrazinamide, has started, following promising results of the regimen in a two-month phase II study.[52]

NC-005, a two-month phase II study looking at pretomanid, bedaquiline, and pyrazinamide, has also begun (this trial will also include moxifloxacin in an arm for people with MDR-TB).[53] Both trials are admirable in their attempts to develop a new compound (pretomanid) in new, optimized combinations (rather than as add-ons to the existing standard of care like bedaquiline and delamanid). Both also offer hope for the tremendous advantage of all-oral regimens with greatly reduced pill burdens, fewer drugs (and potentially fewer side effects), and shorter treatment for DS-TB and some MDR-TB. However, with only three drugs with limited capacity to protect against the development of resistance, the STAND regimen may be risky (especially among persons with MDR-TB) and may require broad access to rapid drug susceptibility testing that doesn't yet exist to detect resistance to the drugs in the regimen. Both trials include people with MDR-TB in an open-label, nonrandomized arm without a control, raising questions about how to interpret these data if follow-up, randomized controlled trials are not planned, especially if STAND's results are equivocal.

DR-TB

While Otsuka completes its phase III trial that adds delamanid to the current standard of care for MDR-TB, investigators are struggling to advance trials to understand how to better use delamanid and bedaquiline as part of optimized regimens for MDR-TB.

Bedaquiline is entering STREAM II – laudably redesigned after TB communities called for the inclusion of a control arm[54] – which will assess its potential to contribute to a six-month regimen, or a nine-month injection-free regimen, in combination with several older drugs.

The NExT study will evaluate bedaquiline in people with MDR-TB in a much sleeker, injection-free, six-month regimen along with linezolid, levofloxacin, pyrazinamide, and either high-dose isoniazid or ethionamide – depending on the MTB genotype. With funding from the South African Medical Research Council, this trial has the potential to change the standard of care in South Africa, which has already been a leader in providing

bedaquiline to people with MDR-TB with limited treatment options.[55] However, Janssen appears unwilling to donate drug for this study. The NExT investigators had originally planned to include delamanid, but even though they proposed a rigorous safety substudy, Otsuka would not permit delamanid and bedaquiline to be studied together until the ACTG's A5343 trial to examine the effects of the two drugs on QT prolongation, a disturbance in the heart's electrical activity, was completed. Unfortunately, due to slow movement from Janssen and bureaucratic delays from the U.S. National Institutes of Health (NIH), A5343 has yet to start.

Two more programmatic-style clinical trials will look at different combinations including bedaquiline or delamanid. The UNITAID-funded endTB trial will evaluate at least five new all-oral regimens containing one new anti-TB drug (either bedaquiline or delamanid), no more than five drugs per arm, and no more than two QT-prolonging drugs per arm (companion drugs are moxifloxacin or levofloxacin and pyrazinamide plus linezolid, clofazimine, or both). The design is still being finalized, but current plans are to compare the five experimental arms with a control arm that includes either bedaquiline or delamanid according to current WHO guidance for their use. The trial is designed to be able to detect up to three effective regimens. The endTB study will be conducted in Georgia, Kazakhstan, Kyrgyzstan, Lesotho, and Peru. Enrollment may begin as early as December 2015. The TB-PRACTECAL trial is a randomized, controlled, open-label, phase II/III trial. It will evaluate the safety and efficacy of six-month regimens containing bedaquiline, pretomanid, and linezolid alone, with moxifloxacin, or with clofazimine for the treatment of adults with MDR-TB or extensively drug-resistant TB (XDR-TB). These experimental regimens will be compared against a control of the WHO standard of care. Médecins Sans Frontières is sponsoring the trial, and the TB Alliance is donating pretomanid. Patient recruitment will start in the third quarter of 2015.

The commendable NiX-TB trial from the TB Alliance is examining the combination of three compounds that are new or to which there is little preexisting resistance due to limited use – bedaquiline, linezolid, and pretomanid – in XDR-TB.[56] Testing this innovative regimen is appropriate in these individuals given their limited other treatment options, and it provides one way, albeit limited, for South Africans in urgent need to gain access to multiple new drugs. If Sequella were to make sutezolid available, the drug would be an excellent candidate for inclusion in this study.

A few other trials seek to improve MDR-TB treatment without new drugs. STREAM I, a randomized controlled trial comparing a nine-month regimen – clofazimine, ethambutol, moxifloxacin, and pyrazinamide plus isoniazid, kanamycin, and prothionamide in the first four months only – with the current WHO standard of care met its enrollment target in March 2015;[57] results are expected at the end of 2017 or early 2018.[58] This experimental modified–Bangladesh regimen (so called as it was first introduced in a flawed observational cohort study in Bangladesh, with cohort sizes undefined prior to starting the study, high risk of selection bias, and sequential enrollment of cohorts allowing confounding due to socioeconomic improvements)[59] is far from ideal given the large number of drugs, associated side effects, and inclusion of an injectable. But it does have potential to provide a shorter, standardized treatment for MDR-TB using older, accessible drugs. The rigorous STREAM II trial is needed to provide definitive answers about the suitability of the regimen for routine use.[60]

Opti-Q, a phase II study led by Boston University and sponsored by the U.S. National Institute of Allergy and Infectious Diseases and the TBTC, is enrolling adults with MDR-TB in South Africa and Peru. As a parallel to the rifampin work for DS-TB, Opti-Q is attempting to determine the optimal dosing for levofloxacin.[61]

Novartis has expressed interest in developing clofazimine for MDR-TB; the drug (approved for leprosy) has already been used as an off-label treatment for decades. The company is designing a more conventional trial to add the drug to a standard background regimen to assess the anti-TB activity of clofazimine, which in a two-week study showed no early bactericidal activity but is thought to work against TB over longer periods of time, especially given its long half-life.[62,63]

A TB Alliance early bactericidal activity trial will look at different dosing strategies for linezolid in the hope of later identifying strategies to minimizing its toxicities while preserving efficacy.[64] The ACTG may develop a two-month study of clofazimine to more clearly define a tolerable dose for use in DR-TB treatment.

Pre-approval Access Spotlight

The TB Alliance, as a nonprofit, has the challenge of identifying funding for its endeavors. To provide compassionate use access for pretomanid – which should be in place already as the drug has entered phase III – the Alliance is looking to establish a precedent of a philanthropically funded pre-approval access program. It is now assessing costs and identifying donor prospects – work that should have begun years ago. The Alliance, along with donors, should include planning for pre-approval access as part of any late-stage clinical development program.

Meanwhile, only a few dozen patients have received delamanid under Otsuka's nominal compassionate use program. Otsuka is withholding compassionate use of delamanid from gravely ill patients receiving bedaquiline. Though there is not enough safety information yet to give the two drugs together routinely for MDR-TB, some people with MDR-TB have no remaining treatment options for combination therapy; alternatives may lower their chances for relapse-free and disability-free cure and increase their chances of developing further drug resistance. For these individuals, the potential benefits far outweigh the potential risks, but Otsuka's inflexibility and short-sightedness leave them at great risk of disability and death.[65,66] Otsuka recently announced an initiative to improve the availability of delamanid with a goal to "reach 20% of all diagnosed and treated patients in quality programmes by 2020," but details are vague, and terms such as "quality" hint at continued highly restricted access to delamanid.[67] Otsuka has still not consulted with community groups on the development of this access strategy.

CONCLUSIONS AND RECOMMENDATIONS

With few new drugs to work with, inadequate investment from drug sponsors, and limited funding, TB treatment researchers are in the difficult position of trying to do more with less. Remarkable advances are being made in TB prevention research, and momentum is gathering for their translation into implementation, though important questions remain about what strategies are best suited for which settings and about which drugs can safely and effectively prevent MDR-TB given the current absence of clinical trial data. For active TB disease, overdue research is finally happening or in development. For all forms of active TB, studies to determine the best dosing, and to test strategies to shorten treatment, are under way. Some truly innovative approaches for DS-TB are also in development, though they carry big questions for eventual implementation if they are successful in trials. And, finally, a number of innovative MDR-TB trials looking at new drugs in better combinations have been designed, testing regimens that may improve efficacy and reduce side effects for DR-TB, though their results are years away. Access to new drugs remains inexcusably slow and difficult for patients, programs, and investigators alike. To resolve this, and to ensure the development and availability of improved treatment strategies for TB:

- **Move promising preclinical drug candidates into clinical development more quickly.** The TB drug pipeline is too sparse and homogenous. Pharmaceutical companies, philanthropic donors, and public institutions must increase funding for TB drug discovery and development to build a robust pool of drug candidates.

  - Top-grossing pharmaceutical companies such as Merck, Roche, and Gilead have been conspicuously absent from TB drug development and should immediately make compound libraries and funding available for TB R&D.
  - Pfizer and AstraZeneca should return to TB R&D and, at a minimum, contribute funding to the institutions that have taken over their TB compounds.
  - GlaxoSmithKline and Sanofi, which are currently investing in TB drug discovery and preclinical work, must sustain their investments and ensure continued collaboration.
  - Otsuka, Johnson & Johnson, and Novartis, which are all currently investing in clinical compounds for TB, should continue investing in early-stage work as well.
  - Vertex should either invest adequate resources immediately to advance VXc-486 or give over the development rights to another organization that will.

- **Revitalize research on compounds languishing in early-stage clinical development.** Sutezolid and AZD5847 have been stalled in phase IIa for years, primarily due to reprehensible neglect from pharmaceutical companies Pfizer and AstraZeneca.
  - Pfizer and AstraZeneca must ensure sustained funding for the development of early-stage potential TB products.
  - Sequella should develop sutezolid in collaboration with other drug sponsors and research consortia and, in its quest for capital to do so, ensure that access provisions are in place.
  - The NIH must resolve the internal bureaucratic delays that contributed to the slow progression of AZD5847.
- **Increase funding for TB R&D.** TB drug R&D is dramatically underfunded. Brazil, Russia, India, China, and other high–TB burden countries with large economies should be investing more in strategies to end TB. Janssen, Otsuka, and Sanofi, the few pharmaceutical companies with functional clinical TB programs, must sustain their investments in TB drug R&D. Other private-sector drug developers must get into TB, including the developers of tedizolid, an approved oxazolidinone that may have potential for TB and may be less toxic than linezolid. Tedizolid is currently caught in an industry merger; its developer, Cubist, was acquired by Merck in December 2014, and the legal and practical challenges of transferring compounds across companies have led to its development stalling.[68,69] Pfizer and AstraZeneca have abandoned the field completely and should at a minimum provide financing to the organizations (Sequella and TB Alliance) to which they've transferred their TB products to ensure their continued advancement.
- **Invest existing resources wisely.** With limited funding, public research agencies and research consortia should pursue only the strategies and drug candidates with true potential for added benefit. Adaptive designs offer one avenue for efficiency. Indeed, the publicly supported MAMS-TB-01 trial was able to reduce its sample size when an interim analysis showed SQ109-containing arms were not worth further investment.
- **Design studies with high scientific rigor.** A desperate need for new MDR-TB treatment options is not an excuse to cut corners scientifically or ethically. The TB Alliance should think seriously about how a regimen tested in people with MDR-TB in a nonrandomized, uncontrolled manner will be received by global normative bodies, TB programs, and communities. Though challenges exist with the current standard of care, by the time STAND and NC-005 have progressed, results from STREAM will be available that may offer a scientifically validated control arm (and potentially a shorter one if the experimental regimen is successful) for follow-up studies in people with MDR-TB, if warranted.

- **Make new drugs available for pragmatic and investigator-initiated research.** As all TB drugs must be used in combination, and we have so little information on the best use of all the new drugs – and many of the older ones – collaboration is essential for advancing TB treatment. In particular, given how sponsors have limited postmarketing access to the new TB drugs, they have an even greater responsibility to make procuring drugs for research easier (they should also more generally expand access to their drugs, as noted below). The MARVEL study was derailed by a lack of collaboration from Otsuka, Sequella, and the TB Alliance.
    - Janssen should make bedaquiline available rapidly and free of charge for essential studies, including A5343 and NExT, and the TB Alliance (which has the rights to bedaquiline for DS-TB) should provide it to TRUNCATE-TB.
    - Otsuka should make delamanid available for study in more innovative regimens, including for MDR-TB prevention, and should not wait for the A5343 results to discuss future plans to include delamanid and bedaquiline in the same regimen.
- **Plan for access earlier and ensure early/emergency access when needed before approval.** Sponsors and regulators are both responsible for ensuring access pre- and post-approval. Pre-approval access, including compassionate use and expanded access trials in places where no framework for compassionate use exists, should be routine components of any clinical development program.
    - Donors such as USAID, UNITAID, and the Global Fund should consider providing support to the TB Alliance to implement an already overdue compassionate use program for pretomanid, which is particularly urgent if it is safe to coadminister pretomanid with bedaquiline.
    - Otsuka still needs to make delamanid available to more people in need under compassionate use, including in certain urgent cases in conjunction with bedaquiline. Otsuka has failed to register delamanid even in countries where it was tested and to make it available through the GDF. With stringent regulatory authority approval, inclusion in the Model List of Essential Medicines, and relatively broad WHO recommendations in place, there is no excuse for these delays.
    - Janssen must make the bedaquiline donation widely available and successful at building a sustainable market for the drug, rather than using it as a promotional, tax-saving public relations gesture that creates onerous and drug-specific parallel procurement systems and doesn't actually broaden access. Janssen still needs to reduce the price of bedaquiline, particularly for middle-income countries, to enable medium- and long-term access.
    - Sanofi must widely register rifapentine for both TB infection and disease, starting in countries where clinical trials to support its registration were conducted.
    - Trial sponsors, when different from drug sponsors, should ensure availability and affordability commitments up front from drug sponsors before conducting research. Innovations resulting from research funded by public institutions have a special obligation to be affordable.
- **Improve regulatory structures and harmonize them regionally.** Flexible, rigorous regulatory agencies are key to protecting citizens and facilitating access to safe, effective new medical interventions. Review processes should be simpler and faster while maintaining high standards. Regulatory authorities need technical support from their counterparts at stringent regulatory authorities in Canada, the European Union, Japan, and the United States, the WHO, and implementing agencies – and more funding to this end.

