

Executive Summary - HIV

By Mark Harrington

THE ANTIRETROVIRAL TREATMENT PIPELINE

In their chapter on Antiretroviral Treatment in this year's *Pipeline Report* [9], Tim Horn and Simon Collins provide a sweeping overview of developments in the past twenty years to put those of the past year into context.

The first decade after the advent of effective combination antiretroviral treatment (ART) was marked by improving safety, tolerability, and ease of administration among ART regimens. This was accompanied by growing awareness of the side effects of the earlier regimens, concerns about the evolution of acquired drug resistance, and outstanding questions about when to start ART and whether structured treatment interruptions (STIs) were safe. Subsequent research culminating in the Strategic Management of ART (SMART) study showed definitively that STIs had serious risks due to a host of inflammatory complications of untreated HIV – including cardiovascular, liver, and kidney disease – which had previously been seen as side effects of ART [1].

In the meantime, with when-to-start guidelines swinging back to later initiation of ART, the International AIDS Conference in Durban in 2000 provided the impetus for an enormous, unprecedented global effort to combat a chronic, incurable infectious disease with life-long ART. This effort encompassed the launch of affordable generic combination ART [2]; the establishment of a number of new institutions such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM) [3], the President's Emergency Plan for AIDS Relief (PEPFAR) [4], and new initiatives such as the WHO '3x5' strategy [5], the U.S. Food and Drug Administration (FDA) program for tentative approval for generic ART combinations for use in developing countries, the tax-funded UNITAID, and others. Over the subsequent 16 years, more than 17 million people have been able to use ART; AIDS death rates dropped; and there are emerging signs that HIV incidence rates are going down at least in some parts of the world.

After SMART, it became imperative to define with a randomized controlled trial whether the benefits of immediate HIV treatment outweighed any risk, partly enabled by easier to use ART, which increasingly came in the form of fixed-dose combinations (FDCs) and single-tablet regimens (STRs). Thus the U.S. NIH and other partners launched the START study [6] and France's ANRS launched TEMPRANO [10]. Both studies, released in 2015, showed that immediate ART led to better clinical outcomes. Several other studies, including HPTN 052 [11] and early results from the PARTNER study [12] demonstrated that virologic suppression dramatically reduced the risk of HIV transmission, and that perhaps this effectively is zero. These advances set the stage for the WHO's revised 2015 "treat all" guidelines," which mean that in the coming years we must continue treating the 17 million people already on ART [7] and add to them the 20 million who are not yet receiving it, while simultaneously scaling up ART-based prevention such as PrEP. Together, if scaled up rapidly, these converging approaches hold out the promise of bringing down new HIV infection rates to very low levels, while enabling people with HIV to live long and healthy lives.

Activists, providers, and program managers are concerned that prevalent austerity policies worldwide – coupled with the Global Fund's narrowing focus which excludes most middle-income countries where millions of people living with HIV, TB, or malaria live [8] will make it harder to secure and sustain the resources required to achieve the promise of these gains, and at the same time the shrinking number of innovator companies in the ART discovery and development space leads to fears that too few players will diminish the fruitfulness of the pipeline while possibly creating unacceptably high prices through limited voluntary licenses which will diminish access for those whose countries cannot pay for their treatment – as is already occurring with direct-acting antivirals (DAAs) in the global hepatitis C virus (HCV) pandemic.

Advancing in the clinical development pipeline this year are a number of new drugs, combinations, and formulations such as long-acting injectable ART, and new strategies such as reduced drug ART using dolutegravir – either alone or with lamivudine (3TC). It's too soon yet to assess whether this approach will prove as durable as initial studies suggest and whether it will work in the diverse settings in developing countries where it has the potential to both increase quality of life (with reduced side effects) and save considerable resources.

Reviewed elsewhere in this year's pipeline are other approaches to optimize ART using lower doses, e.g., of efavirenz at 400mg, or combinations with lower molecular weight, that would reduce the cost of the active pharmaceutical ingredient (API); particularly attractive are combinations of dolutegravir with TAF and 3TC; see Polly Clayden's "Fit for Purpose: Antiretroviral Treatment Optimization".

To validate a new first-line regimen with dolutegravir, additional studies are already underway to get more data for use in women, during pregnancy, and in TB coinfection.

The 2016 ART chapter summarizes the status of twelve drugs and combination therapies in clinical development – seven in phase III, four in phase II, and two in phase I (see Table 1: Summary of Pipeline Compounds in 2016).

FIT FOR PURPOSE: ANTIRETROVIRAL TREATMENT OPTIMIZATION

Polly Clayden leads us on a brisk, bracing walk through the changing landscape of ART optimization in her 2016 "Fit for Purpose: Antiretroviral Treatment Optimization" chapter. [13]

"Since the 2015 Pipeline Report global antiretroviral treatment (ART) guidelines have moved to recommending "treat all" HIV positive people. With this recommendation comes the massive task of starting and keeping everyone with HIV on ART. ART optimization is one of many critical steps to universal access to HIV treatment that is: safe, effective, tolerable, durable, simple and affordable. Antiretrovirals can sometimes be optimized by dose reduction. [14, 15] Reducing an approved dose of a drug might be possible, because when new ones are developed, the highest tolerated doses in phase II are usually selected for phase III and approval. In some cases lower doses might have equivalent efficacy and better tolerability – as has been shown with efavirenz (EFV). [16] But since discussions on treatment optimization began the field has evolved and newer, better, and lower dose antiretrovirals have been approved. [17, 18] With a couple of exceptions, treatment optimization has shifted away from 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 (LMIC) – is now the main focus of ART optimization. [19]

"Experts now agree on a short list of antiretrovirals that have shown superior or non-inferior efficacy compared to existing recommended ones. These drugs offer improved durability and tolerability, higher bioavailability, lower pill burden, and the potential for fewer side effects. [20, 21] The antiretrovirals are: dolutegravir (DTG), tenofovir alafenamide (TAF), efavirenz (EFV) 400 mg, and darunavir/ritonavir (DRV/r)." [13]

