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tagline

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

On Targets and Timelines

By Tim Horn

With growing recognition that science and discovery have forged the tools necessary to effectively diagnose, treat, and, indeed, eliminate three of the world's most lethal infectious diseases—HIV/AIDS, tuberculosis, and hepatitis C—there is a need for greater mobilization and strengthened accountability among all stakeholders. Universal frameworks in which this can be achieved require time-bound targets: collaboratively developed, metrics-driven goals to optimize health outcomes among those living with the disease(s) and to minimize incidence among vulnerable individuals.

In this issue of *TAGline*, we focus on several target-based strategies—or the lack thereof—for HIV/AIDS, tuberculosis, and hepatitis C. The development of regional, national, or global plans, firmly grounded in science and reality, remains a fundamental aspect of TAG's work. No less critical is effective implementation of these plans, which includes advocating for real-time adjustments to account for unanticipated epidemiological trends, emerging best medical- and service-delivery practices, unaddressed needs in heavily affected populations and geographies, evolved research agendas and prioritization, and shifting political support and funding.

We begin with an analysis of potential savings to the New York State Medicaid program that will accompany implementation of a blueprint strategy, developed by a gubernatorial task force, aimed at ending AIDS as an epidemic in NYS by the year 2020. This is followed by Kenyon Farrow's update on the National HIV/AIDS Strategy goals for 2015 and, importantly, the need for a revitalized domestic plan that concretely addresses the first iteration's lack of ambition and glacial pace of outcomes reporting. And though HIV vaccine and cure research and development are in early stages (and, thus, not yet driven by quantified public health targets), Richard Jefferys writes that projections for their advancement are being bandied about as a result of some notable scientific advances.

Woefully absent from the hepatitis C landscape are global elimination targets, though they are forthcoming from the World Health Organization (WHO) later this year. As Tracy Swan notes, despite astonishing therapeutic advances in recent years, surveillance data, diagnostic and monitoring optimization work, gaps in the evidence base, and access barriers have slowed goal-setting and timeline-development efforts. Finally there is the WHO's End TB Strategy, which is striving for TB elimination by 2035. As Mike Frick reports, however, this is dependent on new tools—including new TB vaccines—being introduced no later than 2025, which requires a somewhat radical shift in vaccine research, notably an expanded focus on promising candidates in early-stage development.

As seemingly different as these aspects of TAG's ongoing engagement in target-based strategy development and implementation may appear, they are very much united in core themes. These include unflinching support for high-caliber research, rapid and equitable scale-up of evidence-based interventions and practices, and swift, permanent razing of the structural and economic barriers that are now the greatest threat to our ability to eradicate three of the world's deadliest diseases. •

Ending the HIV Epidemic (ETE) in New York State

Not only is it the right thing to do for the health of New Yorkers, but a new analysis demonstrates that it is also cost-effective

By Ginny Shubert, Housing Works; and Mark Harrington

In June 2014, New York Governor Andrew Cuomo made history by committing New York State to end AIDS as an epidemic by the year 2020. The goal is ambitious, but grounded in reality. NYS has always been a center of innovation in the fight against AIDS and has reduced the number of annual new HIV infections by 40 percent over the last decade while the rest of the nation saw no decline. Deaths from HIV-related conditions have also continued to drop dramatically. With expanded health care coverage and highly effective antiretroviral therapy, taken as treatment or prevention, we now have the means to end the HIV epidemic, even without a cure, by stopping new HIV infections and eliminating AIDS deaths.

To advance his plan, Governor Cuomo appointed an Ending the Epidemic (ETE) task force of HIV/AIDS experts from the public and private sectors and health and community-based organizations. The task force developed recommendations to be incorporated by the NYS AIDS Institute into a gubernatorial blueprint to not only meet the governor's mandate to reduce annual new infections from 3,200 in 2013 to below 750 in 2020, but to exceed that mission with proposals to "get to zero" new infections and HIV-related deaths. With the political will and funding necessary to implement the ETE blueprint, NYS can be the first jurisdiction anywhere to end AIDS, saving the lives of thousands of New Yorkers and providing a model for the rest of the nation and the world.