- **Support robust postmarketing safety monitoring without making it a barrier to rollout.** WHO recommendations for active pharmacovigilance for bedaquiline and delamanid should not prevent programs from getting these drugs. Technical partners should offer assistance to programs in developing simple, effective, and logical systems for monitoring and reporting drug-related adverse events. The WHO, the GDF, USAID, the Global Fund, and other partners should make clear that onerous cohort event monitoring is not a requirement for initiating procurement of these drugs. These partners should also develop an overarching global body to collect and analyze national data and disseminate findings to inform future use of the drugs.

We have a long way to go. But we are building political will to address the structural, financial, and scientific deficits that sustain and encourage this epidemic. And with two new drugs, shorter treatment for TB infection, and potentially dramatically shorter treatment regimens for MDR-TB infection and active DS-TB and DR-TB disease under study, there is potential to do more than ever to treat, cure, and ultimately end TB. Let us not squander this unprecedented and all-too-rare opportunity.

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Momentum in the Pediatric Tuberculosis Treatment Pipeline

By Lindsay McKenna

Introduction

Years of building advocacy and research capacity have finally brought about clinical research for children with tuberculosis (TB). While data gaps and delays between adult and pediatric approvals remain large, there is more activity in the pediatric TB treatment pipeline than ever before.

A recently published consensus on how to shorten the time between adult and pediatric approvals is expected to help expedite research in adolescents and children. A group of experts convened by the U.S. National Institutes of Health (NIH) recommends that pediatric investigation of new TB drugs and regimens begin as soon as efficacy and safety have been established in adults (phase IIb studies).[1] It also recommends that cohorts for pharmacokinetics (PK) and safety studies in children be recruited in parallel, as sequential enrollment does not necessarily offer additional protection for younger children.[2] Furthermore, it suggests the inclusion of adolescents ≥10 years old in TB drug trials at phase IIb and later, as there is no physiological reason for their exclusion.[3]

Investments in pediatric TB research and development (R&D) are also necessary to shrink existing data gaps between adults and children. The World Health Organization's *Roadmap for Childhood Tuberculosis* estimates that between 2011 and 2015, $200 million[4] would be needed for pediatric TB research.[5] At the midpoint of the 2011–2015 period, donors had spent just one-fourth of the targeted $200 million – a significant shortfall in funding for pediatric TB R&D. In 2013, TAG's annual *Report on Tuberculosis Research Funding Trends* uncovered just $25.3 million spent on pediatric TB R&D from 19 donors worldwide.[6] Of the $25.3 million invested in pediatric TB research, the largest share went to drug development: $10.8 million (43% of the total).[7] One-fifth of the total $25.3 million, or $4.7 million, was invested by the Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD) at the NIH.[8] UNITAID's $3.4 million investment in the STEP-TB project was enough to make it the third largest funder of pediatric TB R&D.[9] The reach of these and other investments is documented here.

Disease Burden Estimates

TB Type	Estimated Numbers of Affected Children
Drug-sensitive TB infection	**7.6 million**
Drug-sensitive TB disease	**500,000–1 million**
Drug-sensitive TB disease and HIV	**32,500**
Multidrug-resistant TB infection	**400,000**
Multidrug-resistant TB disease	**50,000**

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Pediatric Pipeline Overview

Researchers continue to play catch-up on pediatric PK data for second-line TB drugs to inform World Health Organization (WHO) dosing recommendations required to advance development of pediatric formulations. Pediatric PK and safety studies of new TB drugs are progressing, albeit at varying rates. Studies under way or starting soon will evaluate preventive therapy for children exposed to multidrug-resistant TB (MDR-TB) and whether it is possible to shorten treatment for less severe forms of TB from six to four months (SHINE) and for tuberculous meningitis (TBM) (SURE-TBM) from 12 to 6 months in children. And appropriately dosed pediatric formulations of first-line TB drugs are approaching market introduction. Table 1 provides an overview of ongoing and planned TB prevention and treatment studies in children.

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

Study/Regimen	Status	Population(s)	Sponsor(s)
PREVENTION			
P4v9 4 months of self-administered daily rifampin for prevention of TB NCT00170209*	Enrollment complete; results expected 2016	HIV-positive or HIV-negative infants, children, and adolescents 0–17 years old with LTBI	CIHR, McGill University
TBTC 35 PK and safety of rifapentine/isoniazid FDC for prevention of TB	Planned; opening Q1 2016; results expected 2018	HIV-negative infants, children, and adolescents 0–12 years old with LTBI; children ≤6 years old will get pediatric formulation	TBTC, Sanofi
TB-CHAMP 6 months levofloxacin vs. placebo for prevention of MDR-TB	Planned; opening 2016; results expected 2019	HIV-positive or HIV-negative infant and child household contacts 0–5 years old; children ≤5 years old will get new pediatric formulation	BMRC, Wellcome Trust, DFID, SA MRC
ACTG A5300/ IMPAACT 2003 (PHOENIX) 6 months levofloxacin vs. isoniazid for prevention of MDR-TB	Planned; opening 2016; results expected 2020	HIV-positive or HIV-negative infant, child, and adolescent (and adult) household contacts	NIAID
V-QUIN 6 months levofloxacin vs. placebo for prevention of MDR-TB	Planned; opening 2015; results expected 2020	HIV-positive or HIV-negative infant, child, and adolescent (and adult) household contacts	NHMRC
TREATMENT – NEW DRUGS			
232 PK and safety of delamanid; OBR for treatment of MDR-TB NCT01856634*	Enrolling; results expected 2017	HIV-negative infants, children, and adolescents 0–17 years old with MDR-TB; children ≤5 years old will get pediatric formulation	Otsuka
233 6 months of delamanid; OBR for treatment of MDR-TB NCT01859923*	Enrolling; results expected 2017	HIV-negative infants, children, and adolescents 0–17 years old with MDR-TB; children ≤5 years old will get pediatric formulation	Otsuka
IMPAACT CS 5004 PK and safety of delamanid for treatment of MDR-TB	Planned; opening Q1 2016	HIV-positive or HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB	IMPAACT
JANSSEN C211 PK and safety of bedaquiline; OBR for treatment of MDR-TB NCT02354014*	Planned; opening Q2 2015	HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB; children ≤12 years old will get pediatric formulation	Janssen

Study/Regimen	Status	Population(s)	Sponsor(s)
IMPAACT P1108 PK and safety of bedaquiline; OBR for treatment of MDR-TB	Planned; opening 2016	HIV-positive or HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB	NIAID, IMPAACT
TB Alliance TBD PK and safety of pretomanid for treatment of TB	Planned; opening 2018	HIV-positive or HIV-negative infants, children, and adolescents 0–12 years old with TB; cohorts to be enrolled simultaneously/in parallel	TB Alliance
TREATMENT – EXISTING DRUGS			
Treat Infant TB PK and safety of FLDs using 2010 WHO dosing guidelines for treatment of TB	Enrollment complete; results expected June 2015	HIV-positive or HIV-negative infants <12 months old with TB	UNITAID/TB Alliance (Step-TB Project)
PK-PTBHIV01 PK of FLDs using 2010 WHO dosing guidelines for treatment of TB NCT01687504*	Enrolling; results expected 2017	HIV-positive or HIV-negative children 3 months to 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 HIV-negative infants, children, and adolescents 0–16 years old with minimal TB	BMRC, DFID, Wellcome Trust, UCL
TBM-KIDS Safety and efficacy of high-dose rifampin +/- levofloxacin for treatment of TBM	Planned; opening Q3 2015	HIV-positive or HIV-negative infants and children with TBM	NICHD
SURE-TBM Safety and efficacy of high-dose rifampin and isoniazid, levofloxacin, and pyrazinamide to shorten treatment of TBM	Planned; awaiting funding decision	HIV-positive or HIV-negative infants, children, and adolescents 0–18 years old with TBM	BMRC, Wellcome Trust, DFID (pending)
MDR-PK 1 PK and safety of SLDs for treatment of MDR-TB	Enrolling; results expected 2016	HIV-positive or HIV-negative infants, children, and adolescents with MDR-TB or LTBI	NICHD
MDR-PK 2 PK, safety, and dose optimization of SLDs for treatment of MDR-TB	Planned; opening 2015	HIV-positive or HIV-negative infants, children, and adolescents with MDR-TB	NICHD, SA MRC
COTREATMENT WITH ARVS			
DATiC PK of FLDs using 2010 WHO dosing guidelines for treatment of TB and interactions with lopinavir/ritonavir and nevirapine NCT01637558*	Enrolling; results expected 2017	HIV-positive or HIV-negative infants, children, and adolescents 0–12 years old with TB	NICHD, UNITAID/ TB Alliance (Step-TB Project)
IMPAACT P1106 PK of rifampin and isoniazid with nevirapine or lopinavir/ritonavir NCT02383849*	Enrolling; opening 2015	HIV-positive or HIV-negative low-birth-weight/ premature infants	NIAID, NICHD, IMPAACT
Rifabutin-PK PK and safety of rifabutin for treatment of TB	Planned	HIV-positive children and adults on PI-based ART with second-line ARVs	ICMR, NACO

Study/Regimen	Status	Population(s)	Sponsor(s)
IMPAACT P1070 PK and safety of efavirenz with rifampin-containing TB treatment NCT00802802*	Enrolling; results expected 2016	HIV-positive children 3 months to <3 years old with TB	NIAID, IMPAACT
PK and safety of efavirenz with rifampin-containing TB treatment NCT01704144*	Enrolling; results expected 2017	HIV-positive children and adolescents 3–14 years old with TB	NICHD
PK and safety of superboosted lopinavir/ritonavir (1:1) with rifampin-containing TB treatment NCT02348177*	Enrolling; results expected 2016	HIV-positive infants and children with TB weighing 3–15 kg	DNDi
PK and safety of nevirapine with rifampin-containing TB treatment NCT01699633*	Enrolling; results expected 2017	HIV-positive children 3 months to 3 years old with TB	NICHD
IMPAACT P1101 PK and safety of raltegravir with rifampin-containing TB treatment NCT01751568*	Enrolling; results expected 2016	ARV-naive, HIV-positive children and adolescents 2–12 years old with TB	NIAID, IMPAACT, PENTA
EARNEST PK and safety of rifabutin with lopinavir/ritonavir NCT01663168*	Discontinued; insufficient sample size	HIV-positive adults and adolescents ≥12 years old	BMRC, Abbott

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

ART: antiretroviral therapy
ARV: antiretroviral
BMRC: British Medical Research Council
CIHR: Canadian Institutes of Health Research
DFID: Department for International Development (United Kingdom)
DNDi: Drugs for Neglected Diseases
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)
NHMRC: National Health and Medical Research Council (Australia)
NIAID: National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health
NICHD: National Institute of Child Health and Human Development, U.S. National Institutes of Health
OBR: optimized background regimen
PENTA: Pediatric European Network for Treatment of AIDS
PI: protease inhibitor
PK: pharmacokinetics
SA MRC: South African Medical Research Council
SLD: second-line drug
TB: tuberculosis
TBD: to be determined
TBM: tuberculous meningitis
TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention
UCL: University College London
WHO: World Health Organization

Pharmacokinetics and Safety Data Updates

Preliminary analyses of data from an ongoing PK and safety study of second-line TB drugs determined that children are being underdosed for several drugs at the currently recommended mg/kg doses.[10,11,12,13,14] New data are emerging from PK and safety studies of first- and second-line drugs in children.

First-Line Drugs

In 2010, the WHO recommended higher doses of first-line TB drugs for children.[15] DATiC evaluated PK targets with these doses in HIV-positive and HIV-negative children and found that 12 mg/kg of isoniazid (recommended range: 7–15 mg/kg) and 35 mg/kg of pyrazinamide (recommended range: 30–40 mg/kg) achieved drug exposures in children comparable to those in adults.[16] But exposures following 15 mg/kg of rifampin (recommended range: 10–20 mg/kg) were variable, with only 17 percent (N = 47) of children achieving adult exposures and reduced exposures in the lowest and highest weight categories.[17]

A study of isoniazid in low-birth-weight and premature infants achieved comparable drug exposure to that observed in adults treated with 10 mg/kg of isoniazid.[18] There was reduced elimination in smaller and younger infants and in slow acetylators – those with a genetically determined trait marking slower metabolism of drugs processed in the liver – which suggests that exceeding the 10 mg/kg dose should be done with caution.[19] Dosing recommendations in infants less than 12 months of age are expected in the second quarter of 2015.[20]

Second-Line Drugs

Preliminary analysis of data from MDR-PK, a PK and safety study of second-line drugs in HIV-positive and HIV-negative children, found that moxifloxacin was well tolerated by children 7–15 years old.[21] With doses of 10 mg/kg (recommended range: 7.5–10 mg/kg), children achieved lower drug exposures than adults.[22] HIV-positive children taking antiretrovirals (ARVs) achieved lower moxifloxacin exposures than HIV-negative children. [23] But the sample size was too small to make accurate predictions about the effects of ARVs on drug exposure.[24]

When levofloxacin was given at 15 mg/kg (recommended range: 7.5–10 mg/kg) in the MDR-PK study, children achieved lower drug exposures than adults.[25] A recent population PK analysis of children treated for MDR-TB disease or infection in the Federated States of Micronesia and Republic of Marshall Islands found that children given 10–20 mg/kg of levofloxacin achieved the minimum inhibitory concentration (minimum drug concentration necessary to inhibit TB bacterial growth).[26]

These data suggest the need for revised doses for second-line drugs in children. More data for both moxifloxacin and levofloxacin in children are expected in the next year.

New Drugs

Otsuka, the sponsor of delamanid, has completed enrollment of the first (12–17 years old; 100 mg twice daily) and second (6–11 years old; 50 mg twice daily) age cohorts in its PK and safety study in HIV-negative children (232/233).[27] Preliminary analysis found slightly higher drug exposures among 12- to 17-year-olds compared with adults, but no safety signals.[28]

Pharmacokinetics and Safety Data Gaps

Significant PK and safety data gaps in children remain, and further research is necessary to determine optimal drug doses and regimens and to ensure safe and effective levels of drug exposure in children. Ongoing and planned studies will help address these gaps; however, many of these data should have been collected years ago, reflecting the historic neglect of children in TB research.

First-Line Drugs

Most PK and safety data gaps for first-line TB drugs are in young or HIV-positive children receiving antiretroviral therapy (ART). Studies (see table 1) to optimize doses of first-line TB drugs in these populations, and to evaluate the PK and safety of efavirenz, nevirapine, superboosted lopinavir/ritonavir, and raltegravir in young children on rifampin-based TB treatment, are being conducted.