As Clayden points out, the 2015 WHO guidelines now include dolutegravir and efavirenz 400mg; generic formulations of dolutegravir are on the way; and the FDA has begun to approve TAF-containing regimens to replace those with tenofovir disoproxil fumarate (TDF). WHO second-line recommended alternative regimens now "include ritonavir-boosted darunavir (DRV/r) or raltegravir (RAL) as alternatives to boosted lopinavir (LPV/r)." [13]

New generic formulations of dolutegravir (DTG), DTG/TDF/3TC, efavirenz 400mg/TDF/3TC, and DRV/r will come on-line in the next year; see Table 3: New generic antiretrovirals available 2016/2017 for adults. "By the end of 2025 the introduction of TAF, EFV 400 mg, and DTG into ART programs in LMIC could mean

savings up to a whopping US \$3 billion” – please see Table 5: Table 5: Market share and cumulative savings 2025. [22]

Clayden reviews studies investigating dolutegravir or efavirenz at 400mg as global first-line ART anchor drugs (see Table 6: New first-line regimen studies), first-line pregnancy studies (see Table 7: First-line pregnancy studies), reviews the urgent case of first-line ART in combination with tuberculosis co-treatment (see Table 8: First-line HIV/TB co-treatment studies), and considers the potential use of darunavir/r/dolutegravir in second-line therapy (see Table 9: Low dose DRV/r studies).

This chapter provides a long view of what to expect in the coming decade and how research can provide answers which will make it easier to treat all of the world’s 37 million HIV-infected persons.

THE PEDIATRIC ANTIRETROVIRAL PIPELINE

In the Pediatric Antiretroviral Pipeline [51] Polly Clayden shows us that developing “new antiretroviral drugs and appropriate formulations for children continues to be far too slow;” and that 40% of children on ART are on suboptimal regimens. Among noteworthy steps forward are the inclusion in the new WHO guidelines of integrase inhibitors, efavirenz 400mg and dolutegravir as alternatives for adolescents, raltegravir as recommended second-line for children, and dolutegravir and darunavir/ritonavir for third-line [52], and FDA approval of dolutegravir tablets for children aged 6 to 12 [53]. New solid lopinavir/ritonavir pellets are now approved for infants and young children [54, 55], but apparently don’t taste very good [56]. Priority formulations identified back in 2013 remain lacking, including AZT or abacavir (ABC) plus 3TC and lopinavir/r and ABC with 3TC and efavirenz [57]. Additional priority formulations from 2014 remain unavailable. [7] Clayden reviews ongoing and planned trials to address gaps in treatment options for newborns [see Table 3: Newborn treatment options (or lack of options to date): including ongoing and planned IMPAACT trials), children, and adolescents. The current pediatric ARV pipeline is shown in Table 4: The pediatric antiretroviral pipeline.

PREVENTIVE TECHNOLOGIES: ANTIRETROVIRAL AND VACCINE DEVELOPMENT

Tim Horn and Richard Jefferys present an overview of developments in their “Preventive Technologies: Antiretroviral and Vaccine Development” chapter [23].

The current paradigm is shifting not only to universal immediate ART among those living with HIV, but to intensified biomedical prevention efforts focusing on pre- and post-exposure prophylaxis (PrEP, PEP), as well as increased use of other prevention modalities such as harm reduction, syringe exchange, opiate substitution therapy, and voluntary male medical circumcision. As Horn and Jefferys write, [this] “fierce commitment to primary biomedical prevention... isn’t simply rhetoric, but rather a public health mandate that is supported by a growing body of epidemiological and other scientific data. [24, 25, 26, 27]

In the U.S., where tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) were first approved for use as PrEP in mid-2012, just 4% of the estimated 1.2 million U.S. residents who might benefit from its use are or have used it. [28, 29] To make a public health impact, however, PrEP will have to be scaled up to reach almost half of high-risk MSM, as well as at least 10% of people who inject drugs and among high-risk heterosexual persons, who may not even realize they are at risk for contracting HIV. [30]

In the U.S., failure to expand Medicaid in states where HIV is infecting the most people today – such as young MSM of color, particularly in the South, creates often-insuperable obstacles for those who need PrEP the most. [31] Elsewhere, PrEP has only been approved in a handful of countries and, even where it is approved and

subsidized, high levels of provider stigma or ignorance plus lack of HIV prevention education among at-risk individuals impedes its successful uptake at the requisite scale. [32] Other potential PrEP approaches now under study include oral maraviroc (MVC) or TAF instead of TDF, but these are in early stages still.

Long-acting (LA) injectable ART such as cabotegravir, if shown safe and effective, could potentially be used as PrEP.

A variety of genital gels, rings, tablets, and films are also being investigated for potential preventive therapy indications in both women and men. There is also tremendous interest in multi-purpose biomedical prevention technologies, notably ring and other extended-release delivery systems that can provide broad-spectrum protection against multiple viral infections—HIV, herpes simplex virus 2 (HSV-2), and human papillomavirus (HPV)—as well hormonal contraception.

NIH is launching large-scale efficacy trials to see whether infusions of broadly-neutralizing HIV antibodies such as VRC01 can be used as a durable HIV prevention intervention[33]; but – as with treatment – it’s possible that combinations of antibodies will be more effective both in protecting from infection and in preventing the rapid emergence of resistance among those exposed. [34, 35]

The long-awaited successor study to RV144, the only HIV vaccine trial that has shown even a marginal level of statistically-significant protection, is finally close to being launched. [36]. “The trial, HIV Vaccine Trials Network (HVTN) 702, is designed to try and duplicate or improve on the 31.2% reduction in risk of HIV acquisition that was observed in RV144, a large-scale evaluation of a prime-boost vaccine regimen that was conducted in Thailand. [37] HVTN 702 will take place in South Africa and, if all goes according to plan, results are anticipated by 2020.” [23]

In the vaccine field, a whopping 52 candidate vaccines are in various stages of clinical trials, as well as three studies of passive immunization with the NIH’s VRC01 and one antibody gene transfer study; see Table 4: HIV vaccines, passive immunization, and antibody gene transfer pipeline. The contrast with the TB vaccine field – with only 14 candidates in clinical trials (see Table 1: TB Vaccines in Development, in Mike Frick’s TB Prevention Pipeline chapter – is stark, though both fields face analogous challenges trying to develop protective immunity against tough and complex intracellular pathogens.

