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tagline

TAG
Treatment Action Group

April 1. This is the day upon which we are reminded of what we are on the other three hundred and sixty-four.
—Mark Twain, Pudd'nhead Wilson

Fool Us Once...

We're being duped by our government agencies. We're being hoodwinked by the Affordable Care Act (ACA). We're being bamboozled by pharmaceutical companies and research networks. In this April Fools' issue of *TAGline*, we highlight several missteps in research and policy that have required some degree of advocacy to remedy and ensure that the jokes don't remain on us.

By Tim Horn

NEWS ON THE FIGHT TO END HIV/AIDS, VIRAL HEPATITIS, AND TUBERCULOSIS

(Continued from cover)

We begin with **Jeremiah Johnson**'s assessment of the U.S. Centers for Disease Control and Prevention's High-Impact Prevention (HIP) strategy (page 2). With its primary focus on the HIV care continuum and the potential benefits of treatment as prevention, HIP fails to account for the comprehensive needs of at-risk HIV-negative individuals, many of whom may be served well by recent advances in biomedical prevention and expanded Affordable Care Act (ACA) coverage opportunities.

In **Mark Harrington**'s review of progress made in achieving the goals of the National HIV/AIDS Strategy (page 5), a World AIDS Day 2013 report from the White House Office of National AIDS Policy (ONAP) delivers an encouraging update on the state of the U.S. epidemic. Yet shortcomings of the available data and methodological flaws in the analysis undermine the credibility of ONAP's progress report.

Despite the anti-discrimination mandate of the ACA, many people living with HIV are facing serious challenges securing affordable care and treatment through qualified health plans (QHPs) in state and federal exchanges. As **Kenyon Farrow** explains (page 8), advocates are scrambling to overcome obvious discriminatory practices, notably efforts to block third-party assistance intended to cover the high costs of QHP premiums and out-of-pocket expenditures.

We also focus on curious questions surrounding drug development and treatment optimization. In collaboration with **Polly Clayden** of HIV i-Base, I review data from a recent clinical trial that suggest we've long been using too high a dose of the antiretroviral efavirenz (page 10). The question remains, however, whether these better-late-than-never findings will translate into cheaper, safer dosing in the near future.

In the TB treatment arena, **Lindsay McKenna** investigates the significant taxpayer investments in research and development of drugs that are ultimately priced beyond reach by those who need them the most (page12). And **Mike Frick** summarizes the scientific challenges associated with a clinical trial attempting to rush two critical questions: the utility of a shortened course of therapy for multidrug-resistant tuberculosis (MDR-TB), and the confirmed safety and efficacy of the new drug bedaquiline for MDR-TB (page 14).

An unavoidable aspect of moving forward with efforts to end the HIV, TB, and viral hepatitis epidemics is having to address potential miscues that have been made along the way, sometimes years after the fact. Determining culpability is invariably part of process. What matters most, however, are the strategies put into place to repair breaches, right wrongful courses, and ultimately turn mistakes into opportunities for advancement. •

Forgotten Negatives: The Limits of Treatment as Prevention

The CDC's High-Impact Prevention strategy takes aim at the stubborn HIV incidence rate in the United States. The only problem: it doesn't include an ambitious plan for those at risk for the virus

By Jeremiah Johnson

There is no shortage of depressing statistics when it comes to HIV prevention in the United States: 50,000 new HIV infections annually; a 12% increase in new infections among gay and bisexual men and transgender women between 2008 and 2010; an estimated infection rate of nearly 50% among black transgender women; and a projected 50% infection prevalence in gay and bisexual men by the time they're 50.

For the people who have been most affected by the epidemic, we have failed to make any measurable progress; if anything, the spread of the virus has worsened.

In 2011, the Centers for Disease Control and Prevention (CDC), the primary funder of HIV prevention efforts in the United States, redesigned and rebranded its approach with a new strategy called High-Impact Prevention (HIP). Recognizing that funding of U.S. HIV prevention programming is unlikely to see necessary increases anytime soon, the CDC designed this approach to target limited prevention dollars to evidence-based and cost-effective interventions in order to maximize results. The strategy was also meant to reallocate funding to the regions and key populations that are most in need of HIV prevention services.

HIP, however, is more than a redistribution of funds. It is in many ways a retreat from prevention services for HIV-negative individuals. Instead of providing effective options to people at risk for the virus, the strategy focuses largely on the HIV continuum of care—finding individuals who are already living with the virus through testing initiatives and linking them to care and treatment. The aim of this so-called prevention-for-positives approach is to lower the number of new infections by reducing the infectiousness of people living with HIV/AIDS (PLWHA).

Strategies including treatment as prevention (TasP) are essential in any national effort to finally rein in new infection rates in the most affected communities. The landmark HPTN 052 study found that, among heterosexual serodiscordant couples, effective treatment of the HIV-positive partner led to a 96 percent reduction in the risk of HIV transmission. Early data from the PARTNER study presented at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI) indicate that the benefits of TasP may also extend to gay and bisexual men and transgender women.

People struggling to find effective ways to avoid HIV need more than just routine testing, advice, and a fistful of condoms.