Tuberculosis Trials Consortium (TBTC) Study 35, a PK, safety, and registration study of three months of once-weekly rifapentine and isoniazid (3HP) to prevent TB in children, is expected to open in early 2016 and currently plans to include only HIV-negative children. While the safety of rifapentine has been previously demonstrated in coinfected adults treated with ART-based efavirenz or nevirapine (non-nucleoside reverse transcriptase inhibitors),[29,30] and in healthy adults given raltegravir (integrase inhibitor),[31] the recommended first-line ART regimen for children younger than three years old is based on boosted lopinavir/ritonavir (protease inhibitor). Interactions between rifapentine and protease inhibitors have been observed.[32] Inclusion of HIV-positive children at least three years old and receiving non-protease inhibitor–based ART is under discussion.[33] Planned enrollment so far is limited to South African sites. If HIV-positive children are not included in TBTC Study 35, a future study of 3HP in HIV-positive children is expected.[34]

Second-Line Drugs

PK investigations of second-line TB drugs at currently recommended doses in children are nearing completion; more results from MDR-PK are expected in 2016, including for terizidone, levofloxacin, amikacin, and ethionamide, although drug-specific findings have been published and presented throughout the MDR-PK study's duration. These data analyses, along with an individual patient meta-analysis, are already under way and are being coordinated by the Desmond Tutu TB Center and Stellenbosch University, and they will inform WHO treatment recommendations, which are critical to advancing development of pediatric formulations of second-line drugs.

PK and safety data for moxifloxacin in children under seven years old remain elusive, largely a result of limitations of the existing formulation. Furthermore, the optimal dose of moxifloxacin has yet to be determined in adults (400 mg vs. 600 mg) – current pediatric PK and safety work evaluates drug exposures achieved in adults at 400 mg. Pending the study site's ability to enroll greater numbers of coinfected children, the MDR-PKstudy will aim to fill existing PK and safety gaps for second-line drugs in children who are HIV-positive and taking ARVs.

A recently awarded joint NIH/South African Medical Research Council grant will support work to further optimize the use of key second-line drugs in children.[35] Data from MDR-PKwill be used to simulate the doses required in children to approximate those achieved in adults.[36] The simulated, weight-based doses will then be prospectively assessed for PK, safety, and treatment response in HIV-negative and HIV-positive children 0–17 years old.[37] The study investigators have prioritized levofloxacin, moxifloxacin, and linezolid, but they hope to expand this work to other second-line drugs and to evaluate new pediatric formulations of second-line drugs should they become available during the study.[38]

New Drugs

The timelines for pediatric investigation of new drugs delamanid and bedaquiline remain discordant. The discordance is likely attributable to differing regulatory requirements between the European Medicines Agency (EMA), which requires studies in children, and the U.S. Food and Drug Administration (FDA), which exempts orphan drugs from pediatric studies altogether (see box 1, Regulatory Spotlight).

Otsuka, the sponsor of delamanid (approved by the EMA in April 2014), has completed enrollment of children down to six years old in its PK and safety study. Recently completed bioequivalence studies of a dispersible formulation will allow for the study of delamanid in younger children. Otsuka plans to open enrollment for the 3- to 5-year-old and 0- to 2-year-old cohorts in 2015 and has reached agreement with the EMA for parallel enrollment for these two age groups.[39]

Janssen, the sponsor of bedaquiline (approved by the FDA in December 2012), has yet to open its pediatric PK and safety study but expects to begin enrolling the first cohort in the second quarter of 2015.[40] Public funding in the form of $1.5 million from UNITAID's STEP-TB project is being used to support the development of Janssen's pediatric formulation of bedaquiline and its PK and safety study in HIV-negative children.[41]

Developer accountability for studies in HIV-positive children, which is not explicitly required under pediatric investigation plans (PIPs) approved by the EMA,[42,43] is nearly nonexistent. Janssen has shirked its responsibility to collect PK and safety data in HIV-positive children, leaving publically funded research consortia to pick up the slack. The NIH's International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group (IMPAACT) is planning to open a PK and safety study of bedaquiline in HIV-positive children in 2016 (P1108). While Otsuka is planning to collaborate with IMPAACT to collect PK and safety data for delamanid in HIV-positive children, U.S. taxpayers will ultimately also foot the bill for this work (IMPAACT CS 5004).

The TB Alliance has started enrolling its phase III study of pretomanid (PA-824), moxifloxacin, and pyrazinamide (together known as PaMZ) in adults, and although it has a pediatric plan in place, further preclinical toxicology work and a semen substudy are required before PK and safety studies of pretomanid can advance in children.[44] Once these data are available, the TB Alliance plans to enroll all age cohorts simultaneously or "in parallel" in accordance with recommendations issued in a consensus statement by an NIH-convened group of experts.[45]

Further complicating the investigation of pretomanid in children is an outstanding question of whether 100 mg or 200 mg is the optimal dose in adults.[46] Analysis of data collected in the phase III trial will answer this question, but not before late 2017 or early 2018.[47] This information is required to determine target drug exposures in children and to evaluate the safety of pretomanid at the correct dose. In the meantime, data on the appropriate dose of moxifloxacin (the "M" in PaMZ) in young children are urgently required.

Sutezolid is another drug for which limitations of adult data inhibit investigation in children. Sequella licensed sutezolid from Pfizer in 2012, and development has stalled since then. Early-stage phase I and II studies of sutezolid conducted by Pfizer before the transition were insufficient to determine the optimal dose in adults[48] – information required for setting the target exposures necessary to advance PK and safety studies in children. Unfortunately, Sequella has done little to advance the development of sutezolid, leaving it suspended in phase II and inaccessible to interested outside investigators.

Box 1. Regulatory Spotlight: FDA versus EMA

Regulatory authorities' ability and responsibility to hold pharmaceutical companies accountable for pediatric investigations is key to closing the gap between adult and pediatric access to new TB drugs and regimens.

The EMA requires submission of a PIP with new drug applications, whereas the Orphan Drug Act[49] allows the FDA to exempt drugs for indications granted an orphan designation (such as TB) from pediatric studies normally required under the Pediatric Research Equity Act.[50] The FDA's subpar alternative to a PIP requirement attempts to encourage research in pediatric populations by offering an additional six months of marketing exclusivity under the Best Pharmaceuticals for Children Act (BPCA).[51] Such opt-in alternatives have proved less effective at ensuring timely completion of pediatric investigations compared with the standard regulatory requirements, especially for orphan drug markets, which are perceived to be small and in which competition is sparse, understandably limiting their attractiveness for just a few months of additional marketing exclusivity.

The EMA works with drug developers to establish their plans for investigation of new drugs in children. Once the EMA approves the PIP, the drug developer is expected to complete the agreed-upon studies before a prespecified deadline (see table 2). Modifications to approved PIPs are possible. While better than the FDA at requiring the inclusion of children in research plans for new TB drugs, the EMA still fails to hold companies accountable for important pediatric studies; neither the PIP for delamanid nor the PIP for bedaquiline requires investigation in HIV-positive children.[52,53] As a result, Janssen and Otsuka have eluded their responsibilities to collect PK and safety data in HIV-positive children. IMPAACT, a publically funded research consortium, is planning studies (P1108; CS 5004) to ensure that this pediatric subpopulation is not neglected and can benefit from new TB treatments.

Timely investigation of new TB drugs in HIV-positive and HIV-negative children, facilitated by the establishment of comprehensive and thoughtful regulatory policies, is critical to closing existing adult-pediatric approval and access gaps.

Table 2. Pediatric Investigation Timelines: Delamanid versus Bedaquiline

	Delamanid		Bedaquiline	
	FDA	EMA	FDA	EMA
Registration status	Not yet registered	Approved for MDR-TB in adults (≥18 years old), April 2014	Approved for MDR-TB in adults (≥18 years old), December 2012	Approved for MDR-TB in adults (≥18 years old), March 2014
PIP-required studies	1. Develop age-appropriate formulation (dispersible tablet) 2. Juvenile rat toxicity studies 3. Bioequivalence of pediatric formulation in healthy adults 4. Pharmacokinetics and safety in children 0–18 years old 5. 6-month extension study of long-term safety and efficacy		1. Develop age-appropriate formulation (dispersible tablet; granules) 2. Juvenile rat toxicity studies 3. Bioavailability of pediatric formulation in healthy adults 4. Pharmacokinetics and safety in children 0–18 years old	
Current status	Enrollment complete (children 6–18 years old) Enrollment planned 2015–16 (children ≤5 years old)		Study protocol complete; country applications submitted Opening Q2 2015	
PIP execution deadline	April 2017		September 2020	

Pediatric Formulations

Treatment of children with TB often necessitates the cutting and crushing of tablets. Five years after the WHO released revised pediatric dosing guidelines for first-line drugs, the market introduction of appropriately dosed pediatric formulations is finally in sight. This is in stark contrast to the situation for second-line drugs, for which we are still determining the pediatric mg/kg dose ranges that will achieve drug exposures comparable to those in adults. While the market introduction of pediatric formulations of second-line drugs may seem far away, there is some reason for optimism. Recent progress in formulation development expected to improve existing medicines for children, their caregivers, and the health care systems supporting their care is summarized in table 3.

Table 3. Pediatric Evidence and Formulation Summary by TB Drug

Drug	Studied in Children	Evidence-Based Dosing Guidance Available	Appropriate Pediatric Formulation Exists/Is in Development	Formulations in the Pipeline
FIRST-LINE DRUGS				
Isoniazid	✓	✓ (WHO)	✓	Updated doses as dispersible tablets: HRZ: 50/75/150 mg HR: 50/75 mg H: 100 mg
Rifampin	✓	✓ (WHO)	✓	
Pyrazinamide	✓	✓ (WHO)	✓	
Ethambutol	✓	✓ (WHO)	✓	Updated dose (100 mg) as dispersible tablet
Rifapentine	✓ (≥2 yrs.)	✓ (CDC)	✓	New as dispersible tablets: HP: 150/150 mg P: 100 mg
SECOND-LINE DRUGS				
Moxifloxacin	✓ (≥7 yrs.)		✓	Updated dose (100 mg) as scored dispersible tablet
Ofloxacin	✓			
Levofloxacin	✓		✓	Updated dose (100 mg) as scored dispersible tablet
Linezolid			✓	Updated dose (150 mg) as scored dispersible tablet
Clofazimine	✓ (for leprosy)			
Terizidone	✓			
Cycloserine			✓	Updated dose (125 mg) as mini capsule
Ethionamide	✓		✓	Updated dose (125 mg) as scored dispersible tablet
Amikacin	✓		(injectable)	
PAS	✓		✓	
Delamanid	✓ (>5 yrs.)		✓	New (20 mg and 5 mg) as dispersible tablets
Bedaquiline			✓	New (20 mg) as dispersible tablet
Pretomanid				Feasibility work under way
Sutezolid				

First-Line Drugs

There are multiple pediatric formulations of first-line drugs at various stages of development.

Sanofi, the sponsor of rifapentine (indicated for use in drug-sensitive TB [DS-TB] and latent TB infection in children as young as two years old), is planning to initiate a bioavailability and safety study of a mango-flavored, fixed-dose, dispersible combination of 150 mg rifapentine with 150 mg isoniazid, as well as a separate 100 mg rifapentine dispersible to facilitate dose adjustments in young children, in the third or fourth quarter of 2015.[54,55] These formulations will then be used in TBTC 35.

The TB Alliance and the WHO Essential Medicines and Health Products department, partners on the UNITAID-funded STEP-TB project, anticipate fixed-dose combinations of HRZ (50 mg isoniazid + 75 mg rifampin + 150 mg pyrazinamide) and HR (50 mg isoniazid + 75 mg rifampin) to become available through the Global Drug Facility (GDF) by the third quarter of 2015.[56] They expect separate formulations of 100 mg ethambutol, a recommended addition to HRZ in children with extensive disease living in settings where the prevalence of HIV or of isoniazid resistance is high,[57] and 100 mg isoniazid, recommended for preventive therapy, to follow six months later.[58] All first-line products are projected to be prequalified by the WHO and on the market by the second quarter of 2016.[59]

The TB Alliance and the WHO continue to prepare countries for uptake of these long-awaited formulations. Multiple strategies are necessary. WHO prequalification, a mechanism put in place to ensure and monitor the quality of medications procured in bulk, is required of manufacturers looking to sell medications through the GDF. For countries that don't purchase pediatric medications through the GDF, namely Brazil, China, India, Indonesia, the Russian Federation, and South Africa, submission of separate in-country dossiers is required.[60] Ideally, the STEP-TB project's work will pave the way for the development and timely introduction of pediatric formulations of second-line drugs.

Second-Line Drugs

Currently, just five of 14 second-line drugs are available in pediatric preparations, and even these are inadequate.[61] Existing oral suspensions (syrups) of linezolid and levofloxacin are difficult to dose accurately, are bulky and difficult to ship and store, and are not widely available. Lucane Pharma developed a dosing spoon to ease weight-based dispensing of para-aminosalicylic acid (PAS) granules to children,[62] but providers continue to report difficulties preparing PAS, possibly from lack of awareness about the availability of this tool designed to help measure out appropriate doses.[63]

Standard formulations affect which second-line drugs are studied in and used to treat children. For example, moxifloxacin is available only in 400 mg tablets that are not scored and are bitter when crushed. As a result, it is not feasible to treat children weighing less than 20 kg (typically children younger than eight years old) within the recommended 7.5 mg/kg to 10 mg/kg range. Instead, children weighing less than 20 kg are treated with ofloxacin or levofloxacin, which are available in 200 mg and 250 mg scored tablets, respectively. Another drug that is difficult to administer to children is clofazimine, which is available only in a softgel capsule form that prohibits splitting or cutting to obtain smaller doses.

However, there is cause for tempered optimism. Macleods Pharmaceuticals has developed scored, dispersible prototypes of levofloxacin (100 mg), moxifloxacin (100 mg), linezolid (150 mg), and ethionamide (125 mg) and a minicapsule of cycloserine (125 mg).[64] TB-CHAMP, a trial to evaluate levofloxacin as preventive therapy for household MDR-TB contacts under five years old, will pilot Macleods Pharmaceuticals' 100 mg scored and dispersible levofloxacin formulation. Investigator-initiated grant funding will support further development of the levofloxacin formulation and its procurement for the trial.