RESEARCH TOWARD A CURE AND IMMUNE-BASED AND GENE THERAPIES

Once again, Richard Jefferys effortlessly guides us through the challenging landscape of “Research Toward a Cure and Immune-Based and Gene Therapies” [39].

HIV cure research is now acknowledged as a central goal of U.S. NIH-funded AIDS research [40, 41] Meanwhile, it is expected that the currently-underway renewal of the Martin Delaney Cure Collaboratories may result in the funding of five or six consortia compared with the current three. amfAR has established a new Institute for HIV Cure Research at U.C. San Francisco. [42]

In Durban the International AIDS Society expects to release an updated global scientific strategy towards an HIV-1 cure. [43]

Currently ongoing and planned cure-related clinical trials are not expected to lead directly to a cure, but rather to define pathways which when further developed and possibly combined may lead to sterilizing or functional cure. The only possible exception to this would be if researchers were able to replicate the one documented case of a cure for HIV-1 in a human being, the case of Timothy Brown. This approach would involve giving stem-cell or bone marrow transplants from a CCR5-delta32 homozygous mutant immune system to an HIV-infected person whose cancer therapy requires such a transplant. [44, 45]

According to Jefferys, “at least six individuals have since been reported who underwent similar procedures, but all of them died due to either the underlying cancers or complications from the transplantation procedure. [46] One new case was described in a poster at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI), and the preliminary signs appear encouraging: the cancer is in remission and HIV cannot be detected by multiple techniques. [47] However ART had not yet been interrupted at the time of the presentation, so it is too early to know if this may represent a second example of an HIV cure.”

Research on putative immune-based therapies for HIV infection seems to be in decline, aside from a few studies such as one of pitavastatin to reduce cardiovascular disease incidence among people on ART. [48]

However there is still a clinical need for therapies for people who in spite of successful virologic suppression on ART fail to reconstitute their immune systems to healthy and safe levels.[49] Late initiation of ART – simultaneous with the diagnosis of AIDS, as is the case with 23.6% of newly-diagnosed HIV in the U.S. as recently as 2013) [50] – greatly increases the risk of becoming an immunologic non-responder (INR). Jefferys states that “TAG is currently collaborating with other activists to explore whether candidate treatments for INRs might be considered orphan drugs, a U.S. Food and Drug Administration (FDA) designation intended to spur the development of treatments for disorders that are relatively rare.” [39]

The 2016 immune-based therapy pipeline (see table 2) includes fifteen agents with a broad variety of putative therapeutic mechanisms; all are languishing or at best moving forward slowly in phase I or II studies.

2016 HIV PIPELINE RECOMMENDATIONS

Antiretroviral Therapy Recommendations

- “With some major pharmaceutical manufacturers retreating from the ARV research and development space, the industry partners that remain should strengthen their resolve to meet the ARV safety, efficacy, acceptability, and affordability challenges that remain in low-, middle-, and high-income countries.
- Manufacturers must commit to the drug prices required to achieve cost-contained HIV care and service delivery in high-income countries.
- Manufacturers must also commit to meet the treatment access needs in middle-income countries, which will be home to 70% of people living with HIV before the end of this decade and are facing both funding losses from donor agencies as well as crippling intellectual property rules that will block access to affordable generics.
- Manufacturers developing new oral drugs are strongly encouraged to follow the emerging trend of evaluating coformulations with historically potent and safe generic ARVs, notably TDF and 3TC. However, these fixed-dose combinations must be priced accordingly.
- 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 virologic suppression rates required to improve disease-free mortality and prevent ongoing transmission of the virus.” [9]

Antiretroviral Treatment Optimization Recommendations

- **“Upgrade the new first-line regimen.** Sufficient evidence to change WHO guidelines to recommend DTG and TAF as part of the preferred first-line regimen (replacing EFV and TDF) needs to be generated in order to convince generic manufacturers to invest in new production for the new regimens. A recommendation from WHO is the strongest signal to generic manufacturers to take the risk and produce new FDCs. Such WHO recommendations will require results from the studies discussed here.
- **Originators donate drugs to strategy studies for LMIC.** Originator manufacturers must take responsibility and supply prioritized antiretrovirals to key investigator-led studies (as well as the supporting substudies) to generate data to support their use in LMIC. And not after several years of deliberation. The lack of information on use of new regimens in pregnancy and with TB treatment – that is critical to treating populations in LMIC – will continue to be a barrier to their universal recommendation however impressive the results from the phase III trials are.
- **Countries get ready to switch.** Countries with high volume ART programs such as South Africa, Kenya, and Uganda, need their guideline committees briefed as results are generated (even before they are publically released), so that they can make new recommendations, hopefully before final WHO decisions.
- **Donors must support switch to new drugs and regimens.** Donors can play a huge part in changing standard of care in countries. UNITAID bought large volumes of TDF and helped to bring down the price and speed up the switch from d4T – so called market dynamics.
- **Timely approval.** Regulatory agencies in LMIC, such as the South African Medicines Control Council, need to register new originator and generic formulations, as swiftly as possible. Ideally this should happen before new WHO and national recommendations.
- **Generic companies need time to plan for high volume manufacture.** Generic manufacturers need to be briefed on when data from key studies are expected to be released, guideline changes, and tender timing in countries, so that they can start planning to compete to supply the newly recommended regimens.
- **Pre-empt possible chaos.** Before introducing new drugs, issues such as stockpiling (and stock outs) need to be discussed and planned, so that hitches with switching from old to new regimens are kept to a minimum.
- **Second-line needs more consideration.** Although there is consensus on the likely best optimized first-line regimen, second-line is not quite there yet and requires more discussion and research and development to ensure best regimens and formulations.” [13]

Pediatric Antiretroviral Recommendations

- **Speed up development.** 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. Optimize use of pharmacokinetic data and modelling.
- **Speed up approval.** 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.
- **Implement WHO recommendations.** As simpler formulations identified to implement the guidelines become available (most topically LPV/r pellets), countries must ensure that they are swiftly approved and distributed, with appropriate training for health workers.