Ending AIDS as an epidemic is not just the right thing to do for the health of New Yorkers—it's also cost-effective. We simply can't afford a status-quo approach to HIV. According to a recent analysis by Bruce Schackman of Weill Cornell Medical College and colleagues, every new HIV infection costs $443,904 in health spending alone (the discounted present value of $798,300 in lifetime HIV treatment and care costs). ETE implementation would improve the health of New Yorkers living with HIV and prevent 10,850 new primary HIV infections between now and 2020 as well as thousands of secondary downstream infections.

The highlights of fiscal analyses conducted by Housing Works and TAG and detailed here focus primarily on costs and savings to the NYS Medicaid program that covers 50 percent of people with HIV in the state. (*Editor's note*: The unabridged analyses, including additional saving expected in Medicare, ADAP, and other public health programs, is available at: http://www.treatmentactiongroup.org/policy/NYS-ETE-fiscal-impact).

Impact of ETE **ARV Treatment Expansion** on NYS Health Care Spending

ETE implementation requires doubling the number of people with HIV in NYS who are retained in continuous antiretroviral (ARV) therapy that results in viral suppression—from 68,000 people with HIV (44% of all people with HIV in NYS) virally suppressed in 2012 to at least 136,000 (88%) virally suppressed as soon as possible. An HIV-positive person successfully and sustainably treated can maintain optimal health and is virtually unable to transmit HIV to others.

Successful ETE testing, treatment, and prevention expansion that reduces new HIV infections statewide from 3,200 in 2013 to 750 or less in 2020 will **reduce Medicaid spending by at least $3.93 billion** for the 50 percent of New Yorkers with HIV who rely on Medicaid. This is calculated as the difference between an investment of $2.25 billion in Medicaid spending for incremental treatment costs and $6.18 billion in offsetting Medicaid savings from improved HIV health outcomes ($1.43 billion) and averted HIV infections ($4.75 billion in avoided costs for prevented primary and secondary HIV infections).

ETE COSTS

$2.25 billion in incremental ARV costs between now and 2020:

- With community support, the state has negotiated volume-based discounts with pharmaceutical companies that represent more than 70 percent of the ARV market, which will significantly reduce new ARV costs to the NYS Medicaid program.
- Annual incremental costs to Medicaid of doubling the number of HIV-positive beneficiaries on ARV medications are estimated at $375 million/year (with total estimated ARV treatment costs to Medicaid of $1.125 billion/year instead of $1.5 billion without discounts).
- Total incremental Medicaid ARV medication costs from successful ETE implementation would therefore be $375 million/year for six years (2015–2020), or a total of $2.25 billion.

ETE MEDICAID SAVINGS

$1.43 billion from improved health for people with HIV:

- 34,000 people with HIV will receive effective ARV treatment from NYS Medicaid (50% of the 68,000 people with HIV newly on ARV treatment).
- People with HIV on ARV treatment incur costs as much as $7,000 less per year than those not on ARVs, according to an analysis published by Angela Hutchinson and colleagues in 2006, due to reductions in avoidable medical costs and longer life expectancies associated with effective ARV treatment.
- Savings in avoidable Medicaid spending would therefore be $238 million/year (34,000 people with HIV at $7,000/year) for six years (2015–2020), or a total of $1.43 billion.

$2.41 billion from prevented primary HIV infections:

- 10,851 new primary HIV infections will be prevented between now and 2020 if NYS implements the ETE plan and reduces annual new infections to 750 or less in 2020.
- Each infection prevented saves $443,904 in lifetime HIV treatment and care costs, generating $4.816 billion in total health care savings, including a $4.07 billion reduction in public sector health spending that breaks down as follows:

  Medicaid: $2.41 billion (50% of people with HIV in NYS);

  Medicare: $795 million (16.5% of people with HIV in NYS); and

  AIDS Drug Assistance Program: $867 million (18% of people with HIV in NYS).

$2.34 billion from prevented secondary HIV infections:

- Averting 10,851 new primary HIV infections would also prevent an estimated 10,525 downstream secondary infections, as the average HIV-infected person is expected to transmit HIV to 0.97 HIV-uninfected persons over his or her lifetime, according to Schackman's analysis.
- Preventing secondary infections will generate $4.672 billion in savings in lifetime HIV treatment costs (10,525 prevented secondary infections at $443,904/infection), including $2.34 billion in savings to Medicaid (50% of people with HIV in NYS).

Impact of ETE Housing Expansion on Public Costs and Spending

Successful ETE implementation will require increased public investments in housing resources for the 10,000 to 12,000 low-income people with HIV in NYS who are currently homeless or unstably housed. Housing status is among the strongest predictors of access to HIV care, viral load, health outcomes/spending, and ongoing risk of HIV transmission.