Collaboration with Macleods Pharmaceuticals and shared investment are urgently needed to expedite the advancement of the remaining formulations from prototype to market, work estimated to cost $3.5 million.[65] In addition, finalized, evidence-based, and WHO-recommended mg/kg dose ranges are necessary for attracting a second manufacturer. The previously described research to determine optimal mg/kg dose ranges of second-line TB drugs in children and data from an individual patient meta-analysis should inform a pediatric treatment chapter in the WHO consolidated treatment guidelines up for review in November 2015.

Because the potential market for pediatric formulations of second-line drugs is small, it is important to encourage additional manufacturers to join the space, which will help improve the likelihood of competitive drug pricing and stable supply. To this end, it is critical that the UNITAID-funded STEP-TB project be expanded to include second-line drugs.

New Drugs

A bioequivalence study of delamanid as 5 mg and 25 mg dispersible tablets in strawberry and cherry flavors is complete.[66] The availability of these formulations will allow the continued study of delamanid in children under five years old (232; 233.

A bioavailability study of bedaquiline as a 20 mg dispersible tablet has been completed.[67] This pediatric formulation will be used in cohorts inclusive of children under 12 years old in Janssen's PK and safety study, expected to open the second quarter of 2015.[68]

The TB Alliance has begun pediatric formulation feasibility work toward a single-drug dispersible tablet of pretomanid, with eventual plans for a dispersible fixed-dose combination tablet containing pretomanid, moxifloxacin, and pyrazinamide.[69] Advance preparation of the pediatric formulation will facilitate planned simultaneous enrollment of all age groups. However, data on optimized dosing of pretomanid and moxifloxacin, especially for young children, are necessary to inform development of the planned pediatric and fixed-dose combination formulations.

Regimens

Several studies of levofloxacin to prevent MDR-TB in children are expected to begin enrolling in 2016 (A5300/P2003; TB-CHAMP; V-QUIN. Levofloxacin is also being evaluated as a component of therapy for children with TBM (TBM-KIDS; SURE-TBM). Levels of cerebrospinal fluid penetration of new drugs and their potential efficacy for the treatment of TBM remain to be explored.

A study to evaluate whether treatment can be shortened from six to four months in children with minimal DS-TB is expected to open this year (SHINE). Similar studies to evaluate whether treatment for children with drug-resistant TB can be shortened and given without an injectable agent are needed,[70] especially considering the low number of TB bacteria (paucibacillary TB disease) and high rates of hearing loss observed in children related to use of injectable drugs.[71]

Studies to evaluate improved regimens for DS-TB and MDR-TB (see "Tuberculosis Treatment Pipeline," in *2015 Pipeline Report* [publishing July 2015]) rarely include pediatric components, but some at least allow for the inclusion of adolescents (≥10 years old). Table 4 provides an overview of ongoing and planned adult studies that include adolescents, a population for which we have a first-ever global estimate of TB disease burden: 655,000 cases per year.[72] Adolescent inclusion in phase III adult trials is especially warranted as there is no physiological basis for exclusion – adolescents achieve similar levels of drug exposures as adults, present with similar forms of TB disease, and tolerate adult formulations.

Table 4. Ongoing and Planned Adult TB Studies That Include Adolescents

Study/Regimen	Status	Population(s)	Sponsor(s)
PREVENTION			
ACTG A5279 4 weeks of daily rifapentine and isoniazid for prevention of TB NCT01404312*	Enrolling; results expected 2018	HIV-positive adults and adolescents ≥13 years old with LTBI	NIAID, ACTG, IMPAACT
ACTG A5300/ IMPAACT 2003 (PHOENIX) 6 months levofloxacin vs. isoniazid for prevention of MDR-TB	Planned; opening 2016; results expected 2020	HIV-positive or HIV-negative infant, child, adolescent, and adult household contacts	NIAID
V-QUIN 6 months levofloxacin vs. placebo for prevention of MDR-TB	Planned; opening 2015; results expected 2020	HIV-positive or HIV-negative infant, child, adolescent, and adult household contacts	NHMRC
TREATMENT			
TBTC 31 Safety and efficacy of rifapentine-containing regimens to shorten treatment of TB	Planned; opening 2015	HIV-negative and HIV-positive adults and adolescents ≥12 years old with TB	TBTC
TRUNCATE-TB Safety and efficacy of 2-month new regimens for treatment of TB	Planned; opening 2015	HIV-negative and HIV-positive, treatment-naive adults with TB; planned inclusion of adolescents ≥12 years old delayed pending Janssen C211	UCL, BMRC, Wellcome Trust, DFID, NMRC
NiX-TB Safety and efficacy of PaLJ(Z) to shorten treatment of XDR-TB NCT02333799*	Enrolling; results expected 2021	HIV-negative and HIV-positive adults and adolescents ≥14 years old with XDR-TB	TB Alliance
ReDEFINe Safety and efficacy of high-dose rifampin for treatment of TBM NCT02169882*	Enrolling; results expected June 2016	Adults and adolescents ≥15 years old with TBM	USAID
endTB Safety and efficacy of new bedaquiline- or delamanid-containing regimens for treatment of MDR-TB	Planned; opening December 2015	Adults and adolescents ≥15 years old with MDR-TB	UNITAID, MSF, PIH, IRD
*National Institutes of Health clinical trial identifiers; for more information go to ClinicalTrials.gov.			

ACTG: AIDS Clinical Trials Group, National Institute of Allergy and Infectious Diseases (United States)
BMRC: British Medical Research Council
DFID: Department for International Development (United Kingdom)
IMPAACT: International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group, U.S. National Institutes of Health
IRD: Interactive Research and Development
J: bedaquiline
L: linezolid
MSF: Médecins Sans Frontières
NIAID: National Institute of Allergy and Infectious Diseases (United States)
NHMRC: National Health and Medical Research Council (Australia)
NMRC: National Medical Research Council (Singapore)
Pa: pretomanid (PA-824)
PIH: Partners In Health
TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention
UCL: University College London
USAID: United States Agency for International Development
XDR-TB: extensively drug-resistant tuberculosis
Z: pyrazinamide

Recommendations

Stand-alone strategies focused on addressing TB in adults are insufficient to achieving the ambitious targets set forth in the End TB Strategy.[73] Recent recognition within the field of the importance of expanding prevention and treatment of pediatric TB has resulted in an increasingly full roster of studies in children. Yet much work remains to be done to expedite studies of regimens and new drugs in children and to advance the development of pediatric formulations of second-line drugs.

Expedite investigation of new drugs and regimens in children.

For drug companies

Pediatric investigation of new TB drugs and regimens should begin as soon as efficacy and safety have been established in adults (phase IIb studies); cohorts for PK and safety studies in children should be recruited in parallel; and adolescents ≥10 years old should be included in TB drug trials phase IIb and later.[74] These recommendations require drug sponsors and investigators planning studies of new TB drugs and regimens in adults to consider work necessary for facilitating eventual expansion of the targeted indication to children early on. Upstream decisions and lack of planning greatly (and often adversely) affect pediatric research and access timelines. Ultimately, knowledge gained from investigations focused on individual drugs should inform the design and implementation of pediatric-friendly treatment regimens (e.g., a nine-month, injection-sparing regimen for MDR-TB in children that incorporates optimized doses of existing and new TB drugs).

For regulatory authorities

More thoughtful requirements from stringent regulatory authorities will also help ensure the timely inclusion of children in TB research. The Orphan Drug Act should be amended so that it does not allow drugs exemption from the Pediatric Research Equity Act when additional pediatric-specific data are necessary for an indication in children younger than 18 years old. The Pediatric Research Equity Act should explicitly require investigation in all affected pediatric subpopulations. Similarly, the EMA Pediatric Committee on PIPs should work with drug sponsors to ensure the inclusion of HIV-positive children in planned investigations of new TB drugs.

Advance the development of pediatric formulations of second-line drugs.

- The WHO must issue formal dosing recommendations for second-line TB drugs in children and invite expressions of interest for pediatric formulations in line with its dosing recommendations. These two steps are required before the development of urgently needed pediatric formulations can advance.
- In tandem, the UNITAID-funded STEP-TB project should be expanded to take forward existing pediatric formulation prototypes of second-line TB drugs and to provide incentives for competing manufacturers to enter the market.

Increase investments in pediatric TB research and development.

- The trend of inadequate pediatric TB R&D funding must be reversed if we are to achieve zero TB deaths, new infections, suffering, and stigma, especially before 2035.
- The NICHD should continue to support studies critical to improving treatment of pediatric TB and to filling both long-standing and new gaps in pediatric PK and safety data, especially for HIV-positive children taking ARVs.
- UNITAID should expand funding for the STEP-TB project to facilitate expedited market introduction of pediatric formulations of second-line and new TB drugs, especially given the limited market size and lack of interest from manufacturers. Public money should be complemented by investment and commitment from manufacturers entering the pediatric TB market.

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The Tuberculosis Diagnostics Pipeline

By Mark Harrington

> *That things just go on like this is the catastrophe.*
>
> —Walter Benjamin[1]

Introduction

Because of the lack of effective, accessible point-of-care (POC) tests for all forms of tuberculosis (TB), 1.5 million people die of this treatable, usually curable disease each year. Annually, 3 million, or one-third of all, TB cases are never detected, reported, or properly treated. Among people with multidrug-resistant TB (MDR-TB), fewer than 20% receive proper treatment.[2] The lack of effective TB diagnosis and drug-susceptibility testing (DST) is responsible both for onward transmission of TB and for unnecessary suffering and death.

The world's failure to invest in a successful effort to render all cases of TB easily diagnosable remains baffling and infuriating. Countries and global donors are investing billions in often poorly functioning TB programs whose greatest needs – for better diagnostics, drugs, and vaccines – are being drastically underfunded by research institutions in both developed and developing countries. Treatment Action Group's most recent report on TB research and development (R&D) funding trends shows that in 2013 the world invested just US$67.77 million in TB diagnostics R&D. This represents a mere 19.9% of the annual US$340 million investment recommended by the World Health Organization (WHO) in its *Global Plan to Stop TB: 2011–2015*.[3,4] Even the few improved new technologies that have been endorsed by the WHO over the past seven years are underused and inaccessible to most people with TB today.

Last year's *Pipeline Report* described TB diagnostics research as being "at a standstill." It would be an exaggeration to say the last 12 months have seen an increase in momentum or investment. This chapter describes the noteworthy advances that have been documented in the published literature or occurred in clinical trials or policy.

Background

For the past 133 years, sputum-smear microscopy for acid-fast bacilli – of which TB is one – has been the most widely used test for TB. The test is nonspecific to TB and misses up to half of pulmonary cases – even more among children and HIV-positive people – and by definition all extrapulmonary ones. TB culture on solid media has also been used to diagnose TB for over a century and in DST since the introduction of TB chemotherapy in the 1940s. But culture on solid media can take months, meaning that results cannot be used to guide therapy at the outset. In 1993, the WHO recommended the microscopy-based DOTS strategy for worldwide TB control. One unanticipated consequence of the recommendation may have been to lead some countries to further degrade – if they had not already dismantled – their TB microbiology (culture) laboratories. In these cases, the ability to diagnose drug-resistant TB or to determine appropriate treatment was being dismantled just as the worldwide MDR-TB epidemic made its explosive debut.

In late 2006, researchers from South Africa and the United States reported an outbreak of extensively drug-resistant TB (XDR-TB) at an HIV clinic in rural KwaZulu-Natal, South Africa.[5] Activists and policy makers realized that countries needed to move fast to improve TB laboratory capacity and to modernize the diagnostics armamentarium used in medium- and low-income-country TB programs. Over the course of 2008,

groups such as the AIDS Rights Association of Southern Africa, Médecins Sans Frontières, Partners In Health, and Treatment Action Group held two workshops to highlight the need for a TB POC test and to develop target product profiles.[58] The following three years saw a surge of new WHO recommendations including:

- liquid culture media such as the mycobacterial growth indicator tube automated platform,[6]
- rapid species identification such as with the Capilia rapid speciation test to distinguish TB from nontuberculous mycobacteria (NTM),[6] and
- line probe assays for rapid detection of MDR-TB such as the GenoType MTBDR*plus* assay.[7]

These tests provided advantages over smear microscopy and solid culture. TB in liquid culture was measurable in weeks rather than months. The speciation test revealed in 20 minutes whether a culture was *Mycobacterium tuberculosis* (MTB) or NTM. The GenoType MDRTB*plus* could diagnose many forms of TB with common genetic mutations to rifampin and isoniazid – resistance to both of which was the signature of MDR-TB – within a day or two.

The WHO continued to broaden the recommended laboratory options for low- and middle-income countries with policy statements on:

- noncommercial culture and DST methods,[8]
- same-day diagnosis by microscopy,[9]
- fluorescence microscopy,[10] and
- the GeneXpert MTB/RIF (rifampin) automated, real-time, cartridge-based PCR nucleic acid amplification test (NAAT) (2010,[11] updated 2013).[12]

Increasingly, NAA-based diagnostic tests are replacing culture-based ones for many diseases and, in the form of HIV and hepatitis C virus viral-load assays, have long been the basis for clinical staging and monitoring of treatment. In only two hours, the Xpert MTB/RIF test can determine from sputum whether TB and rifampin resistance are present; Xpert has also demonstrated sensitivity and specificity using samples from nonpulmonary tissues and fluids where TB is growing (gastric juices, lymph nodes, and cerebrospinal fluid).[12a,12b]

All, however, are expensive laboratory tests requiring electricity, controlled temperature, and trained personnel, all of which are in short or erratic supply at the points of care where most people at risk for or living with TB receive their care.

The WHO also tried to simplify the lives of laboratory workers and defray unnecessary costs to patients and payers by recommending against the use of common serologic (blood) tests for TB[13] and interferon-gamma release assays (IGRAs) in low- and middle-income countries.[14]

The WHO has yet to recommend a new TB diagnostic test since Xpert (2010/2013). In 2013, expert review panels found significant flaws with both the Eiken TB-LAMP[15] (loop-mediated isothermal amplification) and the Hain Lifescience MTBDR*sl* (which aims to detect resistance to second-line fluoroquinolones and injectables) tests,[16] declined to recommend them based on insufficient evidence, and suggested additional research.