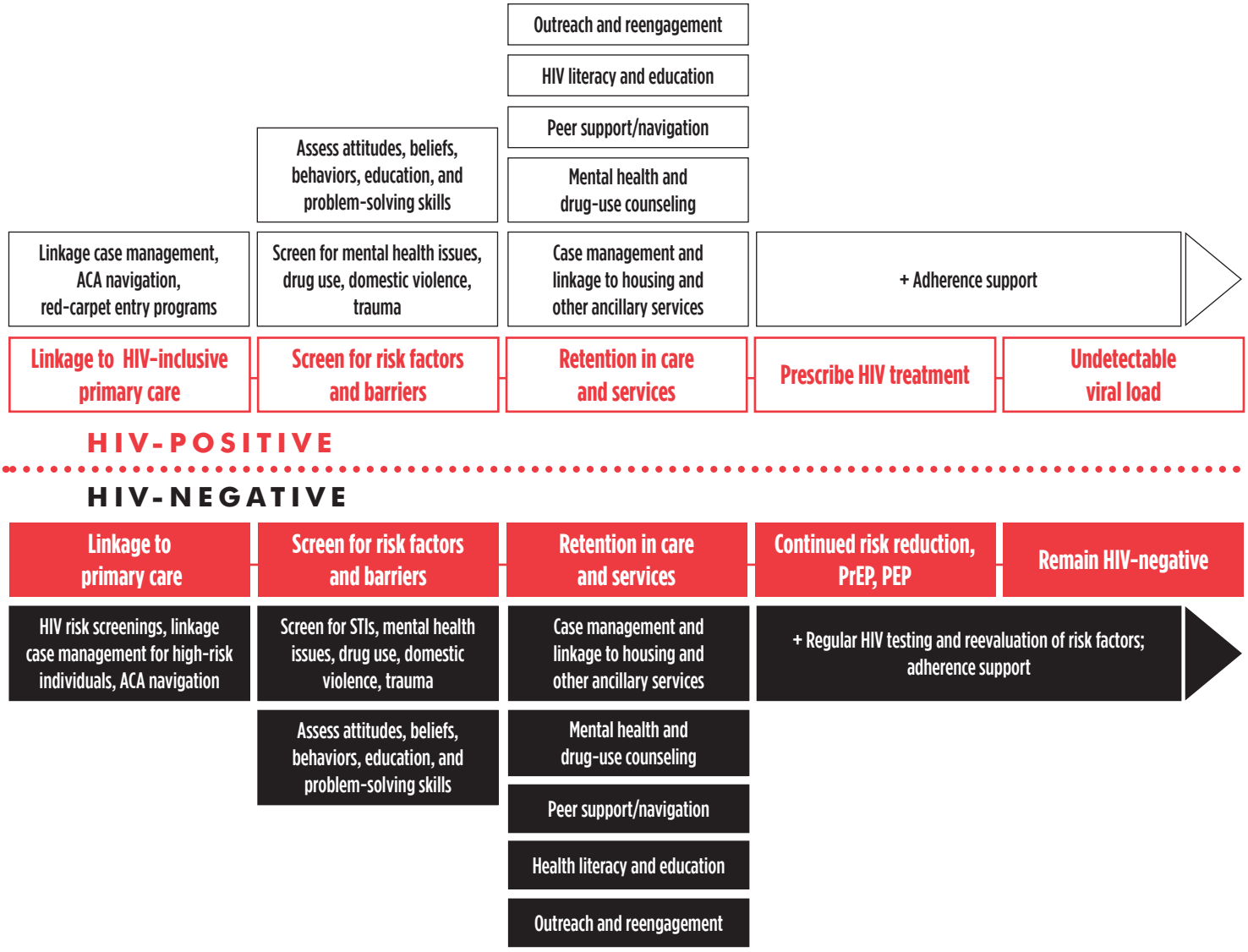
Encouraging study findings aside, TasP is not a prevention panacea. The CDC's lack of focus on HIV-negative individuals represents a tactical misstep and leaves people who are most at risk for acquiring HIV with few effective options. While the HPTN 052 and PARTNER studies certainly establish the preventive benefits of linking PLWHA to treatment, they do not indicate that TasP, by itself, can end the epidemic. Clinical trials in many ways represent a best-case scenario for participants—they may not reflect how such interventions will work in the real world, particularly in the United States, where we have managed to get only around 25 percent of PLWHA to a state of viral suppression.

Many questions remain regarding the rates of viral suppression required to substantially reduce HIV incidence in high-prevalence communities. As summarized in a July 2012 issue of *PLoS Medicine* by David Wilson of the Kirby Institute of the University of New South Wales, TasP has the greatest potential to succeed in high-income countries. In these settings, HIV epidemics are concentrated, and there is generally universal access to antiretroviral therapy, adequate infrastructure, and guidelines supporting early initiation of treatment. However as Wilson points out, such is the case in Australia and France, and yet incidence—particularly among men who have sex with men (MSM)—has remained flat or is increasing.

Most recently, Andrew Phillips of the University College London and colleagues have explored the community-level impact of TasP within the context of the United Kingdom, where it is estimated that 60 percent of HIV-positive MSM are being effectively treated, yet the epidemic in this population continues to worsen. According to mathematical modeling developed by Phillips's team and reported at CROI 2014, viral-load suppression would have to reach 90 percent among MSM living with HIV in order to bring the U.K. epidemic under control. Models are, of course, only as good as the assumptions on which they are based, but these findings call into question the ability of TasP to stop an epidemic on its own.

While we try to understand the population-level impact of TasP, there are also individual-level questions to be answered. Is it ethical to essentially deny HIV-negative individuals an opportunity to avoid infection while we gravitate toward an approach that focuses primarily on people already living with HIV? If no new solutions were available in the field of prevention for HIV-negative individuals, we might be able to justify this insular focus on prevention for people who are positive, given the abysmal prevention record of the past decade. This is far from the case, however. The 2010 iPrEX study established the effectiveness of once-daily Truvada as a preexposure prophylaxis (PrEP) for HIV by demonstrating that, for individuals who took the medication consistently and correctly, the risk of acquiring HIV was reduced by at least 92 percent. At the same time, the Affordable Care Act (ACA) potentially creates a new framework for coordinating the delivery of prevention services—PrEP, as well as mental health care, substance use treatment, sexually transmitted infection (STI) screenings, postexposure prophylaxis, and various ancillary services—through primary care.

To be fair, the CDC has not completely abandoned HIV prevention for HIV-negative individuals. HIP still heralds the virtues of condom distribution; behavioral interventions; and counseling, testing, and referral (CTR) services intended to help keep people negative. But these are the same methods of prevention that have been tried



A double-helix HIV prevention and care continuum. A work in progress by TAG staff, the above schematic depicts key components of successful engagement in care to achieve critical outcomes required to foster disease-free survival and to ultimately end the HIV/AIDS epidemic. The continuum of care for people living with HIV (top half of the graphic) has been well described and embodies health care delivery and the coordination of essential services to fully support linkage to and retention in care, the commencement of antiretroviral therapy, and maintenance of viral-load suppression. A continuum of care for those who test negative for HIV, particularly those being screened for the virus through AIDS service organization and Department of Health programs, does not exist. Under the Affordable Care Act, testing for HIV should be seen as a critical point of care within the health care system, whereby linkage to affordable health insurance and culturally sensitive care is a priority for those who test negative but potentially remain at risk for the virus. Mirroring the HIV care continuum, an HIV prevention continuum (bottom half of the graphic) details some of the core components of HIV risk reduction and maintained wellness made possible through consistent primary care and the coordination of social support and other ancillary services.

for decades, and, while they have almost certainly had some impact, they have not been enough to stop or even significantly slow the epidemic in key populations.

New evidence seems to show the futility of trying these same interventions over and over again. The 2013 findings of Project AWARE—demonstrating that risk-reduction counseling in conjunction with a rapid HIV test did not significantly affect STI acquisition among STI clinic patients—call into question the effectiveness of CTR and contribute to the growing doubt that behavioral interventions have had any meaningful impact on the epidemic. The CDC itself highlighted the limitations of condoms in a 2013 CROI presentation, which found that intermittent condom use essentially had no statistically significant preventive benefit. Given that in the 2011 National HIV Behavioral Survey 57 percent of MSM indicated that they do not always use condoms, there is growing urgency to try something new.

To end the epidemic on a population level, we cannot rely on TasP alone. At the same time, we cannot limit our focus to traditional methods of HIV prevention to empower those at risk. We must completely rethink HIV prevention and learn to take advantage of every new opportunity for progress that has arisen over the past five years. In 2014, TAG will work with government, academic, and community leaders to go beyond HIP in order to do just that.

One strategy being developed and explored by TAG is the creation of an HIV prevention continuum, similar to the HIV care continuum model that has already essentially defined key outcomes required for disease management and TasP (see figure).