Funding safe, stable housing for homeless and unstably housed New Yorkers with HIV will produce **net savings of at least $1 billion in public spending** between now and 2020. This is calculated as the difference between public investments of up to $720 million for new housing supports and $1.72 billion in offsetting public savings in Medicaid spending from improved HIV health outcomes ($1.08 billion), averted HIV infections ($520 million), and public spending on inappropriate homeless shelters ($120–180 million).

ETE COSTS

$600 to $720 million in new public spending on housing between now and 2020:

- An estimated 6,000 people with HIV in NYC and 4,000 to 6,000 people with HIV in the balance of the state have a current unmet housing need and are financially eligible for public housing supports.
- The public costs of required rental subsidies and related supports for the 10,000 to 12,000 homeless/unstably housed people with HIV statewide is estimated at $100 million to $120 million per year—based on estimated fair-market housing costs, minus tenant contributions of 30 percent of disability benefits or other income—or between $600 million and $720 million total over the six years between now and 2020.

ETE SAVINGS

$1.08 billion in Medicaid savings from improved health outcomes:

- The 10,000 to 12,000 extremely low-income people with HIV who are homeless or unstably housed are eligible for and should be enrolled in Medicaid or other publicly funded program(s) for health coverage.
- Improved housing status for people with HIV is strongly linked to reduced viral load and better health outcomes and has been found to reduce avoidable health care spending on emergency and inpatient care by an average of $15,000 per year for each person with HIV who moves from homelessness to stable housing.
- Savings from improved housing status for 12,000 homeless and unstably housed people with HIV in NYS are therefore estimated at $180 million per year ($15,000/person/year in avoided emergency, inpatient, and other crisis health care costs), for a total savings over six years of $1.08 billion in avoidable health spending.

$520 million in Medicaid savings from prevented primary infections (not included in this analysis is an additional $495 million in Medicaid savings for lifetime treatment and care costs attributable to prevented secondary HIV infections):

- Improved housing status is also independently linked to reduced risk of ongoing HIV transmission.
- Housing 12,000 currently homeless/unstably housed people with HIV in NYS can be expected to prevent at least 1,173 new HIV infections between now and 2020, saving the NYS Medicaid program approximately $520 million in lifetime HIV treatment costs ($443,904 in avoided lifetime treatment costs per prevented HIV infection).
- Put another way, continued failure to meet the housing needs of 12,000 people with HIV in NYS can be expected to result in 1,173 new HIV transmissions between now and 2020, undermining the ETE goals described in the ARV Treatment Expansion section above and costing the Medicaid program $520 million in lifetime treatment costs.

$120 to $180 million in savings from reduced use of inappropriate homeless shelters:

- Analysis of NYC administrative data indicates that 700 to 1,000 people with HIV are forced to use Department of Homeless Services (DHS) shelters each night, at a cost of $78/night for single adults and $102/night for families.
- Assuming that 80 percent of sheltered people with HIV are singles and 20 percent have families (according to the current NYC HIV/AIDS Services Administration caseload), the total public cost of shelter for people with HIV in NYC is $21 million to $30 million each year.
- Housing 700 to 1,000 New Yorkers with HIV who use DHS shelters each night would therefore produce savings of $20 million to $30 million annually, or $120 million to $180 million over the six years between now and 2020—funds that could be better spent to provide safe, stable, long-term non-shelter housing.

After 30 years, we know all too well the human toll of AIDS on New York State's individuals, families, and communities—but the ongoing NYS HIV epidemic also costs the state billions in avoidable public spending. Implementing the Ending the Epidemic blueprint will translate into substantial savings in avoided health care and services spending. The ETE plan is expected to generate over $6.8 billion in total Medicaid savings, reducing Medicaid spending by a net $4.5 billion after factoring in the impact of ETE ARV treatment and housing expansions, along with $2.3 billion for incremental treatment costs. The expansion of essential housing services called for in the ETE plan will alone produce net public savings of at least $1 billion through increased stability and improved health outcomes for New Yorkers with HIV who are currently homeless or unstably housed. An AIDS-free New York stands to gain much—in both human and fiscal terms. •

Toward an *Ambitious* National HIV/AIDS Strategy

We won't end HIV as an epidemic with anemic goals, delayed surveillance data, feeble support of state policies and resource needs, and an inadequate implementation science agenda

By Kenyon Farrow

The U.S. National HIV/AIDS Strategy (NHAS) ends its five-year run at the end of 2015 with mixed results. Due to long gaps in HIV surveillance reporting, unambitious targets, and a lack of funding, authority, and incentives to enforce the strategy—not to mention the high turnover rate of leadership at the White House Office of National AIDS Policy (ONAP) since the strategy's inception (there have been three ONAP directors during the Obama presidency)—the impact of the NHAS itself is still unclear.