The WHO has not reviewed the MTBDR*sl* test subsequently, and results of a June 2015 review of LAMP are not yet publicly known.

In June 2015, a WHO expert group reviewed data on the Alere Determine urine lipoarabinomannan (LAM) lateral flow test. The results of this review are not yet public.

Table 1 lists TB diagnostic test candidates relatively late in development with data published since the *2014 Pipeline Report*. For an encyclopedic review of the current TB diagnostic pipeline, see the 2014 UNITAID *Tuberculosis Diagnostics Laboratory and Market Landscape, 3rd edition*.[17] More succinct overviews are available from Pai,[18] Pai and Schito,[19] and Dorman.[20] Table 2 lists other tests discussed in the *2014 Pipeline Report* with no new publications since last year's report.

Table 1. 2015 Tuberculosis Diagnostics Pipeline: Products in Later-Stage Development or on Track for Evaluation by the WHO with New Published Data Since the *2014 Pipeline Report*

Test	Type	Sponsor	Status	Comments
MOLECULAR/NAAT/DST				
BD MAX MTB assay	qPCR for MTB in automated BD MAX	Becton, Dickinson	100% sensitive/specific for smear-positive samples[27]	
EasyNAT	Isothermal DNA amplification/lateral flow to detect MTB	Ustar	Poor sensitivity, especially for smear-negative specimens, in Tanzanian field study[28]	
FluoroType MTB	Semi-automated direct MTB detection; PCR in a closed system; results in 3 hours	Hain Lifescience	Two new studies since 2014[29,30]	Marketed
GeneChip	RT-PCR for RIF + INH DR	CapitalBio	Chinese Center for Disease Control and Prevention and University of Georgia published a paper on 1,400 samples from SW China[31]	Marketed
GenoType MTBDR*sl*	Line probe assay for FQ + SLID resistance	Hain Lifescience	WHO urged further study;[16] 2014 *Cochrane* review equivocal[33]	Sponsor claims 2.0 version superior[32]
LiPA pyrazinamide	Line probe assay for PZA resistance	Nipro	Thai field study 2015[34]	Marketed. No independent studies
MeltPro TB/INH	Closed-tube RT-PCR for INH DR	Zeesan Biotech	3-site evaluation of 1,096 clinical isolates[35]	Chinese FDA-approved
MeltPro TB/STR	Closed-tube RT-PCR for streptomycin DR	Zeesan Biotech	3-site evaluation of 1,056 clinical isolates[36]	
PURE-LAMP	Manual NAAT by loop-mediated isothermal amplification for MTB detection	Eiken	June 2014;[50] WHO review June 2015	WHO review results not publicly known
RealTime MTB/TB MDx m2000	Automated RT-PCR for MTB; can be added to HIV RNA platform	Abbott	Lower limit of detection than Roche Cobas assay[38]	CE marked[37]
REBA MTB-XDR	Line-probe assay for FQ + SLID DR	YD Diagnostics	Initial study 2015[39]	Marketed
Xpert MTB/RIF Ultra	Next-generation cartridge-based detection of MTB + RIF resistance	Cepheid	Initial study CROI 2015[40]	"Data showed the new Xpert MTB/RIF Ultra test with a new sampling processing cartridge is as sensitive as liquid culture. #CROI2015 #TB"[41]
VOLATILE ORGANIC COMPOUNDS				
Giant African pouched rats (*Cricetomys gambianus*)	Trained sniffer rates to detect MTB in sputum	Apopo Foundation	Initial study 2009[42]	Rats detected 80% of MTB species while ignoring Mycobacterium avium/intracellulare[43]
AUTOMATED IMAGING				
CAD 4TB	Digital CXR for TB screening	Delft Imaging Systems	Used in ZAMSTAR study	Three new studies in 2014–2015[44,45,46]
ANTIBODY/ANTIGEN DETECTION				
Determine TB LAM Ag	Urine dipstick for TB LAM protein	Alere	Expert review for WHO, June 2015	Results of WHO review not publicly known

CE: Conformitè Européenne (a safety certification for sale in European Economic Area countries)
CROI: Conference on Retroviruses and Opportunistic Diseases
CXR: chest X-ray
DR: drug resistance
EMB: ethambutol
FQ: fluoroquinolone
INH: isoniazid
MTB: *Mycobacterium tuberculosis*
NAAT: nucleic acid amplification test
PZA: pyrazinamide
RIF: rifampin
RT-PCR: real-time polymerase chain reaction
SLID: second-line injectable drug (e.g., amikacin, capreomycin, or kanamycin)
STR: streptomycin

Table 2. Later-Stage or Marketed TB Diagnostic Test Candidates with No New Published Data

Test	Type	Sponsor	Last Published Paper(s)	Comments
MOLECULAR/NAAT				
FluoroType MTB RNA	MTB RNA for monitoring of anti-TB therapy	Hain Lifescience	N/A	No published data
Genedrive MTB/RIF	Portable RT-PCR for MTB + RIF resistance	Epistem/Foundation for Innovative New Diagnostics, Boston University, the Johns Hopkins University	2014[47]	Licensed in E.U., India; comparative NCT02252198 study under way
LATE-PCR with Lights-On/ Lights-Off Probes + PrimeSafe	Single-tube PCR to detect MTB, resistance to INH, RIF, EMB, SLID	Hain Lifescience/Brandeis University, Stellenbosch University	2012[48]	No published data on TB application
LiPA MDR-TB	Line probe assay for RIF + INH resistance	Nipro	2013[49]	Marketed. No independent studies
REBA MTB-MDR	Line probe assay for RIF + INH resistance	YD Diagnostics	2013[51]	Marketed. One published study[51]
TRC Rapid MTB	Automated rapid rRNA to detect MTB	Tosoh	2010[52]	"Tosoh's molecular testing systems for tuberculosis…are exponentially faster than traditional methods"[53]
Truenat MTB	Chip-based NAAT with RT-PCR on handheld device for MTB	Molbio Diagnostics, Bigtec Labs	2013[54]	Comparative study NCT02252198 under way
TREK Sensititre MYCOTB MIC plate	Dry microdilution plate to detect MICs for FLD + SLD (except PZA)	TREK Diagnostic Systems, Thermo Fisher Scientific	2014[55]	
ANTIBODY/ANTIGEN DETECTION				
MBio Array System	POC cartridge to measure ~57 simultaneous MTB antigen-antibody reactions	MBio Diagnostics, FIND	2014[56]	

DST: drug-susceptibility testing
EMB: ethambutol
FLD: first-line drugs (INH, RIF, EMB, PZA)
FQ: fluoroquinolone
INH: isoniazid
MDR-TB: multidrug-resistant TB
MIC: minimum inhibitory concentration
MTB: *Mycobacterium tuberculosis*
MYCOTB: *Mycobacterium tuberculosis*
NAAT: nucleic-acid amplification test
POC: point of care
PZA: pyrazinamide
RIF: rifampin
RT-PCR: real-time polymerase chain reaction
SLD: second-line drug
SLID: second-line injectable drug (e.g., amikacin, capreomycin, or kanamycin)

It is clear from the paucity of published studies, that, as noted in the UNITAID landscape analysis, despite the potential of some of the newer portable, handheld NAATs' being made available closer to where people get diagnosis and treatment: "[a] significant deterrent to widespread application of NAATs is the need for appropriate field evaluation of newer tests. Currently there have been limited assessments of the next-generation NAATs, with only two evaluations of LoopAMP MTBC™ Detection Kit and EasyNAT™, and one each for Genedrive®, Truelab™ and FluoroCycler technologies. For most of these products, on the market for a few years now, more performance data are needed to inform NTP [national TB program] policies."[17]

The evidence base for most new TB diagnostic tests in the pipeline is shockingly weak for most of the so-called fast followers to the Xpert MTB/RIF test. It is distressing that neither the Hain GenoType MTBDR*sl* test nor Eiken's PURE-LAMP test has yet generated enough evidence to overcome the WHO expert panels' 2013 refusal to recommend these tests due to insufficient evidence.[15,16]

For Xpert, a pragmatic randomized trial conducted in South Africa and presented at the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) showed that the immediate addition of Xpert had no impact on mortality versus standard of care (microscopy, with Xpert deferred). The investigators concluded: "a sensitive diagnostic test needs to be supported by systems linking to appropriate care, particularly ensuring that people know their HIV status and those eligible…start ART promptly."[21] Yet the impact of Xpert on earlier treatment initiation in many settings is undeniable.[21a]

On the more encouraging side, another paper presented at CROI 2015 introduced a new version of the test, the Xpert MTB/RIF Ultra, with sensitivity claimed comparable to culture.[37,38] Other planned improvements to the platform include adding common isoniazid resistance mutations and HIV RNA measurement.

Among people with HIV in a Ugandan study, the Alere Determine TB LAM – a simple urine dipstick that gives results in under 30 minutes – detected over half of those with culture-positive TB[22] and was "highly cost-effective compared with usage of either sputum smear-microscopy or Xpert alone."[23] Indeed, "[t]he sensitivity of the combination of Xpert and LF-LAM was 85% (88/103 95% CI 0.77–0.92), which was superior to either test alone ($P<0.05$) and approached sensitivity of sputum liquid culture testing (94%, 95% CI 0.88-0.98, $P=0.17$)."[24] The test is much less useful among people with higher CD4 counts, however. These results, and a substantial body of additional evidence,[24a] support a WHO recommendation for the use of the lateral flow LAM test, at least among HIV-positive people with low CD4 counts.

Future Directions

Madhukar Pai and Marco Schito write:

> The ongoing rollout of Xpert MTB/RIF has had a positive influence on the TB diagnostics landscape, has attracted new investments and product developers, and has created a robust pipeline of technologies… However, the Xpert technology was not designed to reach lower tiers of the healthcare system or to meet all needs ([e.g.,], it cannot detect latent *M. tuberculosis* infection or resistance against multiple drugs. Despite initiatives to reduce the price, high costs continues to be a hurdle….A recent survey of 22 countries with a high tuberculosis burden (HBCs) showed that, while a majority (86%) of these countries have a policy or algorithm for use of Xpert technology, current implementation is mostly donor funded, dependent largely on testing in centralized laboratories, and primarily involves patients with presumed drug-resistance or HIV infection [see ref. 25]….This suggests that wide-scale implementation of Xpert technology has mostly occurred in South Africa, while other HBCs continue to rely heavily on smear microscopy.[19]

In April 2014, the WHO convened a priority-setting group to develop target product profiles for the highest-priority consensus indications, which were:

- a biomarker test: "[a] point-of-care non-sputum-based test capable of detecting all forms of TB by identifying characteristic biomarkers or biosignatures…";
- a triage test: "[a] point-of-care triage test, which should be a simple, low-cost test that can be used by first-contact health-care providers to rule-out TB…";
- a smear-replacement test: "[a] point-of-care sputum-based test to be used as a replacement for smear microscopy…; and"
- a rapid DST test: "[a] rapid drug-susceptibility test that can be used at microscopy centers…."[26]

It's striking that this consensus group did not identify the need for a more definitive test for latent TB infection (LTBI) as a high priority as the current tests – tuberculin skin testing and IGRAs – have significant flaws, are not specific to MTB, and miss many cases; and in any case treatment of LTBI will be essential to eliminating new TB transmission.

In any case, with current scientific uncertainties and the continued likelihood of inadequate funding for TB R&D overall and for TB diagnostics research, these desiderata seem far away indeed. According to UNITAID:

> In the medium term, the need for a biomarker-based, low-cost, non-sputum-based test remains a key priority for TB diagnostics beyond the microscopy centre where the majority of people first seek care. Although biomarker discovery is an active area and several potential products (e.g. antigen or antibody detection tests; volatile organic compounds (VOCs); enzymatic detection) are under development, *no test under development is likely to be on the market with policy endorsements within the next three to five years* [emphasis added].[17]

With the exceptions of the urine LAM dipstick, the potential Xpert MTB/RIF Ultra, and GenoType MTBDR*sl* and PURE-LAMP – if stronger supporting evidence emerges – there are not a lot of test candidates likely to be reviewed and recommended by the WHO for use in middle- and low-income countries in the near future. The ideal POC biomarker test is clearly years off, and even the potential of VOCs remains remote unless programs have access to the 40 or so expertly trained giant African pouched rats, which can detect TB in sputum samples[43] – and it is unlikely that this innovative live diagnostic method could be scaled up any time soon.

Recommendations

1. **Invest in TB R&D and diagnostics research – including "R&D for new, biomarker-based triage/POC tests."**[57] The world needs to invest an additional US$270 million per year in TB diagnostics research, and US$2.0 billion annually for TB R&D to make this curable disease detectable and treatable for all.
2. **Integrate TB diagnostics research into ongoing treatment regimen studies**, and improve the integration of TB diagnostics and treatment research with implementation research in programmatic settings, including among people with HIV and children.
3. **Implement universal drug-susceptibility testing. "Push NTPs and health systems to think beyond sputum smears. Xpert is the quickest route to upfront DST. In parallel, build capacity for DST-guided MDR-TB therapy (so, capacity for liquid cultures)….We need next-generation DST ready for launch of new drug regimens."**[57] "Advocate for wider use of Xpert…among those with presumed TB, in children, people with HIV, and extrapulmonary TB."[57]

4. **"Eliminate inaccurate/misleading tests such as serology in China; restrict use of IGRAs for latent TB** (especially in India, SA, China)."[57]

5. **Increase screening and treatment for LTBI. "Demand systematic screening of contacts – especially children under 5 and people living with HIV."**[57]

6. **Improve the quality of research studies**, e.g., for follow-on NAA technologies, which have the potential to be cheaper, more portable, and more accessible than Xpert MTB/RIF but for which evidence of their effectiveness has been sorely lacking.

7. **Intensify investments in comparative studies** of new TB diagnostics and algorithms to optimize the use of current and emerging approaches in all important settings.