People struggling to find effective ways to avoid HIV need more than just routine testing, advice, and a fistful of condoms. Individuals at risk for infection need care that is far more comprehensive. Just as treatment and care for PLWHA are considered to be an ongoing process with complex and interconnected parts, prevention for HIV-negative individuals must be understood as a series of related steps that cannot work in isolation. We cannot, in the new ACA era, allow each HIV-negative test to remain an isolated event. Each test is an opportunity to link individuals to health care coverage, provide ongoing and culturally sensitive evaluations of HIV and other disease risk factors, and coordinate medical- and social support services to address barriers to care and evidence-based prevention synergistically.

It is time for us to move on from the siloed interventions housed within HIP to a new kind of holistic prevention approach that helps both HIV-negative and HIV-positive individuals meet their goals in avoiding HIV transmission. By linking heavily affected communities to more comprehensive care, we might even move beyond our singular focus on new HIV infections and work to create general well-being and reduce all-cause morbidity and mortality rates in communities that are often hard hit not only by HIV, but by many other health-related crises as well. •

The White House's Fuzzy Math

An Office of National AIDS Policy progress report obscures the state of the domestic U.S. HIV/AIDS response

By Mark Harrington

On World AIDS Day, December 1, 2013, the White House Office of National AIDS Policy (ONAP) issued a peppy and upbeat status report on the National HIV/AIDS Strategy (NHAS), claiming progress on eight of nine outcome indicators. Yet when reviewed in tandem with a companion document, *HIV Prevention Progress Report, 2013*, released by the U.S. Centers for Disease Control and Prevention (CDC), many of the White House claims are misleading and undermined by flawed methodology.

ONAP contends that HIV incidence in the United States is decreasing. The White House notes an estimated 47,500 new infections in 2010, versus 48,600 in 2006—a drop of approximately 1,100 new infections over four years. The CDC claims that the 2010 NHAS target (48,600) was met. The 2010 target was the same as the estimated number of new infections in 2006. Moreover, the estimated 47,500 new infections for 2010 fall well within the 95 percent confidence interval error bars—a range used to reflect uncertainty in reported measures—which neither ONAP nor the CDC mentioned in their widely disseminated reports. These error bars are shown in

the surveillance data source on which both reports rely, indicating the true incidence likely falls somewhere between 42,000 and 53,000. In other words, we do not know whether HIV incidence actually decreased between 2006 and 2010.

Missing from the White House report are more nuanced incidence estimates, particularly among hard-hit groups such as men who have sex with men (MSM). The CDC report notes that new HIV infections increased 12% among MSM overall and 22% among young MSM ages 13–24 between 2008 and 2010, and that new infections among Blacks/African Americans appeared to rise from 2009 to 2010.

As for the HIV transmission rate—the likelihood that an HIV-positive person will transmit the virus to others—the White House and CDC note that this fell from 4.6 per 100 persons living with HIV in 2006 to 4.2 in 2010, a decrease of nine percent. According to the CDC report, "the 2010 target (4.6) was exceeded... As a result, the number of new HIV infections has remained stable, even though the number of people living with HIV increased 9% from 1,045,800 in 2006 to 1,144,500 in 2010." As noted before, the surveillance data error bars for HIV incidence and prevalence estimates—both of which are used to calculate the transmission rate—are quite broad, so it's not clear whether these data are reliable. Of note, the transmission rate in 2007 was higher than in 2006, at 4.7 per 100 cases; the 2015 target is 3.2 per 100.

An essential goal of the National HIV/AIDS Strategy is to improve the number of people living with HIV who are diagnosed, linked to care, retained in care, and maintaining an undetectable viral load.

ONAP and the CDC are in agreement that knowledge of HIV serostatus is rising. The White House contends that the proportion of U.S. residents who know their HIV status increased from 80.9% in 2006 to 84.2% in 2010, whereas the CDC states that HIV serostatus knowledge increased 9% from 1,045,800 in 2006 to 1,144,500 in 2010. Surveillance source error bars for these data, compared with 2006 estimates, allow for the conclusion that more people are learning their HIV status, which is a good thing.

Linkage-to-care progress is muddier. The White House claims that linkage to care within three months of diagnosis rose from 65% in 2006 to 79.8%—an apparently significant jump. Yet CDC reported that linkage to care actually fell from 81.7% in 2008 to 79.8% in 2010. The CDC technical notes indicate that the metrics here are spotty, as they are based on data reported from jurisdictions that reported all CD4 and viral-load results to the CDC. In 2009, these included 13 jurisdictions such as California (San Francisco only) and New York State (excluding New York City). Kentucky joined up in 2010. New York City and Los Angeles joined in 2011 along with five other states. In effect, we don't have data on linkage to care from 31 states and from all of California except for Los Angeles and San Francisco.

As for retention rates, the White House cited Ryan White data to conclude that 75.7% of people with HIV were in continuous care in 2010, compared with 75.5% in 2011—a 0.2% drop. Nonetheless it claimed that this figure was stable. Meanwhile, the CDC progress report stated that the goal has been increased to 85% for all age groups. Either way, there is no apparent progress towards the original 80% goal or the revised 85% goal.

The White House claimed that the percentage of Ryan White program clients with permanent housing rose from 82% in 2009 to 84.2% in 2010. The White House did not give a data reference for this claim. Nor did it provide a data source for its claim that, in in 2011, transgender and injection drug–using clients were least likely to report stable housing (74.5% and 75.6%, respectively), rendering both reported outcomes inevaluable.

As for rates of viral-load suppression, the White House noted improvements among MSM (40.7% in 2009 to 41.7% in 2010—a 1% increase), Blacks/African Americans (32.7% in 2009 to 34.9% in 2010), and Latinos/Latinas (36.6% in 2009 to 37.2% in 2010).

The CDC progress report claims, "the overall percentage of HIV-diagnosed people with a suppressed viral load remained fairly stable from 2009 (37.3%) to 2010 (39%)." Meanwhile, the CDC technical notes point out that data from 2009 were used to establish the baseline. The problem here, again, is that viral-load data were available from only 13 jurisdictions in 2009.

While most of the other White House baseline data were from 2006, at least here the CDC is being relatively methodologically sound, measuring progress toward NHAS goals that were only established in 2010, from a baseline number at 2009 to 2010. In other metrics, the White House claimed progress from 2006 to 2010 toward a National Strategy that was only launched in 2010—a logical impossibility.

The target numbers for viral-load suppression underscore the breathtaking lack of ambition of the

overall NHAS itself. When President Obama issued the HIV Care Continuum Executive Order on July 15, 2014, he claimed to be adopting the use of the HIV treatment cascade as a metric to monitor overall HIV program quality. Setting 2015 targets for viral-load suppression among those in care at only 48.8% for MSM, 39.2% for Blacks/African Americans, and 43.9% for Latinos/Latinas is totally inadequate if we are to achieve the promise of the HIV continuum of care, and the targets ratify the very health disparities the NHAS is supposed to address.

We must demand much more ambitious targets for the next iteration of the National HIV/AIDS Strategy. In the meantime, we have a right to expect much more honest, rigorous, and methodologically sound data from ONAP and from the CDC itself, whose *Progress Report* at least owns up to far more failures than the White House report does (see figure).