The new director of ONAP, Douglas Brooks, has announced that he's working on an update of the NHAS to be released this year, before his tenure likely ends with the inauguration of a new president in January 2017.

At this point, any National HIV/AIDS Strategy has to help mobilize the country and lead a national discussion about what it actually means to end the epidemic domestically and what the consequences are if we fail to. In addition to providing the kinds of messaging to the larger U.S. public about how we can reduce new infections below epidemic levels, it must also develop new goals and the kind of coordination of policy within the federal agencies charged with different pieces of the strategy.

If we're going to end the domestic epidemic, the NHAS must greatly increase and standardize targets and ensure that policies to achieve those targets are implemented at the federal and local levels. Notable examples are the low—and divergent—viral-load suppression targets. The NHAS has established HIV serostatus knowledge, linkage-to-care, and continuous engagement-in-care targets of 90%, 85%, and 80% for 2015, respectively, for all major race/ethnic and risk factor groups. Yet the viral-load suppression goal is below 50%: 39.2% of blacks/African Americans, 43.9% of people who inject drugs, and 48.8% of men who have sex with men. Not only are these targets unambitious, particularly when they are expressed as percentages of people living with HIV who know their status and have been linked to care, but they buttress the health disparities that have long plagued populations most heavily affected by HIV.

Another significant limitation of the NHAS, particularly with respect to measuring its impact, is the glacial pace at which annual surveillance data are reported to the Centers for Disease Control and Prevention by state health departments and, ultimately, made available to the public by the federal agency. In recent years, reporting of most NHAS indicators has been on a three-year lag—too slow for any kind of relevant program planning, targeted funding adjustments, or prompt response to emerging epidemics. There have been many changes in our society in the last three years that affect the HIV epidemic (e.g., the rollout of the Affordable Care Act; expanded access to and education about pre-exposure prophylaxis; even the rapid emergence of social media and phone hook-up apps that may influence sexual behavior). Relying on old data will not help us rapidly evaluate, and respond to, these major shifts in HIV care and prevention service delivery, or appropriately change the course of programs or targeted resources.

Luckily, this is one area where the CDC is expected to make progress. Eugene McCray, director of the Division of HIV/AIDS Prevention at the CDC, has announced that beginning this year, annual surveillance reports will be available within one calendar year of the time that data are collected. To streamline this process, however, states must scale up their capacity to provide these data to the CDC in a timely fashion. Annual incidence estimates, however, will still go through a peer-review process and will be on approximately an 18-month lag (the peer-review process adding about six months to the publishing cycle).

Though ONAP and the CDC released interim reports on the NHAS in late 2013, hailing successes on most indicators, the bulk of their evidence drew from data that preceded the implementation, or occurred during the first six months, of the strategy. Falling incidence and improved clinical outcomes for some populations nationally can be attributed to the efforts of many states long before the NHAS was implemented.

The expansion of Medicaid and other health coverage to larger portions of the population in places like Massachusetts, San Francisco, and New York, as well as strategies to accelerate access to care for people newly diagnosed in Washington, D.C., and other areas, all contribute to reductions in incidence.In addition, new research has shown that patients in many Ryan White clinics across the country are experiencing better clinical outcomes across the continuum than those receiving care in other settings.

Now, with New York, Washington State, and San Francisco advancing ambitious plans to end the epidemic in those jurisdictions, the NHAS could be critical to leveraging federal resources to implement regional as well as national plans. Additionally, there could be mechanisms in place to encourage states to develop and implement plans. One huge problem, of course, is that Medicaid expansion, as initially envisioned in the Affordable Care Act, is a critical component of reducing HIV incidence and expanding access to treatment for people with HIV. Though this decision is out of the hands of the federal government, a revitalized NHAS could provide a framework for the kinds of state policies needed to end their epidemics.