8. **Improve regulatory capacity to oversee TB diagnostics research** in all countries to ensure that NTPs, providers, and people with TB alike do not waste scarce resources on tests that lack specificity and sensitivity. The WHO has been right to set a high bar for recommending new TB diagnostics – and for recommending which tests *not* to use. Countries need to learn how to better evaluate existing tests with the same high standards. "Advocate for new tools to be rapidly evaluated for policy review."[57]

9. **Implement new TB diagnostic tests and algorithms in a coherent way** across health systems to enable diagnosis of TB as broadly as possible and break out of the deeply inadequate vertical microscopy-center model. Currently some sites equipped with Xpert refuse to use it because they lack MDR-TB treatments – not realizing that many if not most cases picked up by Xpert are simply smear-negative or extrapulmonary TB that is drug-sensitive. TB prevention, care, and treatment need to be integrated into health systems more broadly and effectively.

10. **Institute open access to all TB R&D publications.** Keeping research with results critical for the health of millions in resource-limited settings behind a firewall inhibits the free circulation of new scientific knowledge.

11. **Insist on universal access to and, where needed, uptake of all new evidence-based TB diagnostic tests without stock-outs, excessive prices, or arbitrary access barriers among different sectors of the health system, such as the current restriction of concessional Xpert pricing to public-sector programs.**

12. **Involve communities affected by TB, people living with TB, survivors of TB, and activists** in TB diagnostics research, implementation, rollout, and evaluation to improve community understanding and create greater demand for better solutions.

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CROI: Conference on Retroviruses and Opportunistic Infections

Unless noted otherwise, all links were accessed on July 5, 2015.

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The Tuberculosis Vaccines Pipeline: A New Path to the Same Destination?

By Mike Frick

Call it a paradigm shift, a pivot, or a turn – tuberculosis (TB) vaccine research and development (R&D) is entering a period of basic science. After years of focusing on phase II clinical trials, some of the field's largest players are now redirecting attention and resources to the beginning of the pipeline – basic discovery and preclinical development. This change is motivated by a growing consensus that the guiding assumptions of the last 10 years of TB vaccine research require updating in the face of emerging evidence from the clinic and the lab.

All along, some of the largest funders of TB vaccine research (e.g., the U.S. National Institutes of Health and the European Commission) have concentrated resources on basic-science and discovery activities. The momentum steering other funders in this direction picked up speed in 2014 when the Bill & Melinda Gates Foundation (BMGF), the largest funder of TB vaccine R&D globally, revised its TB vaccine R&D strategy, along with its overall TB R&D strategy, calling for efforts to "shift to the left" of the clinical development pipeline. As the BMGF envisions it, resources should transfer from a limited number of large, expensive phase IIb/III trials (events located on the far right side of the pipeline) to basic discovery, preclinical development, and phase I studies.[1,2] Whereas a phase III TB vaccine trial could cost $100 million to validate the efficacy of a single vaccine candidate,[3] investing in smaller, earlier-stage studies would enable the exploration of a wider array of vaccine concepts. This approach would "de-risk" vaccine development by winnowing vaccine concepts and advancing only those most likely to succeed in later clinical trials, where failure comes with a heftier price tag in terms of financial resources and community stamina for hosting large-scale research.[4]

The changes in TB vaccine R&D are a response to systemic weaknesses in the TB vaccines pipeline, which contains 16 candidates in active clinical development. Three of these candidates employ a single antigen of *Mycobacterium tuberculosis* (MTB), the bacterium that causes MTB infection and TB disease. Many candidates contain the same handful of antigens in different combinations; all together, the viral-vectored and protein/adjuvant vaccines in the pipeline include just 12 of the 4,500 targetable antigens encoded in the MTB genome.[5] Furthermore, in selecting these antigens, most current candidates are designed to trigger a strong cell-mediated immune response driven by CD4+ and CD8+ T cells. By contrast, most licensed vaccines work primarily through humoral immunity, or antibodies produced by B cells. In short, the antigenic repertoire targeted by vaccines in the pipeline is narrow, overlapping, and aimed at a single arm of the immune system.

Seasoned HIV/TB activists and investigators could be forgiven a feeling of déjà vu over this movement back to basic science. Present discussions in the TB vaccine world echo a call in 1993 for a return to basic science in HIV research. In TAG's *Basic Research on HIV Infection: A Report from the Front*, Gregg Gonsalves interviewed 36 scientists about key obstacles slowing basic research on HIV/AIDS.[6] The thematic areas that emerged from those interviews – correlates of immunity, research in vivo, pathology of HIV infection, viral life cycle, and events in host response – mirror the scientific sticking points in TB vaccine R&D today.

The central insight of Gonsalves's report holds true for TB prevention: the pipeline for new medical technologies is only as strong as the basic science and preclinical studies from which testable ideas emerge. In recognition of that, this chapter first reviews progress in basic science and preclinical development. Advances in these areas owe much to new ways of looking for clues to protective immunity in the blood, genome, and lung. The second section discusses ways of testing vaccine candidates through innovative clinical trial designs. The chapter closes with a call for researchers, funders, and vaccine developers to find new ways of working together – not just with each other, but also with an expanded definition of who counts as a partner, including activists, TB-affected communities, regulatory agencies, and developing-country vaccine manufacturers.

New Ways of Looking, but What Are We Seeing?

In January 2015, the biennial Keystone Symposia on TB, titled "Host Response in Tuberculosis," opened with one of the organizers admitting discomfort at making any distinction between MTB and its human host.[7] By the end of the meeting, a common refrain had emerged: the characteristics of host-pathogen interaction are more surprising, heterogeneous, and entangled than we had imagined. One speaker after another expressed his or her opinion that future research endeavors must look deeper, recognize increasing layers of complexity, and remember that what we think we know may have come from gazing at just a sliver of the full picture.

New visions from genomics

The full picture, it turns out, is painted with the complexity of tens of thousands of years of evolutionary back-and-forth between MTB and humankind. Over the long stretch of evolutionary time, MTB has transformed from a soil-dwelling microbe into the most lethal killer in human history.[8] Seventy thousand years of coevolution with *Homo sapiens* have given MTB sufficient time to learn to harness the human immune response to its benefit.[9] This ability upends traditional metaphors that relate the immune system to an army at war against pathogenic invaders. Rather than exist in either a state of full war (active TB disease) or an uneasy truce (latent MTB infection), MTB appears to establish a dynamic coexistence with the human host, the conditions of which give it fertile opportunity for persistence, replication, and onward transmission.[10]

These opportunities appear to hinge on MTB's attracting recognition by CD4+ T cells, a counterintuitive notion given that most pathogens hope to escape notice by the immune system.[11] Genomic analyses suggest that the parts of the MTB genome that code for the epitopes (cell-surface proteins) recognized by CD4+ T cells are hyperconserved, meaning they appear the least changed over time compared with other segments of the genome.[12] This genomic stability over 70,000 years suggests an evolutionary advantage to MTB being recognized by CD4+ T cells. That is, the cell-mediated immunity triggered by T cells may create a lung environment favorable to MTB under certain conditions.[13] One explanation implicates the release of type 1 helper T (Th1) cytokines such as interferon-gamma (IFNγ), tumor necrosis factor-alpha (TNFα), and interleukin-2 (IL-2) by CD4+ and CD8+ T cells responding to MTB. These cytokines are signaling proteins that help call and direct the behavior of other immune cells. However, certain cytokines also cause inflammation, and while some inflammation is necessary to mount a successful immune response, too much can have the unintended consequence of damaging lung tissue. This damage may create a microenvironment that favors MTB persistence by sheltering MTB from immune killing. Eventually, the scarring and cavitation (the formation of holes in tissue) produced by poorly controlled inflammation permit onward transmission by giving MTB a pathway to escape the lung into the air via aerosolized droplets.[14,15]

Consistent with the apparent hyperconservation of T-cell epitopes, clinical trials of TB vaccines have observed a repeated disconnect between strong IFNγ (Th1, T-cell-favored) responses and protection against TB disease. There is now widely shared agreement that IFNγ is a necessary but insufficient marker of protection.[16,17,18,19] However, a holistic picture of the biological markers that correlate with protection against either MTB infection or TB disease remains lacking. As a first step toward identifying biomarkers of protection, some researchers have turned their gaze to the human genome in search of correlates of risk. A subset of the broader set of biomarkers, correlates of risk serve as predictive signifiers composed of genes, biological processes, or clinical phenotypes that act as precursors to disease states or responses to vaccination or drug therapy.[20]

In the context of TB vaccine R&D, biomarker discovery is a tactic for informing and streamlining clinical development. The identification and validation of a biomarker (or biosignature comprised of multiple markers) would greatly aid TB vaccine R&D by giving investigators glimpses of efficacy earlier in a vaccine's development. These early suggestions of efficacy could improve the selection of candidates for late-stage trials and, once validated, might enable shorter, smaller trials by serving as surrogate endpoints for TB disease.[21] However, the identification of possible biomarkers would not transform the clinical pipeline overnight, as

any correlates would require validation in a successful phase III trial before they could function as reliable surrogate endpoints. In addition, biomarkers are by nature proxies for disease and may not fully represent the intricacies of host-pathogen interaction unfolding at sites of infection.[22]

Two major initiatives are pursuing biomarker identification from a genomics angle. The first is a prospective cohort study of South African adolescents spearheaded by the South African TB Vaccine Initiative (SATVI). The study enrolled over 6,300 adolescents with MTB infection and followed them over two years before looking for genes differentially expressed in those who developed TB disease and those who did not.[23] The second effort is the TB biomarker consortium organized under the BMGF-funded Grand Challenges 6 initiative that seeks to find correlates of risk of progression to disease among HIV-negative adult household contacts of people with TB in several African countries.[24] Investigators in the two projects have combined portions of their data and identified 1,531 genes that are differentially expressed between individuals who progress to active disease and those who remain healthy, although full analyses of this intriguing finding remain unpublished.[25]

New visions from radiography

Genomic and transcriptional analyses open a window onto the history of host-pathogen interaction and its effects across populations over time. Visions of what this complexity looks like within individuals appear through a very different kind of technology: PET/CT. The combination of positron emission tomography (PET) and X-ray computed tomography (CT) aligns the depiction of biochemical activity in the body with anatomical images represented in two or three dimensions. Researchers are taking advantage of PET/CT to map the appearance and growth of individual lesions in the lung. These lesions, or granulomas, are collections of macrophage cells that flock to sites in the lung where MTB is present. Traditionally, macrophages have been described as initial responders that huddle together to form immune fortresses that contain MTB. PET/CT has helped to overturn the idea of granulomas as stolid, stable fortresses by showing that a dynamic range of activity exists across lesions, even during so-called latent phases of MTB infection.

PET/CT imaging has been applied in at least one TB treatment trial – a phase II study of linezolid functional monotherapy in patients with chronic extensively drug-resistant (XDR-TB) in South Korea.[26] In a substudy nested into this trial, 19 participants received three PET/CT scans at different times before, during, and after treatment with the linezolid-containing regimen. Among the five participants who had PET/CT scans before the linezolid-containing therapy, all had evidence of progressing, regressing, and newly forming lesions over a two-month period. The implication is that TB activity varies throughout the lung and that the response to MTB, whether driven by drug therapy or the body's adaptive immune response, is locally heterogeneous as well.[27] With these data, as well as results from autopsy studies of granuloma patterns,[28] the previous assumption that all lesions within an individual behave similarly has been disproved.

In vaccine research, the application of PET/CT has focused on preclinical work in cynomolgus macaques, the field's dominant nonhuman primate model. PET/CT imaging is being used to study immune activity (i.e., inflammation) in macaques whose quiescent, latent infection with MTB is reactivated by treatment with anti-TNF, an immunosuppressant. Findings so far suggest that macroscopic granuloma patterns seen during primary MTB infection may differ from those observed during re-activated disease.[29] Whether anti-TNF treatment can stand in for the immunosuppressing conditions (e.g., HIV, diabetes, and silicosis) that increase the risk of MTB infection progressing to TB disease in people remains unknown.

Researchers have also sought to overlay granuloma patterns observed through PET/CT imaging with T-cell responses measured by intracellular cytokine staining to better understand whether and how T cells and the cytokines they produce are responsible for inflammation. This work points to marked variability in the T-cell response to MTB across granulomas – even within granulomas located in the same lobe of the same lung of the same macaque.[30] While each granuloma contains many T cells making a variety of cytokines, most individual T cells appear to produce just one type of cytokine. This stands in juxtaposition to the common

practice of judging TB vaccine candidates by their ability to trigger polyfunctional T cells that produce multiple cytokines. Notably, granulomas with T cells producing both pro- and anti-inflammatory cytokines appear more likely to reach sterilization. In addition, levels of granuloma inflammation in macaques are more strongly predictive of whether MTB infection will progress to active disease than the number of bacteria present (bacterial burden).[31]

By revealing the expansive range of granuloma activity in the lung, PET/CT has helped to replace the idea that MTB infection and disease exist as distinct binary states with the notion that a continuum of host-pathogen responses underlies infection and disease. While distinguishing latent from active TB may still hold clinical relevance when diagnosing patients, within the lung, distinctions between active and latent TB dissolve in the face of heterogeneous, localized activity between MTB and a range of immune cells. Using PET/CT to create macroscopic composites of inflammation unfolding across the lung raises the tantalizing possibility of defining inflammation-based markers of response to drugs or vaccines for use in future clinical trials.[32] In short, radiography has made a compelling case for casting aside old ideas that treat MTB and the host response as discrete and uniform and has offered a way to look at host-pathogen interaction outside of the strict cellular context of traditional immunology work.

New visions from blood and bronchial samples

One of the guiding principles of the field's shift to earlier phases of research is the need for iterative learning between experiments in the laboratory and trials in the clinic. Instead of progressing in a strict linear fashion from lab to clinic, vaccine research should move back and forth between these two stages of research. Samples collected in human studies should be studied in the lab to better understand the biology of MTB infection and TB disease, the knowledge of which can then be used to refine the preclinical models that will inform future clinical development. This iterative approach entails making use of observational cohort data alongside evidence from randomized, controlled trials.[33] Several presentations at the Santa Fe Keystone Symposia demonstrated the potential of using blood and lung samples collected in cohort studies to investigate specific questions of immunologic importance.