Simply put, the White House and CDC need to do a better job of documenting the actual epidemic situation in the 2014 report on the National HIV/AIDS Strategy. •

PROGRESS AT A GLANCE		Baseline Estimate	Most Recent Estimate	2015 Target	ONAP Says	CDC Says	TAG Says
Lower new HIV infections by 25%	General	48,600	47,500	36,450	👍	👍	👎
	MSM	28,900	31,000	21,675	?	👎	👎
	People who inject drugs	5,300	3,900	3,975	?	👍	👍
	Blacks/African Americans	21,200	20,900	15,900	?	👍	👎
	Latinos/Latinas	9,000	9,800	6,750	?	👎	👎
Reduce HIV transmission rate by 30%		4.6	4.2	3.2	👍	👍	👎
Increase knowledge of HIV-positive status		80.9%	84.2%	90%	👍	👍	👍
Increase linkage of newly diagnosed persons to HIV medical care within three months	General	66%	79.8%	85%	👍	👍	👎
	Blacks/African Americans	77.3%	75.9%	85%	?	👎	👎
	Latinos/Latinas	83.2%	81.8%	85%	?	👎	👎
	Whites	83.6%	85.1%	85%	👍	👍	👍
Increase percentage of Ryan White program clients in continuous care		75.7%	75.5%	80%	👎	?	👎
Increase percentage of Ryan White program clients with permanent housing		82.0%	84.2%	86%	👍	?	👎
Increase rates of viral suppression	MSM	40.7%	41.7%	48.8%	👍	👍	👎
	Blacks/African Americans	32.7%	34.9%	39.2%	👍	👍	👎
	People who inject drugs	36.6%	37.2%	43.9%	👍	👍	👎

Marketplace Menaces: Discriminatory Practices by the ACA's Qualified Health Plans

Advocates scramble to stay ahead of coverage rejections, formulary concerns, and exorbitant out-of-pocket expenses facing people living with HIV

By Kenyon Farrow

#GetCovered

That's the White House's official hashtag and marketing campaign to spike the number of Americans enrolling into qualified health plans (QHP) through the Affordable Care Act (ACA). The deadline for individual enrollment without penalty was March 31.

But many people with HIV who tried to join the ranks of the enrolled found their third-party payments—primarily Ryan White subsidies to offset monthly premiums—rejected by insurance plans. Others discovered that their drug regimens weren't covered, leaving them with huge out-of-pocket coinsurance expenses. In short, for many people hoping that the ACA would mean better and more affordable access to treatment, April Fools' Day came earlier than expected. But the gaps and the discriminatory practices causing them are no laughing matter.

When the ACA was signed into law four years ago, it gave many AIDS advocates plenty of hope that more uninsured people would be able to get comprehensive health coverage. The law was structured around several core principles:

1. expanding Medicaid eligibility for poor single adults (including all people with HIV meeting the other Medicaid eligibility requirements);
2. creating national standards for insurance plans and the services they need to offer;
3. shifting our model from fee-for-service to one based on outcomes;
4. bringing more people into the insurance market to balance the risk pool (through the individual mandate); and
5. removing barriers to care, such as preexisting conditions clauses that have historically been used by the insurance industry to reject patients.

Prior to ACA implementation, close to 70,000 people living with HIV were uninsured. According to Kaiser Family Foundation estimates, roughly 23,000 of those would gain coverage through state or federal QHPs, the majority of whom would also qualify for financial assistance. Approximately 47,000 would be eligible for Medicaid if all states expanded the program (only 26 states have agreed, thereby reducing the number of uninsured people living with HIV gaining coverage through Medicaid by more than 40 percent). So expanding Medicaid should help many people with HIV who are poor gain critical access to health care. Opening the private insurance market to people with HIV (especially those who live in states where their HIV status made them "uninsurable") should, in theory, greatly expand their access to treatment and care. In practice, the outcomes of these changes have been much more mixed.

One of the first problems to emerge was that, for many people with HIV, their HIV medications weren't explicitly included on plan formularies or—worse, covered at all. Others found that their antiretrovirals were placed in a special tiered pricing system that offered minimal cost sharing, which translated into consumers paying as much as half of their drugs' retail costs out of pocket as a coinsurance expense.

While many were commemorating World AIDS Day 2013, AIDS activists (including TAG) sent a letter to Health and Human Services (HHS) Secretary Kathleen Sebelius detailing the issues that were occurring, mostly (but not exclusively) with health plans in Southern states that did not establish their own state exchanges. Due to advocacy by the AIDS community, several insurers made changes to their drug formularies, but there has yet to be any movement from Secretary Sebelius on this issue.

And discriminatory practices in drug formularies with QHPs are not the only problem. Several insurance companies that have attempted to block people with HIV from signing on to their health plans. On February 25, after a class-action lawsuit was filed by Lambda Legal, a federal judge granted an emergency injunction forcing three Louisiana insurance plans to accept third-party subsidies and maintain coverage for people living with HIV, regardless of the premium payment source.

John East, a 59-year-old health care worker, had been insured by Blue Cross and Blue Shield (BCBS) of Louisiana for 30 years. He learned that his policy was being dropped because the insurer was no longer going to accept Ryan White payments. When the story first leaked, BCBS of

Louisiana announced that the decision was due to ACA regulations barring them from accepting third-party payments. The Centers for Medicare and Medicaid Services rebutted the statement by saying there was no such federal policy preventing insurers from accepting payments from Ryan White.

To bolster support for federal direction on this problem, activists sent a letter to Secretary Sebelius on March 3 asking her to urgently address the issue by making the following policy changes:

- Require that QHPs accept third-party payment of premiums from government-supported programs, including the Ryan White/AIDS Drug Assistance Program, on behalf of qualified low-income clients.
- Amend the essential health benefits rules to require coverage of specialty drugs and prohibit coinsurance from exceeding 25 percent for these treatments, particularly those widely accepted as standard-of-care and for which no generic equivalents exist.
- Require all Marketplaces to ensure that QHPs provide complete and accurate formulary information in a standard format, including the actual out-of-pocket costs that will be imposed on enrollees.

But there's some good news. On March 10, Louisiana state insurance companies agreed to continue to accept Ryan White payments through November 15, which is the end of this enrollment period. In order to ensure that people living with HIV get affordable care, however, we need policy changes that don't rely on the benevolence of insurance companies.

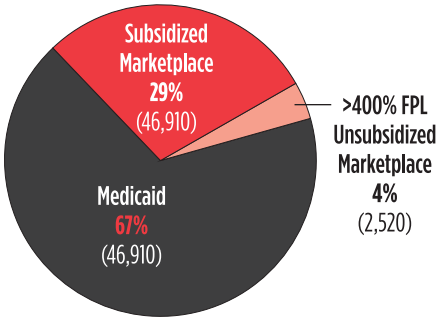
On March 19, HHS published a new rule in the Federal Register entitled, "Patient Protection and Affordable Care Act; Third Party Payment of Qualified Health Plan (QHP) Premiums"; a public comment period on the rule ends in May. The hope is that the new rule will solve the issue of Ryan White premium assistance across all states. Unfortunately, the rule also encourages QHPs to reject third-party payments from drug companies, which could be a headache for Marketplace-covered people living with HIV who face high out-of-pocket costs for antiretrovirals, particular when low-cost generic versions aren't available.