We have effective interventions for quickly diagnosing HIV, improving engagement in care, and safely and effectively treating people living with HIV. What we don't yet know is how to efficiently and effectively scale them up in all heavily affected areas and populations. It is here that implementation science—operational and dissemination research; cost-effectiveness, modeling, and economic evaluations; research to strengthen personnel and health systems; comparative effectiveness, evaluations of the impact of policy changes on public health outcomes; etc.—is not only useful, but critical. For instance, how much would diagnosing more acute infections with fourth-generation HIV tests at health departments and in clinical settings increase our rate of people who are diagnosed? What impact would that have along the care continuum?

THINKING **BIG**: Reducing New HIV Infections

2015 goals of the NHAS in 2010	Possible 2020 goals for a new NHAS
↓ annual number of new infections by 25% (relative to baseline year 2006)	↓ annual number of new HIV infections by at least 45% (relative to baseline year 2010)
↓ HIV transmission rate, which is a measure of annual transmissions in relation to the number of people living with HIV, by 30% (relative to baseline year 2006)	↓ HIV transmission rate by at least 50% (relative to baseline year 2010)
↑ from 79% to 90% the percentage of people living with HIV who know their serostatus (relative to baseline year 2006)	↑ to at least 90% the percentage of people living with HIV who know their serostatus (with an emphasis on identifying seropositivity as soon as possible after HIV infection)
	↓ the already low number of diagnosed persons living with HIV who engage in unprotected, serodiscordant, transmission-relevant risk behavior by at least 50% (relative to baseline year 2010)

Where there is agreement among stakeholders that the original 2015 goals are conservative—and likely unachievable, given that appropriate funds were not invested in key programmatic areas—there is not yet consensus regarding the targets that might be realistically achievable, with sufficient investment, in a revitalized NHAS. To foster this discussion, David Holtgrave of the Johns Hopkins Bloomberg School of Public Health has proposed an updated NHAS for 2020, based on mathematical modeling yielding goals that are bold yet achievable. Presented here are goals pertaining to HIV incidence, with the original 2015 goals listed on the left and Holtgrave's proposed targets on the right.

Source: Holtgrave DR. Development of year 2020 goals for the National HIV/AIDS Strategy for the United States. AIDS Behav. 2014 Apr;18(4):638–43. doi: 10.1007/s10461-013-0579-9.

These are some of the questions that implementation research can help us address—in ways that could help us target resources that would better meet the goals of the strategy. The Office of AIDS Research is putting into action a research agenda that includes implementation science, and we must ensure that the findings are used to effectively scale up federal, state, and local policies, programs, and funding streams.

The new NHAS will also have to more explicitly identify populations and jurisdictions that need resources and support to address their epidemics and what the federal government should do to support affected communities. That means scaling up strategies to curb transmission among black gay and bisexual men, transgender women of color, and other groups for whom traditional efforts have failed.

NHAS should be more than a skeletal framework of limp ambitions. It should be a mechanism for accountability at all levels, with an eye toward ending the epidemic. Not simply controlling it. •

An HIV Cure and a Vaccine within the Next 15 Years?

Optimism is not without merit, but the science remains incredibly fragile

By Richard Jefferys

We're pretty optimistic in this 15-year period we will get those two new tools.
—Bill Gates, World Economic Forum, January 23, 2015

Earlier this year, Bill Gates caused a ripple in the media by expressing optimism that a vaccine and a cure for HIV will become a reality within the next 15 years. Gates didn't exactly offer a prediction, but the resulting headlines inevitably steamrollered over the subtleties: "Bill Gates Just Predicted We'll Basically Have a Cure for AIDS in the Next 15 Years" trumpeted *Business Insider*; the *Guardian* chimed in with "Bill Gates Predicts HIV Vaccine by 2030."

From TAG's perspective, Gates's buoyancy does have some scientific basis—there have been encouraging signs of progress on both the vaccine and cure fronts in recent years—but the challenges that lie ahead must not be underestimated.

The first compelling hint that vaccination may be able to prevent HIV infection in humans arrived in 2009 with the results of a large randomized clinical trial in Thailand, RV144. A prime-boost combination of an ALVAC canarypox vector and AIDSVAX B/E (a combination of gp120 proteins from clades B and CRF01_AE) reduced the risk of acquiring HIV by 31.2%—a slim but statistically significant degree of protection. After a disconcertingly long lag due to the need to produce new gp120 protein components—an example of the type of problem that can undermine predicted timelines—studies are now getting under way in South Africa that will begin to assess whether the RV144 results can be reproduced, and possibly improved, in other populations at higher risk of HIV infection.