One of these questions concerns the role of antibodies produced by B cells in preventing, controlling, and clearing MTB infection. Efforts to understand humoral, B-cell-based immune responses to MTB have trailed investigations of cell-mediated immunity generated by T cells. This overshadowing is so extensive that all of the speakers in the "B-cell responses to TB" session at the Santa Fe Keystone meeting emphatically assured the audience that their research focus lay elsewhere. The last presenter, however, did something unexpected: she turned a room of B-cell skeptics into cautious believers. Using plasma samples from 120 South Africans with TB, some with latent MTB infection and others with active TB disease, Galit Alter and her lab at the Ragon Institute showed how MTB-specific immunoglobin (IgG), a type of antibody, is capable of recruiting other immune cell types – including macrophages and natural killer cells – to the site of infection, and that differences observed in the structural properties of IgG can even distinguish patients with latent MTB infection from those with active TB disease.[34]

Although B cells may attract more attention moving forward, findings about the role of humoral immunity in controlling MTB are likely to augment, rather than supplant, efforts to better understand cell-mediated immunity. The emphasis on designing vaccines that trigger robust cell-mediated immunity rests on the incontrovertible observation that CD4+ T-cell depletion in people with HIV hugely increases their risk of developing TB disease. Even this long-established story is adding chapters as researchers look closely at the mechanisms at play in the lungs of people with TB/HIV coinfection. Observational cohort data from Malawi show there is a delayed recovery of MTB-specific CD4+ T cells in adults with HIV on antiretroviral treatment (ART) – even among individuals taking ART for at least four years. This suggests that HIV makes the lung environment more susceptible to MTB infection and progression.[35] People with HIV also appear to face a higher risk of TB disease before CD4+ T-cell depletion. One recent study from South Africa found that HIV

infection increases the risk of TB disease even at high CD4+ T-cell counts. Individuals with HIV with CD4+ T-cell counts greater than 600 cells/μL had half the frequency of MTB-specific immune responses compared with study participants without HIV, as measured in both blood and airway samples.[36] This growing literature argues for the importance of considering how comorbidities may change characteristics of host-pathogen interaction from the outset of TB vaccine development.

New Ways of Testing, but Have the Measurements Changed?

People with HIV, on and off ART, are underrepresented in TB drug trials. So are children, although the historic exclusion of younger age cohorts from TB drug research is beginning to change. In the coming period, these two patient populations may also play a less central role in TB vaccine trials, which until recently focused on infants and people with HIV in phase II investigations. Future TB vaccine clinical trials, particularly those supported by the BMGF, will focus instead on adolescents and adults without HIV or other comorbidities. This new emphasis by some funders reflects a move toward preventing MTB infection, as opposed to TB disease, in the design of clinical trials. Two lines of thinking are motivating this shift.

First, for a new TB vaccine to interrupt MTB transmission, the target population must be adolescents and adults, as disease in these age groups drives the majority of MTB transmission globally. Children, who typically have paucibacillary and nonpulmonary forms of TB, are less likely to transmit TB to others. Similarly, people with TB/HIV coinfection have lower bacterial loads, though recent work challenges the notion that they do not contribute to TB transmission.[37] Mathematical modeling commissioned by Aeras suggests that an adolescent or adult vaccine with 40% efficacy against TB disease would avert 70% of the expected TB burden in low-income countries between 2024 and 2050.[38] An infant vaccine of equal efficacy and duration, however, would avert less than 12% of the TB burden – partly because many infants in the vaccinated groups would not have reached adolescence, an age when the risk of TB disease increases markedly, by the end of the 20-year period under simulation. Buried in the paper presenting these scenarios is this sentence: "A vaccine targeted at adolescents and adults . . . is likely to prevent, before 2050, more infant cases of TB than a vaccine targeted at infants due to the reduction in transmission."[39] This claim rests on the promise of vaccines to protect not just those persons directly vaccinated but also neighboring individuals who may not be immunized. Future modeling exercises and in vivo studies should interrogate the validity of this statement as our understanding of the biological and social drivers of TB transmission evolves.

Second, using prevention of infection as the primary endpoint will enable smaller, faster, and cheaper clinical trials. In any given population, rates of MTB infection typically exceed those of TB disease. This difference is even more pronounced in high-risk groups such as household contacts of newly diagnosed TB cases, health care workers, and miners. Because the outcome of interest occurs more frequently, prevention-of-infection trials require smaller sample sizes and shorter durations of follow-up than prevention-of-disease trials.[40] Consequently, prevention-of-infection studies may offer a more efficient way of testing vaccine concepts before deciding which ones to advance to phase IIb/III trials, where prevention of TB disease is likely to remain the primary endpoint. For this strategy to work, the mechanisms of protection against infection and disease must overlap – which seems far from guaranteed given the increasingly complex picture of host-pathogen interaction emerging from basic-science work.

Although heralded as a paradigm shift, prevention-of-infection trials may simply transpose the current strategy to an earlier event in TB pathology. As designed, prevention-of-infection trials do not circumvent the thorny issue of how to judge vaccine efficacy if classic Th1 cytokines such as IFNγ are important but only partial aspects of protective immunity. All TB vaccine trials described below continue to assess immunogenicity by measuring IFNγ. Rather than replace the object of measure with a more relevant marker, prevention-of-infection studies merely shift our measurement of it to earlier points in the infection process.

Further complicating things, this moment (incidence of MTB infection) is difficult to measure with available diagnostic technologies. There is no gold standard diagnostic for MTB infection, and the best currently available tools, interferon gamma release assays (IGRAs), come with serious limitations. The repeatability of the QuantiFERON Gold In-Tube (QFT) blood test, the most common IGRA used in TB vaccine R&D, has come under scrutiny for the tendency of QFT tests taken on the same individual at different times to produce discordant results, whereby initial tests read MTB-positive and follow-up tests read MTB-negative.[41,42] This poor reproducibility creates a risk that prevention-of-infection trials using QFT may overestimate the true incidence of MTB infection among trial participants. This could occur if a high proportion of MTB-positive test results reflect QFT variability rather than true infection with MTB.[43] Compensatory efforts to measure sustained IGRA positivity at multiple times in clinical trials allay but do not resolve concerns about the fragility of QFT-defined endpoints. Alternatives, such as using PET/CT to assess infection and disease by inflammation and lesion activity, are not yet ready for routine use in clinical trials. Given these limitations, the most we can hope is that prevention-of-infection studies will unveil insights into the biology of MTB infection and that this information will give us the tools we need to truly do things differently.

Table 1. Tuberculosis Vaccines Pipeline

Agent	Strategy	Type	Sponsor(s)	Status
M. vaccae	Immunotherapeutic	Whole-cell *M. vaccae*	AnHui Longcom	Phase III
M72/AS01	Prime-boost	Protein/adjuvant	GlaxoSmithKline, Aeras	Phase IIb
Hybrid 4 + IC31	Prime-boost	Protein/adjuvant	Statens Serum Institut (SSI), Sanofi Pasteur, Valneva, Aeras	Phase II
Hybrid 56 + IC31	Prime-boost	Protein/adjuvant	SSI, Valneva, Aeras	Phase IIa
Hybrid 1 + IC31	Prime-boost	Protein/adjuvant	SSI, Valneva	Phase IIa
MTBVAC	Prime	Live genetically attenuated *M. tuberculosis* (MTB)	University of Zaragoza, Biofabri, TuBerculosis Vaccine Initiative (TBVI)	Phase IIa
VPM1002	Prime	Live recombinant bacille Calmette-Guérin (rBCG)	Serum Institute of India, Vakzine Projekt Management, TBVI, Max Planck Institute for Infection Biology	Phase IIa
RUTI	Immunotherapeutic	Fragmented MTB	Archivel Farma	Phase IIa
Ad5Ag85A	Prime-boost	Viral vector	McMaster University, CanSino	Phase I
Crucell Ad35 + MVA85A	Prime-boost	Viral vector	Crucell, Oxford University, Aeras	Phase I
ChAdOx1.85A + MVA85A	Prime-boost	Viral vector	Oxford University	Phase I
Dar-901	Prime-boost	Whole-cell *M. obuense*	Dartmouth University, Aeras	Phase I
MVA85A (aerosol)	Prime-boost	Viral vector	Oxford University	Phase I
MVA85A-IMX313	Prime-boost	Viral vector	Oxford University, Imaxio	Phase I
ID93 + GLA-SE	Prime-boost	Protein/adjuvant	Infectious Disease Research Institute, Aeras	Phase I
TB/FLU-04L	Prime-boost	Viral vector	Research Institute for Biological Safety Problems	Phase I

Hybrid 4 and Hybrid 56 flex their immunogenicity in phase I/IIa

Hybrid 4 + IC31 has the distinction of being the first TB vaccine candidate tested under the new prevention-of-infection approach. This vaccine pairs a fusion of MTB antigens Ag85B and TB10.4 with the IC31 adjuvant owned by the French company Valneva. In 2014, Aeras announced a three-arm phase IIa study to evaluate the safety and immunogenicity of Hybrid 4 + IC31 and bacille Calmette-Guérin (BCG) revaccination in nearly 1,000 BCG-vaccinated, HIV-negative adolescents in South Africa.[44] BCG, the existing TB vaccine first introduced in 1921, protects infants and children against severe forms of disseminated TB but does not confer significant protection against pulmonary TB to adolescents and adults.[45] One-third of participants will receive two doses of Hybrid 4 + IC31; one-third will be revaccinated with one dose of BCG; and the final third will receive two doses of placebo. The first 90 participants will constitute a safety and immunogenicity cohort with intensive data collection on safety, adverse events, and immunogenicity using the standard assays that assess the frequency and magnitude of Th1 cytokines like IFNγ. The remaining 900 participants will form a correlates cohort and undergo evaluation for safety, biomarker discovery, and prevention of MTB infection. This will be the first randomized controlled trial to assess whether BCG revaccination can prevent MTB infection in adolescents.

The Statens Serum Institut (SSI) of Denmark continues to advance the development of Hybrid 56 + IC31 in partnership with Aeras. Hybrid 56 + IC31 is an adjuvanted subunit vaccine that combines three MTB antigens (Ag85B, ESAT-6, and Rv2660c) with Valneva's IC31 adjuvant. Hybrid 56 + IC31 is currently undergoing several clinical evaluations at trial sites in South Africa. One phase I/IIa study nearing completion is investigating three different doses of Hybrid 56 + IC31 in BCG-vaccinated, HIV-negative adults with and without MTB infection who have no history or evidence of TB disease. A second phase of this study will evaluate the dose formulation selected in phase I in two-dose and three-dose regimens in individuals with and without MTB infection as measured by QFT.[46] A second trial is comparing the safety and immunogenicity of Hybrid 56 + IC31 with Hybrid 4 + IC31 and BCG revaccination in HIV-negative South African adolescents. This trial will enroll 84 participants with the objective of identifying immune responses to vaccination for further evaluation as potential correlates of risk or protection.[47] A third phase I study is evaluating the safety and immunogenicity of Hybrid 56 + IC31 in a different population: HIV-negative adults who have recently completed treatment for drug-susceptible TB. The trial will enroll 24 participants and compare two intramuscular doses of Hybrid 56 + IC31 versus placebo to see whether the vaccine should be evaluated in larger studies aimed at preventing disease recurrence (defined as either relapse or reinfection). Investigators have vaccinated the last participant in the trial and have reported no safety concerns so far.[48]

SSI is also exploring opportunities to study Hybrid-56 + IC31 as an adjunct to drug therapy. A study planned for early 2016 will evaluate whether vaccination with Hybrid-56 + IC31 in combination with COX-2 selective inhibitors, a type of nonsterile anti-inflammatory drug (NSAID), helps reduce harmful inflammation in the lungs of patients undergoing treatment for active TB disease.[49] As envisioned, the study will contain three arms: the first giving COX-2 inhibitors alone, the second giving Hybrid-56 + IC31 alone, and the third combining Hybrid-56 + IC31 with COX-2 inhibitors. This approach grows out of basic science and preclinical work suggesting that modulating lung inflammation may help generate a positive host response to TB. The initial study will probe the safety of this approach, but the larger goal is to see whether vaccination as an adjunct to chemotherapy can shorten treatment duration as measured by faster sputum conversion.[50] Participants in the planned study will receive Hybrid-56 + IC31 after their sputum samples convert from positive to negative out of concern that vaccination at an earlier time might pose a safety issue by increasing the MTB antigen load in the lung when the body is still awash in actively replicating bacteria.

M72/AS01 moves into phase IIb

In August 2014, Aeras and GlaxoSmithKline Biologicals (GSK) announced the opening of a phase IIb trial of M72/AS01,[51] an adjuvanted subunit vaccine that combines MTB antigens 32A and 39A with GSK's AS01 adjuvant. This phase IIb study follows a raft of phase IIa evaluations of M72/AS01 in infants in Gambia; adults with MTB infection in the Philippines; adults with HIV in Chennai, India; adults with TB disease in Taiwan and Estonia; and adolescents and adults in South Africa.[52,53,54] The phase IIb trial will enroll 3,500 HIV-negative adults with MTB infection in South Africa, Kenya, and Zambia. Participants will be randomized to receive either two doses of M72/AS01, administered intramuscularly, or two doses of placebo spaced 30 days apart. As a primary outcome, the trial will assess whether M72/AS01 offers participants significant protection against progressing to TB disease up to 36 months of follow-up.[55] A subcohort study will evaluate the cell-mediated immune response to M72/AS01 by measuring the frequency of CD4+ and CD8+ T cells expressing the cytokines IFNγ, TNFα, and IL-2, either singly or in combination, as well as M72-specific antibody responses. An independent, optional substudy sponsored by Aeras will collect biological samples for future biomarker investigations.[56] Investigators expect to complete follow-up and release results in 2018.