Without ensuring access to quality care that is affordable to people with HIV, we will fail in our efforts to fill the gaps in the HIV care continuum. According to the Centers for Disease Control and Prevention, 82% of all people with HIV have been diagnosed, but only 66% are linked to care, and worse, only 37% are retained in care, with 33% on antiretroviral therapy. One way to fix this is to remove policy barriers that prevent people from getting health insurance. For people who lack access to Medicaid, the continuation of Ryan White funds will be essential to efforts to get and keep people in care.

HHS must continue to actively enforce the ACA's promise to prohibit discrimination on the basis of preexisting conditions in the insurance market. Otherwise the Obama administration's public charge to #GetCovered will leave people with HIV out in the rain. •

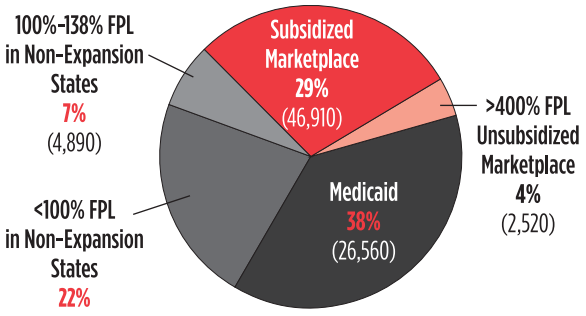
Health Insurance Coverage Options under the ACA for Uninsured Adults with HIV in Care

All States Expand Medicaid



Total=69,720

26 States Expand Medicaid



Total=69,720

Based on state Medicaid decisions as of October 22, 2013.

Kates J. Assessing the impact of the Affordable Care Act on health insurance coverage of people with HIV. Kaiser Family Foundation; 2014. Available from: http://kff.org/report-section/assessing-the-impact-of-the-affordable-care-act-on-health-insurance-coverage-of-people-with-hiv-issue-brief. (Accessed 2014 March 30)

Better Late Than Never: Efavirenz Dose Optimization

After a study suggests that we've been using too high a dose of efavirenz for a decade and a half, the move toward scaling up a lower and more cost-effective one faces some hurdles

By Tim Horn and Polly Clayden

Fifteen years after efavirenz was approved by the U.S. Food and Drug Administration (FDA) for the treatment of HIV and went on to become one of the most widely prescribed components of antiretroviral (ARV) therapy worldwide, a question has arisen: have we been using an unnecessarily high dose to treat adults living with HIV?

The question follows the recent publication of clinical trial results demonstrating that 400 mg of efavirenz is no less efficacious—with some evidence of improved tolerability—compared with the standard 600 mg dose, ultimately confirming data from a study completed (but never published) in 1998 suggesting that a lower doses of the drug would suffice. As tempting as it may be to point fingers and rue the possibility of misguided dosing decisions made early in the course of the non-nucleoside reverse transcriptase inhibitor's development, what's ultimately important is our ability to capitalize on the better-late-than-never clinical trials results to optimize the drug's use.

Efavirenz is sold under the brand names Sustiva and Stocrin and is a component of Atripla and generic single-tablet regimens (STRs). Since its approval in 1998, it has been used in regimens to treat millions of people throughout the world.

Though its efficacy is revered, the side effects of efavirenz are less than ideal—notably, high rates of central nervous system problems that result in approximately 25 percent of people (at least in countries where ARV options are plentiful) discontinuing its use.

The cost of the originator drug has increased steadily (the U.S. wholesale acquisition cost for efavirenz alone is more than $8,500). But the Clinton Health Access Initiative (CHAI)-determined annual ceiling price for generic efavirenz for use in low-income countries is currently US$48 (US$130 for STRs containing efavirenz and tenofovir).

Treatment optimization efforts to improve the tolerability and cost of efavirenz are now under way; these include the study of lower doses that won't compromise efficacy.

The process by which the 600 mg dose of efavirenz was selected is shrouded in some mystery. According to preliminary data that, curiously, were never published in a peer-reviewed medical journal, a phase II dose-finding comparison (DMP 266-005) of 200, 400, and 600 mg efavirenz suggested comparable viral-load suppression rates after 16 weeks of treatment. In fact, while the clinical trial wasn't powered sufficiently to determine superiority of one dose over another—each study arm included up to 36 volunteers—81% of those in the 200 mg group, compared with 71% of those taking 600 mg, achieved viral loads below 400 copies/mL, with more than twice the rate of dizziness in the 600 mg group (44% vs. 19% in the 200 mg group).

While FDA approval documents from 1998 note that the 600 mg dose was selected by the manufacturer (then DuPont Merck) to safeguard against the emergence of mutations conferring resistance to efavirenz, it is not clear whether there was sufficient scrutiny of this claim.

More recently, data were reported from two studies involving people living with HIV taking 600 mg of efavirenz and the tuberculosis drug rifapentine. Because of a known interaction between the drugs, rifapentine reduced patients' blood concentrations of efavirenz to the equivalent of a 400 mg dosing. It did not, however, compromise viral-load suppression rates in either clinical trial.

An official comparison between 400 mg and 600 mg of efavirenz was initiated in 2011, conducted by the Kirby Institute at the University of New South Wales with funding from the Bill & Melinda Gates Foundation. Forty-eight week data from the 96-week ENCORE1 study being conducted at 38 trial sites in 13 countries were initially reported at the 2013 IAS Conference on HIV Pathogenesis, Treatment and Prevention in Kuala Lumpur and published online by the *Lancet* in February.

Six hundred and thirty individuals were included in the analysis; roughly 68 percent were men, and the distribution of Africans, Asians, and whites was divided evenly into thirds. Median viral load at study entry was

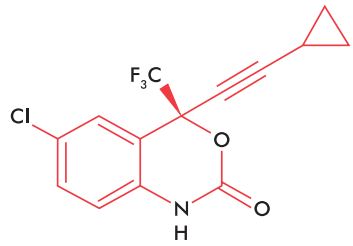
Approaches to HIV Treatment Optimization

Reformulation

This strategy employs technology or inactive ingredients to increase plasma or cellular concentrations of a drug, thereby allowing for a newly formulated version of the drug with a lower dose.

Dose Reduction

HIV drugs lacking well-defined dose-response relationships may be candidates for dose-reduction studies. In addition to efavirenz, atazanavir and darunavir dosing with ritonavir, as well as zidovudine and stavudine, are undergoing dose optimization.



Process Chemistry

It may be possible to alter a drug's manufacturing process, potentially leading to more efficient and less expensive production of a drug's active pharmaceutical ingredient(s).

Adapted from: Clayden P. Retrofitting for purpose: treatment optimization. In: Clayden P, Harrington M, Swan T, et al.; i-Base/Treatment Action Group. 2013 pipeline report. New York: Treatment Action Group; 2013.