- **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. Plans need to be in place to phase out suboptimal formulations and phase in new ones. Donors need to ensure the availability of low volume products in a diminishing market.

Preventive Technologies: Antiretroviral and Vaccine Recommendations

- Consider “how to incorporate PrEP into background standard-of-care options in vaccine and prevention-based immunotherapy clinical trials. In HVTN 702, for example, South African study participants will receive referrals to local programs where they may obtain TDF/FTC, as opposed to active provision of PrEP as a component of prevention services (e.g., free condoms and lubricant, counseling, and access to STI testing and treatment). This is similar to the standard-of-care approach being employed in the VRC01 AMP Study (HVTN 704/HPTN 085), although in that case US participants have access to a specific referral program that allows their primary care provider to offer TDF/FTC PrEP free of charge. It has been argued that TDF/FTC should be offered through these trials themselves.⁸² This is, however, a difficult issue to wrestle with, as active provision of PrEP may substantially increase the person-years of followup required—and, with it, the study’s population size and expense—to reach the statistically sound number of seroconversion events needed for efficacy analyses. Indeed, the local Institutional Review Boards and both local and global Community Advisory Boards responsible for reviewing and approving both HVTN 702 and the AMP Study appear to have found the practice of referring participants to external sources of PrEP to be acceptable, at least at the current time.”
- Promote “registrational trial methodologies that are necessarily rigorous in their design, yet feasible for the sponsors of new biomedical prevention candidates—a large number of which are not-for-profit programs that are dependent on finite public and philanthropic support. A major factor influencing study designs is the ethical principle of beneficence, which requires the abandonment of placebo comparisons and the inclusion of proven interventions, such as oral TDF/FTC, in control groups. Regulatory agencies, however, still want proof that an experimental PrEP regimen is more effective than placebo. This in turn requires reliable background incidence estimates, which have repeatedly proven to be difficult to come by in PrEP clinical trials. Also required are many person-years of follow up—and, by extension, extremely large, long, and expensive clinical trials—to yield the number of seroconversions necessary for standard non-inferiority comparisons, particularly with a highly efficacious regimen such as TDF/FTC.”
- “Close attention to these issues, particularly as an increasing number of products enter phase II and III stages of development, is critical. A stringent, but amenable, regulatory climate is necessary to ensure the availability of necessary safety, efficacy, and acceptability data, without being prohibitively costly and ultimately deterring critical investments by product sponsors, particularly those heavily dependent on limited public and philanthropic funding.” [23]

Research Toward A Cure and Immune-Based and Gene Therapies Recommendations

- Continue to increase funding for cure-related research.
- Promote dialogue between regulators, researchers, funders and community stakeholders on trial design issues, with a particular view to smoothing the pathway toward the evaluation of combination approaches
- Support efforts to develop novel means to make potentially complex interventions such as gene therapy more convenient, accessible and affordable.
- Improve communication on concepts of HIV remission, and be clear that the maintenance of low viral

load in the absence of ART may not necessarily be equivalent to suppression of HIV by ART in terms of long-term health outcomes.

- Broaden community education efforts on HIV cure research and promote and facilitate participation of diverse populations in clinical trials.
- Invest in webcasting for all cure-related scientific conferences in order to facilitate greater global sharing of information.
- Be vigilant for any evidence that interventions could benefit immunologic non-responders (INRs) even if they fail in the cure research context, and conduct studies in this population when appropriate.
- Convene a scientific workshop (or workshops) on drug development and trial design for the INR population.
- Develop a research agenda to resolve outstanding uncertainties on the value of probiotics as an adjunctive therapy for individuals on ART.

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Executive Summary - Tuberculosis

TUBERCULOSIS DIAGNOSTICS

The year 2015–2016 saw more concrete progress in moving new TB diagnostic tests from research to recommendation by the World Health Organization (WHO) than any year since 2010, when the WHO recommended GeneXpert MTB/RIF. As Erica Lessem shows in this year's "Tuberculosis Diagnostics Pipeline," in the past year, the WHO "approved Alere's lipoarabinomannan (LAM) test – a very affordable, simple, rapid, noninvasive, point-of-care (POC) rule-in test for people with HIV with very low CD4 counts... New versions of line-probe assays [LPAs] – Hain's MTBDR_{plus} and MTBDR_{sl} and a product from Nipro [NTM+MDR-TB Detection Kit 2] – received WHO recommendations... Improvements on nucleic acid amplification tests such as GeneXpert Omni and Ultra and Molbio's TrueNAT are being validated... Further upstream, encouraging research into gene sets that can predict active TB disease and reliably distinguish it from latent TB and other infections may eventually underpin new blood tests... Incremental advances are being made to improve the detection of pediatric TB." [1]

Lessem cautions, however, the deployment of new TB diagnostic tests remains abysmal, with 3.6 million of the world's estimated 9.6 million new TB cases in 2014 undiagnosed; "59% of cases of multidrug-resistant (MDR-TB) undetected... [and] a mere US \$65 million in 2014 funding out of an estimated annual need of \$340 million in research investment in new TB diagnostics tests." Furthermore, WHO guidance on how to implement recently-approved tests remains in development, while the funds to scale-up their use remain elusive. Disappointingly, fourteen TB diagnostic test candidates are in later stages of development or already marketed (in some countries) without any new published data since the *2015 Pipeline Report* [see table 2].

An implementation science study carried out in South Africa, Tanzania, Zambia, and Zimbabwe showed that "among 578 people with HIV... using LAM was associated with an absolute reduction of all-cause mortality at eight weeks of four percent, and a relative risk reduction of 17 percent... [apparently] attributable to the test's allowing earlier initiation of ... anti-TB therapy." [2] The LAM test should be deployed rapidly in hospitals and clinics in high-HIV burden settings so that this benefit may help to prevent some of the hundreds of thousands of cases of TB disease and death among people with HIV.

The newer line probe assays (LPAs) are a step forward in making drug-susceptibility testing (DST) more available, but their drawbacks include technical difficulty, requirement for separate rooms for each stage of the process, and the possibility of contamination, which could yield inaccurate results. The newer innovations with Xpert platforms such as Xpert XDR, Omni, and Ultra, will each be a step forward, and less difficult to carry out than the LPAs, but suffer from incomplete penetration of the health care sector, maintenance issues, and the high cost of the machine itself.