MVA85A is down but not out

Despite disappointing results from a second phase II trial published in March 2015, MVA85A, the first TB vaccine to enter efficacy trials since 1968, still has a lot to teach us. That trial, which took place in South Africa and Senegal, gave two intradermal doses of MVA85A spaced six to 12 months apart to adults with HIV.[57] (Participants randomized to the placebo arm received a *Candida* skin test antigen instead of vaccine.) Participants not on ART had to have a CD4+ T-cell count greater than 350 cells/μL at study entry, and those with latent MTB infection had to have completed at least five months of isoniazid preventive therapy. The primary outcome was the safety of MVA85A; as a secondary outcome, investigators evaluated the vaccine's efficacy for preventing TB disease. The trial showed that MVA85A is safe to give to people with HIV but does not afford them significant protection against TB disease.[58]

One caveat to keep in mind when interpreting these findings: the sample size of this trial was revised down from 1,400 to 650 participants after the trial of MVA85A in South African infants published negative results in February 2013.[59] In that trial, MVA85A did not confer significant added protection against either TB disease or MTB infection to infants vaccinated with BCG.[60] Consequently, investigators in the adult trial revised the study design to test safety, not efficacy, as the primary outcome using a smaller sample size and a shorter duration of follow-up of six months instead of two years. Additionally, the immune response MVA85A provoked in adults with HIV was qualitatively different than the response seen in the infant trial. In the adult study, CD4+ T cells stimulated by MVA85A were primarily monofunctional (single-cytokine-producing) rather than polyfunctional, as observed in infants vaccinated with MVA85A. Whether a vaccine built around a single MTB antigen, such as MVA85A, can provoke a strong enough immune response to prevent TB disease or MTB infection remains an open question.[61]

These results do not foreclose a future for MVA85A. Helen McShane, the lead developer of MVA85A, and colleagues at Oxford University are studying MVA85A in combination with other vaccine candidates and on its own using aerosolized administration. Delivering MVA85A by aerosol makes intuitive sense given that MTB is an airborne pathogen. It also builds on evidence from mouse and nonhuman primate models suggesting that delivering a vaccine directly to the mucosal tissues lining the respiratory tract might increase protective immune responses at the site of infection.[62,63] To test this idea, McShane's group conducted a phase I study comparing the safety and immunogenicity of MVA85A administered by aerosol versus intradermal injection to 24 BCG-vaccinated adults in the United Kingdom.[64] The first two participants who received aerosolized MVA85A displayed such potent cellular immune responses – higher than those seen in nonhuman primates – that the investigators revised the protocol to reduce the dose by a full order of

magnitude. By study's end, aerosolized MVA85A appeared to be safe and produced a stronger CD4+ T-cell response than intradermal MVA85A in circulating blood and the lung, as measured by production of the Th1 cytokines IFNγ, TNFα, IL-2 and IL-17.[65]

McShane's group is also pairing nonaerosolized MVA85A with other vaccine candidates in novel prime-boost combinations. A phase I trial combining MVA85A with Crucell Ad35 recently concluded among 40 adult participants at Oxford University.[66] Crucell Ad35, a viral-vectored vaccine using the MTB antigens Ag85A, Ag85B, and TB10.4, was originally devised as a stand-alone TB vaccine and, at one point, was poised to enter a phase IIb study with a projected enrollment of 4,000 BCG-vaccinated, HIV-negative infants.[67] After an early look at immunogenicity data, investigators cut the sample size of that trial to just 500 participants.[68,69] The combination of Crucell Ad35 and MVA85A seeks to pair the strong CD8+ T-cell response provoked by Crucell Ad35 with the robust CD4+ T-cell response generated by MVA85A.[70]

A separate phase I study will combine MVA85A with IMX313, a carrier protein created by fusing a small DNA sequence to an antigen-coding protein. IMX313 is a proprietary technology of Imaxio, a biopharmaceutical company based in Lyon, France, and is designed to enhance the immune response to different vaccine constructs. The phase I evaluation will compare the safety of two escalating doses of MVA85A-IMX313 with that of MVA85A alone in BCG-vaccinated healthy adults.[71] Preclinical work showed that MVA85A-IMX313 induced quantitatively higher cell-mediated immune responses in mice and rhesus macaques than either MVA85A or BCG.[72] This will be the first human evaluation of IMX313, although Imaxio has hinted at plans to evaluate it in vaccines against flu and malaria.[73]

Finally, MVA85A is being evaluated as a boost to ChAdOx1.85A, a simian adenovirus vector that expresses MTB antigen Ag85A. A phase I study is evaluating the safety of ChAdOx1.85A vaccination alone and in combination with MVA85A in BCG-vaccinated adults in the United Kingdom.[74] ChAdOx1 may offer advantages over other adenovirus vectors because it primarily infects nonhuman primates, reducing the likelihood that vaccine recipients will demonstrate preexisting immunity to the vector due to previous exposure.[75]

Other candidates in phase I

Phase I is the most well populated and diverse stage of the TB vaccine pipeline. In addition to the studies of MVA85A in combination with Crucell Ad35, IMX313, and ChAdOx1.85A, phase I includes other viral-vectored vaccines (Ad5Ag85A, TB/FLU-04L), an adjuvanted subunit vaccine (ID93+GLA-SE), a whole-cell mycobacterial vaccine (Dar-901), and a vaccine using genetically attenuated MTB (MTBVAC).

Developed by the University of Zaragoza, Spain, and the Spanish biotech company Biofabri, the MTBVAC vaccine uses live, genetically attenuated MTB weakened through the deletion of two genes related to MTB virulence: phoP and fadD26.[76] While the majority of vaccines in the pipeline are constructed using one or more MTB antigens and aim to boost BCG, MTBVAC is a live, whole-cell vaccine (and thus contains all the antigens of MTB) and could either replace or boost BCG. A phase I dose escalation study recently concluded in Lausanne, Switzerland. Three cohorts of 12 adult participants tested the safety and immunogenicity of escalating doses of MTBVAC versus BCG. There were no vaccine-related serious adverse events. Investigators observed a dose-response relationship between higher doses of MTBVAC and the expression of polyfunctional CD4+ T cells.[77] Based on these favorable results, MTBVAC is completing a second phase I study in newborns less than a month old in South Africa and preparing for a phase II trial in South African adults.

TB/FLU-04L is the newest vaccine to come to international attention and the first viral-vectored vaccine candidate to employ a live, attenuated flu virus to deliver MTB antigens. Developed by the Research Institute for Biological Safety Problems (RIBSP) in Almaty, Kazakhstan, TB/FLU-04L uses replication-deficient, recombinant influenza virus A to present two MTB antigens, ESAT-6 and Ag85A, intranasally using a delivery

platform similar to the FluMist vaccine.[78] A phase I study in 36 BCG-vaccinated, QFT-negative adults tested the safety and immunogenicity of two doses of TB/FLU-04L spaced 21 days apart. There were no serious adverse events, and no infectious flu virus could be recovered from nasal swabs taken after vaccination. RIBSP and its collaborators in St. Petersburg, Russia, are planning to further evaluate TB/FLU-04L as a boost to BCG in a phase IIa trial in QFT-positive adults.[79]

A whole-cell mycobacterial vaccine called Dar-901 is nearing completion of a phase I dose escalation study in BCG-vaccinated adults in the United States. Developed at Geisel School of Medicine at Dartmouth University, Dar-901 consists of inactivated *Mycobacterium obuense*, a nontuberculous mycobacterium. The phase I study contains six groups; participants in each will receive three intradermal injections of either vaccine or placebo spaced two months apart. The first three cohorts enrolled HIV-negative adults and have completed all doses of vaccine or control. The 1 mg dose judged safe in these groups is now being evaluated in three cohorts enrolling both HIV-positive and HIV-negative participants.[80] Dar-901 is very similar to an earlier TB vaccine candidate developed at Dartmouth, SRL-172, which was studied in the phase III DarDar trial. Both Dar-901 and SRL-172 are manufactured from the same strain of *Mycobacterium obuense*; the primary difference is that Dar-901 is grown in broth rather than agar, a more scalable production method.[81]

New Ways of Working Together, but Who Counts As a Partner?

The changes in TB vaccine R&D make this a moment of significant potential. The defeatist, inward-looking rhetoric of the last few years is ceding ground to the optimism of concrete plans and revised, if not totally new, thinking. This scientific momentum, however, stands at odds with a remote, almost regressive approach toward engaging civil society and TB-affected communities in TB vaccine research. The early-phase state of TB vaccine science is no excuse for the lack of community engagement in TB vaccine R&D. Quite the opposite – now is the time to ensure that the next chapter of TB vaccine R&D is more inclusive than the last.

Over the past year, major funders and vaccine developers have taken steps to form the Global TB Vaccine Partnership (GTBVP). So far, this body includes all the usual suspects – vaccine developers (Aeras, the TuBerculosis Vaccine Initiative), funders from high-income countries (BMGF, the European Commission, the European Investment Bank), and research networks (the European and Developing Countries Clinical Trial Partnership).[82] Although the recent addition of the South African Medical Research Council is a move toward greater representation of TB-endemic nations, development of the GTBVP has proceeded without input from members of civil society and TB-affected communities.[83]

This oversight would be problematic for any global health research endeavor but is particularly troubling in the case of TB vaccine R&D. As the writer Eula Biss has noted, immunity is a public space; vaccines promise to protect not just a single body, but also the collective body of a whole community.[84] Research, too, is a public space in that clinical trials of new TB vaccines are hosted by communities, supported overwhelmingly by public funds, and designed to produce technologies that will need to garner the trust and acceptance of societies affected by TB. The noticeable lack of community voices in the governance structures of TB vaccine R&D ignores this reality.

Community voices also remain absent from the design and conduct of TB vaccine trials. In last year's *Pipeline Report*, TAG noted the absence of community engagement programs in TB vaccine R&D – the exemplary community advisory boards of SATVI and the Kenya Medical Research Institute excepted.[85] A year later, there is still no global community advisory board that can connect vaccine developers to community priorities, concerns, and perspectives, although Aeras has taken exploratory steps to create such a mechanism.[86] The pace of these steps must quicken. Communities have a right to participate in research as more than just trial participants,[87] and the early state of TB vaccine R&D means that they will be asked to do so time

and again. Guidelines such as the *Good Participatory Practice Guidelines for TB Drug Trials*, and the field experiences of TB drug developers implementing community engagement programs, offer TB vaccine developers plenty of models for how to begin this important work.[88,89]

The current concentration of TB vaccine funders, developers, and university-based research labs in North America, Europe, and Japan makes it easy to forget that vaccines were originally a South-to-North technology transfer. For example, inoculation against smallpox came to colonial America through the knowledge of slaves brought from Africa and to Europe from the Ottoman Empire.[90] (Upon returning to London from her husband's diplomatic posting at the Ottoman court, Lady Mary Wortley Montague inoculated her own children against smallpox, prompting the English crown to further study the procedure in a "trial" among six prisoners).[91] The conditions of these transfers were far from equal. It is imperative that TB vaccine R&D, even as it turns toward basic science and earlier stages of clinical development, keep considerations of equity at the fore.[92] One way to achieve this is to establish governance structures for the sharing of intellectual property (IP), knowledge, and technology to ensure that once a new vaccine is judged safe and effective in phase III trials, it can be made quickly and equitably available to the communities that need it the most.

Without concerted efforts, equity in access is far from guaranteed. Traditionally, more than a decade can elapse between the licensure of a vaccine by a stringent regulatory agency in the United States or Europe and widespread introduction of that vaccine in developing countries.[93] Reducing this gap will require that vaccine developers license IP and transfer technology and expertise to developing country vaccine manufacturers (DCVMs) to enable local vaccine production.[94] It is encouraging to see major TB vaccine developers such as Aeras establish relationships with vaccine manufacturers, regulators, and scientific partners in India, China, and South Africa.[95] This work to identify developing country partners should continue under a more open, transparent, and strategic framework. A more inclusive GTBVP – one that includes civil society and community representatives in governance roles and throughout the organization's structures – might be the right platform for bringing together the range of stakeholders with financial, legal, or medical interests in vaccine access. This work must start now, before any particular candidate enters phase III trials or prepares for regulatory approval.[96,97] Fulfilling the promise of new TB vaccines to end the TB epidemic's grip on humanity will depend on orienting TB vaccine R&D along the twin axes of meaningful engagement of communities in research and equity in access from the very beginning.

Recommendations

- **Capitalize on the shift to the left to increase funding and support for basic science.** Much basic-science work remains to be done but, broadly speaking, efforts that look at host-pathogen interaction from new angles – moving beyond frameworks that see events in MTB infection and the host response as binary, uniform, and discrete – deserve support. Initial areas of investigation should include identifying new vaccination targets, exploring arms of the immune system beyond cell-mediated immunity, interrogating the at-times deleterious effects of inflammation, and understanding the geography and kinetics of immune processes unfolding in the lung. These endeavors should go beyond exploring mechanisms of protection driven by the host response to considering mechanisms of evasion from the perspective of the MTB pathogen itself.

- **Create opportunities for robust immunology work in clinical trials.** Immunology substudies are often the first thing cut from a trial protocol when funding is scarce. Yet these substudies are instrumental for bridging preclinical work in the lab and results from clinical trials.[98] A growing chorus of voices is calling for more experimental medicine studies that, nested within clinical trials of any phase, probe hypotheses in fine-grained immunologic detail.[99] These experimental medicine studies would sit within and alongside product development efforts and create opportunities to iteratively test new concepts in what has formerly

been a linear product-development pathway.[100] These channels for testing vaccine concepts in addition to candidates should become more established.

- **Adapt clinical trial designs to enable iterative, parallel learning between laboratory and clinic.** The application of PET/CT in clinical trials of TB drug therapy and preclinical models of MTB infection in macaques offers a model for this type of integration. Another approach would involve conducting human studies in phase I in parallel with challenge studies in nonhuman primates to simultaneously learn about immune responses under different experimental conditions. Small-animal models will remain important, and the predictive value of animal models for vaccine selection should be thoroughly evaluated based on findings from the clinic. In addition, the application of adaptive trial designs to larger clinical trials would allow for real-time modification of study protocols in response to emerging safety and efficacy data.[101]
- **Establish meaningful partnerships with civil society organizations and TB-affected communities.** The first step to engaging the broader public in TB vaccine R&D is engaging TB-affected communities in all aspects of research – from clinical trial design to trial conduct to the delivery of new vaccines. Advocates who understand the science of TB vaccine R&D will be best positioned to advocate in its support before governments and funders. Major milestones toward this goal include the formation of a global TB vaccine community advisory board, the development of active community engagement programs at trial sites, and the inclusion of representatives from civil society in the governance of joint initiatives like the GTBVP.
- **Be guided by principles of equity and prepare for access to tomorrow's vaccines today.** Achieving this objective will require action on both global and country levels. Globally, the creation of a patent pool to share TB vaccine IP and the formation of a central clearing house for the transfer of technology and expertise would reduce financial risks for both vaccine developers and the communities that will host and pay for TB vaccine research. These platforms would also help developers prepare to create equitable access to new TB vaccines in the event of success. Vaccine developers will also need to identify DCVMs to receive IP, technology, and information and build country capacity to regulate, manufacture, and introduce new TB vaccines.

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