57,000 copies/mL, though roughly 34 percent had viral loads in excess of 100,000 copies/mL. CD4 counts at study entry averaged 273 cells/mm^3. Efavirenz was combined with tenofovir/emtricitabine for the study.

At week 48, 94.1% in the 400 mg efavirenz group, compared with 92.2% in the 600 mg group, had viral loads below 200 copies/mL. Lower-dose efavirenz was also found to be "non-inferior" in patients with high baseline viral loads (>100,000 copies/mL), in patients with lower (<22) or higher (>25) body mass indexes, and in ethnic origin comparisons.

Overall, rates of adverse events—including central nervous system–related problems and rash—and treatment discontinuation were similar in the two groups. However, when looking exclusively at adverse events "definitely or probably related to study drugs," rates of treatment discontinuation were significantly higher in the 600 mg group than the 400 mg group.

Though the tolerability benefits of reduced-dose efavirenz remain uncertain—investigators in the United Kingdom plan to explore this further in a 200 mg dose comparison—the potential for cost savings is tremendous. According to modeling reported by CHAI staff at the Second Conference on Antiretroviral Drug Optimization in April 2012, an efavirenz dose reduction of 33 percent may translate into three-year cost savings of up to US$336 million.

These dollars will be critical to efforts to secure the availability of ART for the 66 percent of the 28.6 million people living with HIV in low- and middle-income countries who are eligible for treatment under the 2013 World Health Organization (WHO) guidelines and lack access to the drugs.

The ENCORE1 study investigators conclude that 400 mg efavirenz should be recommended as part of routine care. However, WHO guidelines are unlikely to reflect this recommendation until additional research is completed, particularly among women in the third trimester of pregnancy (when plasma concentrations of efavirenz are significant reduced) and in areas where TB is endemic and rifampicin-inclusive regimens are routinely prescribed.

Generic manufacturers are prepared to switch to producing STRs containing 400 mg efavirenz, but their incentive to do so hinges on guidance from the WHO and FDA tentative approval in association with PEPFAR.

In the United States and other high-income countries, the results of ENCORE1 may be applicable immediately. But as efavirenz is in the twilight of its patent protection, it is highly unlikely that Bristol-Myers Squibb or Merck (marketers of Sustiva and Stocrin, respectively) will push for the approval of a 400 mg dose. Though 400 mg dosing is possible (two 200 mg capsules), generic drug manufacturers will likely be the first to introduce STRs containing reduced-dose efavirenz and tenofovir—several years from now. •

Punked by Pharma: Public Funds for Private Products

Tax dollars are making it easier for the drug and diagnostics industry to develop and market essential TB products. Is the public getting a fair return on its investment?

By Lindsay McKenna

Motivating the pharmaceutical industry to step up and respond to the burgeoning tuberculosis (TB) epidemic is one thing. Publicly funding its research and development (R&D) only to have it yield prohibitively expensive drugs is something else entirely.

Public-private partnerships, particularly when it comes to diseases that largely affect the world's poor, are essential. TB has seen only three new drugs developed over the past 40 years. TAG's *2013 Report on Tuberculosis Research Funding Trends, 2005–2012* cites a US$1.39 billion funding shortfall for TB R&D investment, as well as a 22 percent reduction in private-sector investments. And in the past year alone, both Pfizer and AstraZeneca have pulled out of anti-infectives altogether, despite the recent U.S. Centers for Disease Control and Prevention's (CDC's) report, *Antibiotic Resistance Threats in the United States, 2013*, which listed multi- and extensively drug-resistant TB (M/XDR-TB) as a "serious threat."

The problem is that U.S. tax dollars end up supporting the development of private products that, once on the market, are priced out of reach of the populations that would benefit most. Companies also benefit from tax credits, priority review vouchers, and other incentives that potentially far outweigh their minimal R&D investments.

Sanofi's rifapentine is currently approved for treating active, drug-sensitive TB and shows promise for shortening treatment for both latent and active disease. Yet Sanofi is listed as the primary sponsor of just one of 18 clinical trials of rifapentine documented on clinicaltrials.gov and as a collaborator on only two others. Eleven of 18 trials are sponsored by the taxpayer-funded CDC or the U.S. National Institute of Allergy and Infectious Diseases (NIAID).

It would be unfair to say that Sanofi has contributed nothing to rifapentine's development. In addition to donating money to the CDC Foundation, it is providing study drug to the Tuberculosis Trials Consortium, financing the development of a fixed-dose combination, contributing to the study of rifapentine in children, and looking at potential interactions between rifapentine and Atripla (efavirenz/emtricitabine/tenofovir). While Sanofi does not publicly report its spending on TB research, the average cost of each of the aforementioned studies has been estimated at US$500,000–650,000. These investments, along with US$2 million in donations to the CDC Foundation, bring Sanofi's financial contribution to a measly US$3.65 million, far from the US$20 million-plus invested by the CDC.

Public dollars overwhelmingly funded the expensive studies critical to rifapentine's pending approval for the treatment of latent TB infection (see table). The contributions Sanofi has made are valuable in expanding new treatment options to children and people with HIV, but they also broaden the drug's potential market and profitability, especially as these populations are generally prioritized for the treatment of latent TB infection.

Similarly, AstraZeneca has capitalized on public funding to bring a drug to market without sufficiently matched investments. AstraZeneca's exit from TB R&D came with a purported commitment to continue developing the novel antibiotic AZD5847; however, the US$10.3 million that AstraZeneca invested in 2012 went primarily to preclinical work unrelated to the development of the drug. While AstraZeneca supported both single- and multiple ascending dose studies for AZD5847—at an estimated US$800,00 and $1.2 million, respectively—NIAID invested twice that in a phase IIa early bactericidal activity trial.

TB drug developers aren't the only private companies taking advantage of public dollars. Cepheid, the developer of GeneXpert, a fully integrated and automated molecular diagnostic system, received significant public-sector research funds to bring GeneXpert to market and then shirked its moral obligation by pricing the diagnostic technology out of reach for most TB-endemic countries.

Cepheid claims to have invested US$300 million to develop the GeneXpert platform and an additional US$25 million to develop the Xpert MTB/RIF cartridge for TB diagnosis. The U.S. Department of Defense invested US$120 million in the platform's development, and NIAID and the Bill & Melinda Gates Foundation (BMGF) invested US$21 and US$9.73 million, respectively, in the TB cartridge's development. While the amount Cepheid invested in the platform's development appears far greater than the public investment, Cepheid has also adapted this platform to diagnose a variety of other infections and diseases, allowing it to reap substantial benefits from public-sector investments.