As Lindsay McKenna points out in a special section on diagnosing pediatric TB, in the past year, WHO doubled the estimated annual number of TB cases among children to one million. TB diagnosis among infants and children is more difficult than in adolescents or adults. Research to improve the situation remains insufficient and lags behind the advances mentioned above. The next-generation Xpert tests are expected to have increased sensitivity and ability to diagnose paucibacillary disease common in children. The LAM urine dipstick was not particularly sensitive or specific in pediatric studies to date, but the WHO recommendation to use the test includes HIV-positive children with CD4 counts below 100/mm³ along with adults. As with all aspects of pediatric tuberculosis, more research, program implementation, resources, and political will are needed to move forward. [3]

TUBERCULOSIS PREVENTION – VACCINES AND PREVENTIVE THERAPY

After two-and-a-half decades when efforts to contain tuberculosis focused principally on treating the disease – especially in its drug-sensitive form – the TB policy and research world has recently begun to expand its focus to include greater emphasis on prevention, as Mike Frick demonstrates in “The Tuberculosis Prevention Pipeline.” [4]

Last year the WHO released its first-ever *Guidelines on the Management of Latent Tuberculosis Infection* [5]. Earlier this year UNITAID adopted TB prevention as a new area of emphasis for intervention [6]. In spite of the flatlined infectious diseases research agenda at the U.S. National Institutes of Health (NIH), the White House issued an (unfunded) *National Action Plan for Combatting Multidrug-Resistant Tuberculosis* last December [7]. (The President’s proposed fiscal year 2017 budget, proposed in January of this year, recommended cutting global TB control funding by \$45 million, or 19% [8, 9].) WHO’s new “End TB Strategy” concludes that reaching the proposed elimination targets will require intensified efforts to prevent TB transmission through chemoprophylaxis and – when available – a vaccine. [10]

Frick discusses a number of high-priority questions in TB prevention research, including efforts to identify genetic signatures of risk for progression of TB infection – whose discovery and validation could help speed up research in both TB vaccines and preventive therapy – disparities between measurable immune responses in the blood and in the lung where most TB disease occurs, the mystery of the mycobacterial granuloma, and the perennial question of MTB persistence in the face of a partially-effective immune response and sometimes-curative chemotherapy.

The TB vaccine field is experiencing a move back towards basic and early-phase clinical research, one reminiscent of what happened with the HIV vaccine field after the setback of the STEP trial, in which the adenovirus-5 vector in which the HIV immunogens were delivered actually caused increased HIV infection as compared to the study’s placebo arm [11, 12]. Just one trial is in phase III, one in phase IIb, six in phase IIa, and five in phase I. The predominant approaches include whole-cell preparations of *M. vaccae*, genetically attenuated MTB, recombinant BCG, whole-cell *M. obuense*, and ‘fragmented’ MTB; prime-boost studies of various TB antigens with various adjuvants; while the phase I studies are all prime-boost approaches using viral vectors and TB proteins [see Table 1. TB Vaccines in Development].

TB vaccine R&D is massively underfunded – investments in 2014 totaled just \$111.3 million, less than one-third of the Global Plan-recommended \$380 million annual target [13] – and it is difficult to see how the TB vaccine field will produce a safe, effective vaccine by the 2025 target required by The End TB Strategy [10: Figure 2. Projected acceleration in the decline of global tuberculosis incidence rates to target levels; p. 5]. The field is moving towards earlier-stage translational studies and novel clinical trial designs targeting TB incidence rather than prevention of disease as a primary endpoint. The problem here is that diagnosing TB infection definitively is even harder than diagnosing TB disease. We already know that 3.6 million of the world’s annual 9.6 million cases of active disease already go unreported. Proving that TB infection has been prevented would require a test better than the currently-used tools of tuberculin skin testing (TST) and interferon gamma release assays (IGRAs), which are all too unspecific, insensitive, and likely to give contradictory results in different hands or in different settings. Other approaches such as targeting TB reactivation or reinfection suffer from the same lack of a definitive measurement tool, except for genetic fingerprinting in cases of active TB disease when reactivation can be distinguished from reinfection by a different molecular fingerprint, in cases where the original disease-causing strain is still on hand for comparison.

Lack of resources is leading to excessive caution in the populations prioritized for research, as Frick points out: “[b]y conducting fewer clinical trials in children and people with HIV, TB vaccine developers are effectively making the decision to direct research away from the two groups most vulnerable to TB... developers should acknowledge that the current strategy risks leaving behind two key TB-affected populations with greatly enhanced risks of disease and death that rightly draw significant attention from global health actors.” [4]

Luckily, this is not the case in TB preventive therapy research, where “children and people with HIV still occupy the center of efforts to develop new or improved preventive therapies.” [4]. According to Frick, “Eight studies are underway or in late development, six of which are examining different dosing schedules of rifapentine, administered either in combination with other drugs such as isoniazid or alone. Two studies are investigating preventive therapy for individuals exposed to DR-TB, one looking at daily delamanid vs. INH and the second comparing 6 months daily levofloxacin vs. placebo.” (See Table 2, Clinical trials of TB treatments to prevent tuberculosis disease; and Lindsay McKenna’s Table 1: Ongoing and Planned TB Prevention and Treatment Studies in Children.)

TUBERCULOSIS TREATMENT

TB treatment remained largely unchanged in 2015 with five new drugs at various stages of clinical development. Of these, two – bedaquiline and delamanid – have approved accelerated approval from the US FDA (in 2012 for bedaquiline) and conditional approval from the European Medicines Agency (EMA, in 2014 for delamanid) as additive therapies to use with background regimens to treat multidrug resistant (MDR) TB. Pretomanid, formerly PA-824, a drug similar to delamanid but further behind in clinical trials, is being studied in various combinations for drug-sensitive, MDR, and extensively-drug resistant (XDR) TB. Sutezolid, a drug which spent the first decade on the shelf after the acquisition of Pharmacia and Upjohn by Pfizer, then came to life briefly when an early bactericidal activity (EBA)/phase IIa study showed anti-TB activity in the clinic, and is now paralyzed due to the inaction and lack of resources of Sequella, Inc., which bought the drug from Pfizer when the latter abandoned infectious disease research. The past year saw the abandonment of AstraZeneca’s AZD5847 due to lack of anti-TB activity and the emergence into the clinic of Qurient’s Q203, a new drug from a new class developed by a company in South Korea.