The Development of Rifapentine Following Its Acquisition by Sanofi in the Early 2000s

Study Name	Study Description		Study Sponsor(s)
For treatment of active drug-sensitive TB (approved)			
22	Phase III	1x week rifapentine and isoniazid vs. 2x week isoniazid and rifampicin in continuation phase of treatment	CDC
25	Phase II	Tolerability of higher-dose rifapentine	CDC
For treatment of latent TB infection (indication pending)			
26 (PREVENT TB)	Phase III	3 months once weekly rifapentine and isoniazid vs. 9 months daily isoniazid	CDC
26 PK	Phase III	Pharmacokinetic study of 3 months once weekly isoniazid and rifapentine in children 2–11 years old	CDC
33 (iAdhere)	Phase III	3 months once weekly rifapentine and isoniazid comparing self-observed therapy to directly observed therapy	CDC
--	Phase I	Initial single-dose study and pharmacokinetic modeling of rifapentine in children	Sanofi
35	Phase II	Pharmacokinetics of rifapentine in children	CDC, Sanofi
A5279	Phase III	4 weeks daily rifapentine and isoniazid vs. 9 months daily isoniazid in people with HIV	NIAID
For active drug-sensitive TB treatment shortening (phase III protocol under development)			
29	Phase II	Rifapentine 10 mg/kg vs. rifampicin 10 mg/kg	CDC, Sanofi
29B	Phase I	Higher doses of rifapentine	Johns Hopkins University, CDC, Sanofi
29X	Phase II	Higher dose rifapentine vs. rifampicin	CDC
29X PK	Phase II	Pharmacokinetic study of higher-dose rifapentine given in single vs. divided doses	NIAID
--	Phase I	Pharmacokinetic interaction study of rifapentine and Atripla	Sanofi

The AIDS Clinical Trials Group (ACTG) and the Foundation for Innovative New Diagnostics (FIND) were the primary funders of the evaluation studies required for both U. S. Food and Drug Administration (FDA) approval and World Health Organization (WHO) endorsement. The ACTG, funded by the U.S. National Institutes of Health (NIH), invested US$1.4 million in clinical evaluation studies conducted in the United States, and FIND, with funds from the BMGF, invested US$5.63 million in multicountry evaluation studies and demonstration projects.

Even more public money was invested to reduce the price of both the platform and its testing cartridges. The President's Emergency Plan for AIDS Relief (PEPFAR) and U.S. Agency for International Development (USAID) contributed US$3.5 million, and UNITAID and the BMGF put in US$4.1 and US$3.5 million through a 2012 market intervention agreement, which reduced the cost of individual Xpert cartridges by 40 percent. Yet, the price remains unacceptably high, at US$17,000 for the platform and US$10 apiece for the cartridges, and only for a set number of preapproved public-sector purchasers in resource-poor countries, regardless of increased demand and procurement by TB programs.

The TB community has been grateful for even anemic private-sector contributions to R&D and hesitant to demand more accessible pricing, largely out of fear that private-sector companies will abandon TB. Yet private companies are benefiting from publicly funded research, tax credits, and priority review vouchers, while continuously and shamelessly privileging profits over patients.

The NIH actually has legislative power to protect public interests from private companies that fail to make innovations to which public funds have contributed available. In 1980, Congress enacted the Bayh–Dole Act, which includes a clause allowing funding agencies "march-in rights" to reclaim innovations from companies that fail to make them publicly accessible. However, in the 33 years since the Bayh–Dole legislation was passed, only four march-in rights petitions have been seriously considered by the NIH, all of which were later rejected.

The NIH needs to prioritize public interests and start proactively using the legislative power provided by the Bayh–Dole Act to improve access to new tools. Federal funding agencies and the TB community have ignored private-sector abuse of public funds for too long. If we are to achieve zero TB deaths, new infections, suffering, and stigma domestically and abroad, we need to stop the private sector from taking advantage of public funds while ultimately putting profits before patients. •

Fool's Errand: The Sloppy Science of the MDR-TB STREAM Trial

Confirming the efficacy and safety of bedaquiline-inclusive regimens is a priority. Comparing them to unvalidated MDR-TB drug combinations in the planned STREAM study is not the way to go about it

By Mike Frick

They should have left well enough alone. The original design of a landmark clinical trial evaluating a shortened course of treatment for multidrug-resistant tuberculosis (MDR-TB) was just what was needed to confirm its potential benefits over the World Health Organization's (WHO's) standard of care. The clinical trial's aim has since been conflated with another research priority—confirming the safety and efficacy of new MDR-TB drug bedaquiline—resulting in a study design that detracts from the importance of validating a tweaked Bangladesh regimen and may potentially undercut a scientifically sound assessment of bedaquiline in today's MDR-TB armamentarium.

The Evaluation of a Standardized Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB (STREAM) study is the largest MDR-TB clinical trial in history. Sponsored by the International Union Against Tuberculosis and Lung Disease, STREAM will evaluate whether a standardized nine-month MDR-TB treatment regimen first studied in Bangladesh is noninferior to (not less effective than) the current WHO standard of care, in which treatment lasts for two years or more. The STREAM sponsors have now partnered with Janssen to add two bedaquiline-containing arms to the study. Janssen has signaled that these arms will take the place of a separate phase III trial of bedaquiline and will test whether the addition of bedaquiline can improve the Bangladesh regimen by replacing the injectable drug kanamycin or reduce the duration of MDR-TB treatment to just six months, all the while attempting to address important safety signals that arose during the phase IIb randomized controlled trial of the drug.

Shortening MDR-TB treatment would revolutionize the TB field. But the proposed design of STREAM downplays concerns about the Bangladesh regimen and may not provide the additional safety data on bedaquiline for which TB-affected communities have called. Without revisions to STREAM's current design, the clinically unvalidated Bangladesh regimen may replace the current WHO standard of care as the foundation on which future knowledge of bedaquiline's safety and efficacy will be based. This slippage from standard of care to presumptive alternative is especially troubling given the scientifically dubious origins of the Bangladesh regimen.

In 1997, a year when bedaquiline remained just an unproven compound in the preclinical wilderness, the Damien Foundation began a prospective cohort study in Bangladesh to see if the two-year duration of MDR-TB treatment could be shortened using novel combinations of existing drugs. The study, which took 12 years to complete, assigned patients to sequential cohorts, with regimen optimization along the way. The sixth and final cohort evaluation of a seven-drug regimen—gatifloxacin, clofazimine, ethambutol, and pyrazinamide throughout the nine-month treatment period supplemented by high-dose isoniazid, kanamycin, and prothionamide during the first four months—resulted in 87.9% of patients completing treatment without relapse, a remarkable outcome in a field where MDR-TB cure rates have ranged from 11 to 79 percent.

Results were published in 2010, under the title *Short, Highly Effective, and Inexpensive Standardized Treatment of Multidrug-Resistant Tuberculosis*. Although the regimen was short and inexpensive, the title of the paper took significant scientific liberties in deeming it a "highly effective standard," considering the observational nature of the study and major flaws in its design and conduct, notably:

- Cohort sizes were not predefined, a decision the study authors justified with the odd statement that "ethical concerns always overrode statistical power considerations." In fact, appropriate statistical power constitutes an essential component of ethical research since studies not powered to produce scientifically valid results unnecessarily place participants at risk.

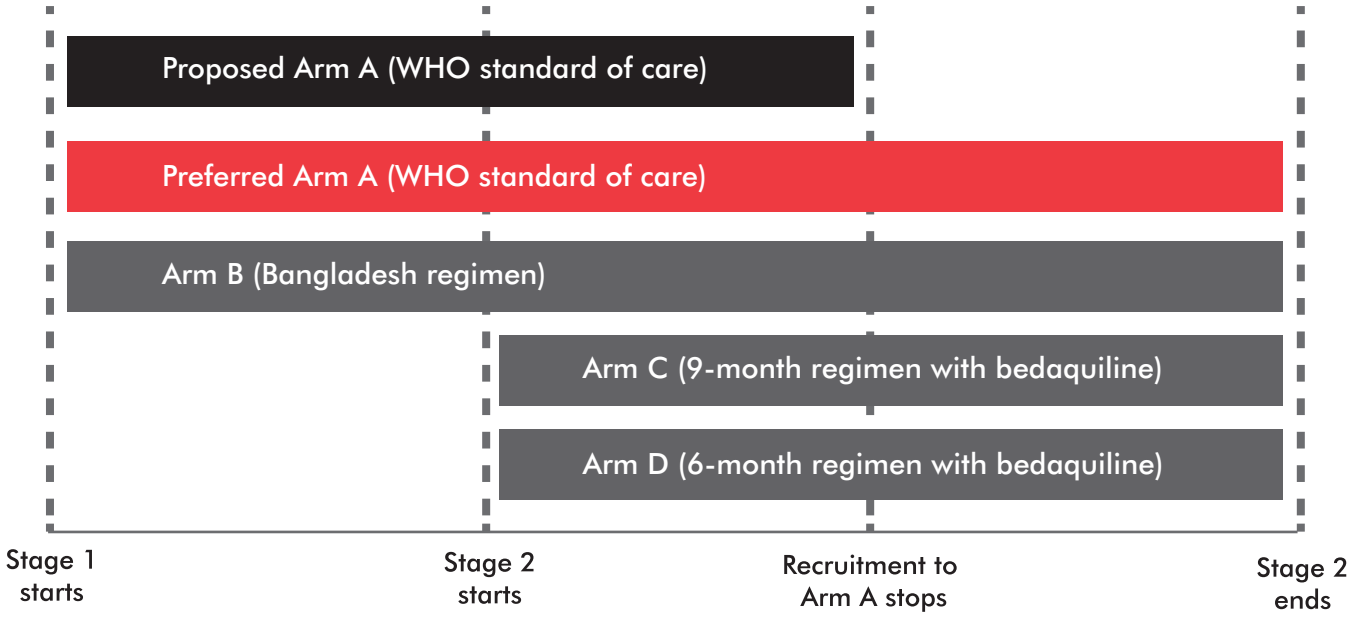
- More eligible patients chose not to participate than to participate (578 vs. 486), but for unknown reasons, posing a profound risk of selection bias.

- Cohorts were enrolled sequentially, meaning that the various regimens were studied during different periods of time. During the twelve years of the study, Bangladesh increased its human development index score (a composite measure of a country's development status that combines health, income, and education indicators) by 28 percent and raised life expectancy at birth by six years, thereby creating a cloudy picture about how evolving socioeconomic forces in the country might have influenced the more favorable results seen in the later cohorts.

STREAM was originally designed to validate a modified version of the Bangladesh regimen—gatifloxacin will be replaced with moxifloxacin—by comparing it with the current WHO standard of care under the more stringent criteria of a randomized controlled trial. With bedaquiline entering STREAM, the trial will now include two stages. Stage 1 will evaluate the noninferiority of the Bangladesh regimen (arm B) to the WHO standard of care (arm A). Stage 2 will assess whether the nine-month bedaquiline-containing regimen (arm C) is superior to the Bangladesh regimen and, as an exploratory endpoint, test whether the six-month bedaquiline-containing regimen (arm D) is noninferior to the Bangladesh regimen.

This raises several ethical and scientific concerns. Stage 2 will likely complete enrollment before investigators know the results of Stage 1. If the Bangladesh regimen proves inferior to the WHO standard of care, then patients in stage 2 will have been randomized to arms C and D in vain. Safety of bedaquiline remains a secondary endpoint in stage 2, even though clarity on bedaquiline's safety profile is arguably the most sought-after information given the higher mortality among patients receiving bedaquiline in Janssen's phase IIb study.

Addressing these concerns will require revisions to the STREAM protocol.



TAG and Global TB Community Advisory Board guidance to the STREAM study investigators includes enrolling patients in arm A throughout the duration of the trial, powering the trial to allow for multiple comparisons (arm B vs. arm A; arm C vs. arm A; and arm C vs. arm B), and establishing safety as a primary endpoint during stage 2 of the trial.

Both the International Union and Janssen bear responsibility for enacting these revisions and setting the trial on sounder ethical and scientific footing. The additional resources required to continue enrollment in arm A throughout the duration of STREAM should be assumed by Janssen, which has a commitment to conduct confirmatory trials of bedaquiline's safety and efficacy under the conditions of bedaquiline's accelerated approval by the U.S. Food and Drug Administration. For its part, the International Union must create avenues for meaningful community engagement on these controversial design questions. While STREAM investigators have allowed TAG and the Global TB Community Advisory Board to review the protocol and issue suggested protocol revisions, the International Union lacks the structured community engagement programs seen at other TB research networks. The absence of community engagement is unacceptable given the trial's potential to dramatically reshape clinical practice.

STREAM offers an unparalleled opportunity to advance MDR-TB treatment, but the proposed design has allowed excitement about treatment-shortening to leapfrog the science with little chance for community input.•

RECENT TAG PUBLICATIONS

The goal of eliminating tuberculosis (TB) in the United States is under threat, a new policy brief released in March shows. *Flatlined: U.S. Government Investments in Tuberculosis Research and Development, 2009–2012*, indicates that spending on TB research and development (R&D) among U.S. government agencies has declined in the face of budget instability, sequestration, and the rising costs of biomedical research. The policy brief is available at: http://www.treatmentactiongroup.org/tbrd2014/usg.

TAG, in collaboration with amfAR, The Foundation for AIDS Research, has also called for a deliberate and expedited research agenda designed to end the AIDS epidemic in the United States. Several recommendations are outlined in a report released in December 2013: *Filling the Gaps in the U.S. HIV Treatment Cascade: Developing a Community-Driven Research Agenda*. The report is available at: http://www.treatmentactiongroup.org/hiv/filling-gaps.

New to the TAG website is blog for TAG's HIV and Global Policy staff. Tim Horn, Jeremiah Johnson, and Kenyon Farrow will be posting news, views, and calls to action on a regular basis. Be sure to check the blog regularly for updates: http://www.treatmentactiongroup.org/blog.

The Michael Palm Basic Science, Vaccines, and Cure Project blog also remains active at: http://www.treatmentactiongroup.org/basic-science.

SUPPORT TAG

Supporting TAG is a wise investment in AIDS treatment advocacy. Every donation brings us one step closer to better treatments, a vaccine, and a cure for AIDS. Donate online: **www.treatmentactiongroup.org/donate**.

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When you shop on Amazon, enter the site at smile.amazon.com. Choose **TAG Treatment Action Group** as your designated charity, and 0.5 percent of the price of your eligible purchase will benefit TAG.

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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