As Erica Lessem shows in “The Tuberculosis Treatment Pipeline: Activity, but No Answers,” the rollout of both bedaquiline (BDQ) and delamanid (DLM) has been painfully slow. Safety concerns following the apparent excess of late deaths in the phase IIb study of bedaquiline, along with the general and pervasive delays of TB programs in adopting new technologies, have slowed its uptake. It took almost four years for the sponsor, Janssen, to start its phase III study following accelerated approval in December 2012 – surely a massive abuse of the accelerated approval system. Similar delays afflicted a long-agreed-to drug-drug interaction study of BDQ and DLM to determine if their QTc-prolonging activity (a marker of cardiac toxicity) was additive and compromised safety, or whether the two drugs could safely be co-administered; legal foot-dragging by Janssen means that the study still has not begun today, even though both sponsors agreed to conduct it in December 2012.

Increasing amounts of programmatic data, particularly from South Africa, indicate that the addition of BDQ to background treatment appears to be increasing cure rates for pre-XDR and XDR-TB, without an excess of cardiac deaths. Otsuka, the maker of delamanid, has been so tardy in registering the drug or even allowing its compassionate use, that few safety and no additional efficacy data are yet available. The ongoing phase III study is expected to be reported out in 2018. Meanwhile, the company has an ethical obligation to register the drug in the many high-TB-burden countries where it carried out its phase II studies, and in places with high burdens of DR-TB. The soon-to-launch ACTG/IMPAACT PHOENIX study, which will compare 6 months of DLM to INH among household contacts of people with MDR-TB, will provide considerable new safety data on the drug, as well as showing whether it can prevent MDR-TB acquisition or disease among these high-risk individuals.

Ambitious plans for pretomanid came to a standstill last fall when the ongoing STAND study of pretomanid-moxifloxacin-pyrazinamide (PaMZ) among people with DS and DR-TB was put on clinical hold because of three sudden hepatic deaths among people in the DS-arm who were receiving PaMZ. Nine months later the study’s data safety monitoring board has signaled that the study can proceed with additional safeguards.

Sutezolid remains paralyzed by the sponsor's lack of funds or willingness to cooperate with other players. However, the drug's patent status suggests that outside manufacturers could make the drug, and it is hoped that this will allow phase IIb studies to begin in the next 18 months.

A number of studies are looking at repurposed older drugs in new indications or at new dosing levels. High-dose studies of rifampin and rifapentine are ongoing. One study, TRUNCATE-TB, seeks to accelerate the validation of a super-short-course two-month regimen for DS-TB by comparing four two-month regimens. It's understood that failure levels will be higher than with six months of the current regimen, but it is hoped that the majority of people would be cured in two months and that the others would still respond to standard therapy.

Other studies continue to look at, and sometimes to compare, fluoroquinolones such as levofloxacin and moxifloxacin in drug-resistant disease. (and – cControversially, – gatifloxacin, which was removed from developed-world markets for toxicity some years ago, has also been re-recommended by the WHO for the treatment of MDR-TB) in drug-resistant disease.

Dose-ranging studies are being planned at last for two old drugs whose importance in TB treatment has recently become clearer, clofazimine and linezolid.

An EBA study presented at the 2016 CROI showed that the carbapenem meropenem, given with amoxicillin/clavulunate intravenously [IV] three times a day, had measurable anti-TB activity without grade 3/4 toxicity. Another drug in the class, ertapenem, may also have activity, though it too requires IV administration. [14]

Pediatric TB treatment research is one of the brighter spots in the overall clinical TB research landscape, as Lindsay McKenna shows in "The Pediatric Tuberculosis Treatment Pipeline: Beyond Pharmacokinetics and Safety Data" [15]. Long-neglected formulations suitable for children have finally advanced towards market and new studies in preventive therapy, dose optimization, and treatment for drug-resistant disease are finally beginning to be carried out. McKenna shows five studies are planned or underway for TB prevention, five for treatment using new drugs (3 DLM, 2 BDQ), and fourteen studies of various existing drugs, combinations, and interaction studies with commonly-used antiretrovirals (see Table 1: Ongoing and planned TB prevention and treatment studies in children). Researchers continue to try and optimize dose-levels for first-line therapy in young children, where achieving pharmacokinetic levels similar to those of adults has proven challenging. Co-treatment for HIV and TB remains an issue for children, again because of the lack of previous drug-drug-interaction studies and necessary formulations. Meanwhile, research on second-line drugs and how to shorten and simplify treatment for drug-resistant disease in children is even further behind.

Otsuka has completed pediatric dosing studies of delamanid for 12-to-17-year-olds and 6-to-11-year-olds; a study using the DLM pediatric formulation in children aged 5 and younger is expected to be complete in time for the launch of PHOENIX, which will compare delamanid to INH among household contacts – including children 5 years and under, TST-positive persons, and those living with HIV – of MDR-TB cases, to see whether six months of DLM can better prevent transmission and progression to active disease of MDR-TB.

Janssen has been further behind in its pediatric research on BDQ, principally because the FDA – unlike the EMA – lacks the power to mandate pediatric studies, even of drugs where there is such a high global burden of pediatric disease. Its first PK/safety study in HIV-negative children opened in May 2016, 3.5 years after FDA approval in adults – another unacceptable delay by Janssen.

McKenna highlights the importance of conducting TB treatment research in pregnant women, where data are lacking not only on drug safety and activity, but even on TB incidence, though it is estimated that almost a quarter-million women may develop active TB each year. The IMPAACT network is conducting two studies of TB prevention and one TB treatment study in pregnant women. (See Table 2: Ongoing and planned TB

prevention and treatment studies in pregnant women.) McKenna recommends the establishment of a TB Pregnancy Registry, similar to the Antiretroviral Pregnancy Registry which that has been underway since 1989.

Finally, McKenna reviews current progress on pediatric formulations for first-line therapy (several fixed-dose combinations of HRZ, HR, or HP from five companies; four single-drug dispersible tablet forms of E, H, Z, and P from Macleods and Sanofi; and 7 second-line drugs in dispersible tablets or mini-capsules; see Table 3: Pediatric formulations in development). [15]

2016 TUBERCULOSIS PIPELINE RECOMMENDATIONS

TB Diagnostics Recommendations

- “Both R&D on and access to evidence-based TB diagnostic tests need dramatic infusions of funding and political will.
- National governments and donors must substantially increase funding for TB programs to allow for best diagnostic practices. This includes the widespread scale-up of NAAT to supplant microscopy, universal DST using liquid culture or LPAs, digital X-ray, and the rapid adoption of LAM testing in areas with high HIV burdens.
- National governments, donors, and the private sector must invest far more in TB R&D to advance better tests, including those for children. This should include a commitment to rapidly and rigorously evaluating new technologies and to publishing peer-reviewed results.
- National governments and donors should work closely with the nonprofit and private sectors to ensure only quality and affordable tests are used. In countries with large proportions of care-seeking in the private sector, access to appropriate diagnostics is extremely limited and can be catastrophically expensive.
- Developers must commit to timely and rigorous validations of their tests prior to marketing, and health and regulatory authorities and private practitioners should hold them accountable for doing so. Epistem and other companies who market ineffective or as-yet-unproven tests must cease doing so immediately. National governments should ban the import and use of inappropriate tests and enforce those bans. Those working in TB globally should call to task companies such as Epistem that inappropriately market them.” [1]
- “Greater efforts to identify children at risk for TB – especially within maternal and child health programs, where sick children often first present for care – and referral systems and decentralized capacity to diagnose childhood TB, clinically or with available tools, are urgently needed.
- Developers should validate tests in adults and children in parallel to expedite access to improved diagnostic technologies for children. These evaluations should include a variety of sample types in children with and without HIV and should assess age-related performance.
- Developers and donors should increase investments in research to discover and validate biomarkers and innovation to translate these biomarkers into simple and affordable tests that can rapidly and accurately diagnose TB, monitor treatment, and predict disease progression in children. In 2014, less than \$2.3 million and \$2.8 million was spent globally on research and development for pediatric TB diagnostics and basic science, respectively;

- Developers and research networks should establish and support harmonized and collaborative pediatric biorepositories important for biomarker discovery and development.
- Developers and researchers should support and create networks of sites that support rigorous evaluation of new diagnostics and can pool data to more rapidly demonstrate the impact of new tools.
- Programs should scale up and decentralize the use of existing technologies and strategies to diagnose pediatric TB infection and disease, especially within maternal and child health programs.
- Programs should train health care workers to improve their ability and confidence to clinically diagnose children with TB when tests are unavailable or come back negative.” [2]

TB Prevention Recommendations

“For funders: Ensure financing mechanisms are sufficiently flexible and durable to support the multi-year, collaborative research endeavors that will be required to make progress against a challenge as complex and intractable as MTB infection. For example, nearly ten years passed between when the South African adolescent cohort enrolled its first participant in 2005 and when it published results announcing the discovery of a risk signature of disease progression in *The Lancet* in 2016. This was not time wasted, and the cohort will likely yield publications and results for years to come. Further advancing our knowledge of MTB infection and TB disease may require larger cohorts with even longer periods of follow-up. In addition, funding agencies should support translational work to bridge advancements in basic science with clinical development and maintain openness to a wide range of approaches that probe the nature of MTB infection from the perspective of both host and pathogen, and through the application of new assays and imaging technologies in both humans and animal models.

For vaccine researchers and developers: Continue to explore a greater diversity of approaches to TB vaccine development through the use of experimental medicine studies and trials designed around novel endpoints. Ultimately, this will likely require developers to introduce wholly new vaccine candidates whose designs look beyond the narrow focus on cell-mediated immunity that has dominated past efforts. The development and introduction of new assays that are able to translate signals of immunogenicity between lung and blood (or capable of safely measuring vaccine responses directly in the lung itself) should also be a priority. Developers and their sponsors should not foreclose on clinical trials among infants and people with HIV, two of the groups most in need of a new TB vaccine. Although previous trials in these two populations have fallen short of expectations, there is much that can be learned from past failures. Rather than wholly abandon vaccine concepts and constructs that did not work, vaccine researchers and developers should more forthrightly interrogate the reasons behind disappointing results.

For drug researchers and developers: Accelerate research to understand MTB persistence and the nature of latency to develop new drugs targeting latent infection. Efforts to understand MTB persistence would benefit from initiating a dialogue with researchers involved in vaccine development about differences in how the TB drug and vaccine fields approach preclinical testing. Each field is confronting challenges related to MTB persistence and the nature of latency, but vaccine and drug developers do not always measure the same pathology or immunological events using relatable endpoints or definitions of scale in the animal models in which much of this work will be conducted. Closer collaboration with their vaccine counterparts might also open the door for drug developers to use vaccines as adjuncts to shorten therapy or reduce the risk of relapse. In the meantime, ongoing efforts to shorten and simplify TB preventive therapy for children, people with HIV, pregnant women, and household contacts of people with DR-TB should continue. The advanced stage of many of TB prevention trials obligates pharmaceutical companies involved in this research – namely, Sanofi and Otsuka – to take steps to register their products more widely and facilitate equitable access through measures such as affordable pricing.

For all researchers and developers: Recognize community engagement in research as the ethical complement to good clinical practice and take steps to involve representatives from TB- affected communities in all stages of R&D. The potential of ongoing or planned TB preventive therapy and vaccine studies to refashion clinical practice in ways that could render many more people with asymptomatic MTB infection eligible for medical intervention makes it imperative that developers create meaningful spaces for community voices, concerns, and priorities to enter the research process. Communities must become true partners in TB prevention research, and not merely its silent beneficiaries.

For activists: Take up TB prevention as a unified cause and break with the habit of advocating for vaccines, preventive therapy, and infection control as separate and unrelated technological fixes. With the exception of TB PROOF – a South African advocacy group founded by doctors who contracted TB that is dedicated to preventing MTB infection among healthcare workers – activist voices in TB prevention have been few in number and modest in volume. This absence does not reflect a lack of need. A global shortage of BCG continues into its third year, needlessly endangering the lives of millions of infants. Rifapentine, the cornerstone of TB preventive therapy research, is registered for the treatment of MTB infection in just one country, despite being studied in at least a dozen more. Individuals exposed to MDR-TB have few evidence-based options to treat probable drug-resistant infection. And countries remain slow to rollout proven interventions such as IPT to people with HIV, 400,000 of whom died from TB in 2014. We are one year closer to 2025, the year WHO says new prevention tools must be introduced to reach the End TB Strategy’s goal of eliminating TB by 2035, and there is no new vaccine or transformative preventive drug regimen on the immediate horizon. The clock is ticking.” [4]

TB Treatment Recommendations

- “1. Government agencies, pharmaceutical companies, and foundations must dramatically scale up funding for TB R&D. In line with the third pillar of the WHO’s End TB strategy, which calls for R&D, countries must commit more resources to TB drug development.⁷⁷ The U.S. government, which is the leading funder of TB R&D, should increase funding levels to \$300 million by 2018 to keep its critical investments at pace with inflation. TAG suggests that this should entail an additional \$17 million from the NIH, \$15 million from USAID, \$16 million from the U.S. Centers for Disease Control and Prevention, and \$5 million from the FDA for TB R&D.⁷⁸ European Union countries, particularly Germany, should double their TB R&D funding, and Brazil, China, India, Russia, and South Africa should each triple their funding for TB R&D.⁷⁹ Activists in other countries should call for commensurate increases in their own settings. Companies such as Otsuka and Sanofi should maintain strong levels of investment, and Janssen needs to recommit to further developing bedaquiline, as significant work remains despite bedaquiline’s conditional approval, and to moving the most promising of its pipeline of bedaquiline analogues further toward clinical study. Other pharmaceutical companies and philanthropic organizations should also begin to invest in TB R&D.
2. Donor and high-TB-burden governments should create and invest in mechanisms that build access to TB drug development, and drug developers should participate in them. The inability to access data hampers collaborative TB drug development, which is essential because TB must be treated with a combination of drugs to prevent the development of resistance. The inability to access drugs hampers TB treatment and cure and threatens to render the limited R&D that is occurring less useful. Fortunately, members of the TB community have proposed feasible and appealing solutions that should be actively pursued. These include remedying loopholes in the FDA’s priority review voucher system to ensure innovation and drug availability and fair pricing and should also entail product developers licensing their compounds to and sharing data with the MPP, which recently received a mandate to work on TB drug development and could possibly play a key role in brokering combination drug development.⁸¹ MSF’s proposed 3P (“Push, Pull, Pool”) project may also provide an interesting, innovative, and potentially transformative approach to spur the

development of regimens and ensure their availability post-approval, though the devil here will lie in the details of how it is actually executed.

3. Drug and trial sponsors must expedite the development of preclinical and clinical candidates. Delays in TB research and development are widespread and atrocious. The TB drug development pipeline remains frighteningly sparse, pointing to the urgent need to advance preclinical work to allow viable candidates into clinical studies. Clinical development for the few products in the pipeline has been unacceptably slow, with drugs taking over five years to advance from one stage to the next. In particular, Janssen's and Sequella's failures to rapidly move bedaquiline and sutezolid, respectively, through important studies are deplorable.
4. Ministries of health, regulatory authorities, and ministries of finance should prioritize the timely introduction of evidence-based TB treatment, and donors and providers of technical assistance should ensure they are supporting rather than hindering scale-up. Drug development will not affect the TB epidemic and improve the lives of people affected by TB unless new interventions are available to communities and people who need them. Unfortunately, country-level demand for important new products such as delamanid and bedaquiline has been weak, and implementation slow. USAID, which has partnered with Janssen to make bedaquiline available via a donation program, literally cannot give the drug away for free to enough people. Poor advice from technical assistance providers has worsened the situation and excused complacency. All parties, national and global, must be much more ambitious and supportive of new ways to find and treat TB.

Pediatric TB Treatment Recommendations

“For researchers:

- Consider children when planning adult studies. Building PK investigations into studies that evaluate higher doses of TB drugs in adults is necessary to inform future PK targets in children.
- Determine which PK value(s) correlate best with efficacy for TB drugs in children and establish PK targets based on adult data, taking into consideration the variability in severity and type of TB disease among, and challenges defining efficacy in, children.
- Enroll children two years of age and younger in pediatric studies, as this is the period during which drug disposition changes the most for children, increasing risk for high or low drug exposures.
- Include HIV-positive children in studies of new TB drugs and regimens.
- Include pregnant women in studies of new TB drugs and regimens.

For policy makers:

- Incorporate emerging data into guidelines for children more rapidly, especially those for new and second-line TB drugs in children.

For regulatory authorities:

- Enforce more thoughtful requirements to ensure comprehensive and timely investigations of TB drugs
- in children. Mandatory and time-bound pediatric investigational plans that also require studies in HIV-positive children will help to shrink the persisting evidence and access gaps that exist between adults and children for new TB drugs.

- Follow the important precedent set by the EMA and allow parallel enrollment of pediatric cohorts in PK and safety studies.
- Be transparent and clear about requirements to register pediatric formulations for both existing and new drugs.
- When possible and appropriate, consider waived requirements and registration fees to facilitate access.” [15]

For donors:

- Maintain and adequately fund momentum in pediatric TB drug R&D, for which global investments totaled \$11.6 million in 2014. Recent attacks on the budget for and AIDS research priorities of the NIH are particularly concerning for pediatric TB R&D. Not only is the NIH the leading funder, but its investments support studies that are 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.
- Further attention to and investments in pediatric TB trial infrastructure and site capacity development are urgently needed to support the increasingly full research agenda for prevention and treatment of TB in children.
- UNITAID, whose investments have led to the market introduction of appropriately dosed FDCs of first-line TB drugs for children, and whose planned investments will ensure global uptake of these new formulations, should invest in a project modeled after STEP-TB that is focused on expediting development and market introduction of pediatric formulations of second-line TB drugs.

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