A preliminary trial has shown that the original RV144 regimen induces immune responses that are at least comparable, and in some cases of greater frequency, in South African individuals. February 2015 saw the launch of HVTN 100, a clinical trial that will evaluate the safety and immunogenicity of modified versions of the vaccines based on HIV-1 clade C, the prevalent virus in South Africa, and also include an additional boost after 12 months (analysis of RV144 after the first year suggests protection may have been around 60% at that early period, providing a rationale for the extra immunization). Should HVTN 100 prove successful, a 5,400-person follow-up efficacy trial will be conducted (HVTN 702) with the potential to lead to licensing of the regimen if a sufficiently significant degree of protection can be achieved. The Bill & Melinda Gates Foundation is a member of the Pox Protein Public Private Partnership (P5) that is sponsoring this research. The work of the P5 may represent the best hope for the development of a licensable vaccine within the time frame Gates cited in Davos, but there is no guarantee that efficacy will be demonstrated.

There are other burgeoning areas of HIV vaccine development that hold promise, but are at an earlier stage. New technologies have contributed to the identification of many broadly neutralizing antibodies (bNAbs) capable of potently inhibiting multiple HIV isolates from all clades. There is now an intense focus on creating strategies capable of coaxing B cells into generating bNAbs using sequential

immunizations with HIV antigens specifically designed for this purpose. Researchers have also made progress in constructing HIV envelope proteins that more closely mimic the natural form—the three-pronged trimer structure is unstable, making it difficult to preserve for creating vaccine antigens—and preliminary results in animal models suggest that this approach may induce antibodies with improved neutralization capacity.

A potential shortcut to providing bNAbs to individuals at risk for HIV infection is passive immunization using a gene transfer approach. A phase I human trial began last year in the United Kingdom testing an adeno-associated virus (AAV) vector as a delivery vehicle for a gene encoding a bNAb. The AAV takes up residence in muscle cells where it acts as a factory for manufacturing the antibody; however, it remains to be seen if protective levels of bNAbs can be obtained. The technology also needs to be proven safe in healthy HIV-negative individuals.

An alternative means of protection involves rapidly eliminating infected cells before they can ignite a systemic infection. Evidence suggests that this type of mechanism may have been involved in the outcome of RV144, since the vaccine regimen did not induce neutralizing antibodies. Rather, researchers believe that antibody-mediated cellular cytotoxicity, in which non-neutralizing antibodies flag infected cells for destruction, played an important role. Work is under way to develop methods to maximize this activity with future vaccine candidates. Macaque studies involving a replicating CMV vector have shown that effector T-cell responses could have the potential to clear HIV infections, and several vaccine candidates based on other replicating vectors are under evaluation in early clinical trials (with the CMV vector possibly entering human testing in the not-too-distant future).

While no particular HIV vaccine strategy in the pipeline is certain to bear fruit in the next 15 years, the field clearly is far from fallow, and there is at least reason to hope that Bill Gates's optimism will turn out to be justified.

A larger question mark may hang over the near-term prospects for a broadly effective HIV cure. Timothy Brown is still the only individual considered cured; he has not shown any signs of a viral return since receiving two stem cell transplants from a donor lacking the CCR5 co-receptor (part of a daunting and risky series of treatments he required for a life-threatening cancer eight years ago). The doctor responsible for Brown's transplants, Gero Hütter, recently published a letter describing six other HIV-positive individuals with cancers who received stem cell transplants from CCR5-negative donors; sadly, none survived more than a year, due to either cancer recurrence or complications from the transplantation.

For a brief period in 2013, it was thought that three additional cases of HIV cures had been identified: the "Mississippi Baby" who acquired infection perinatally, received ART almost immediately and showed no return of virus after a treatment interruption, and two adult men in Boston who received stem cell transplants for cancers (from CCR5-positive donors) and subsequently stopped ART without an immediate viral load rebound. But HIV eventually returned: after 27 months in the child in Mississippi and around three and eight months in the two individuals in Boston.

In all three of these cases, the HIV reservoir had been diminished to levels that were too low for any current technology to detect. It is estimated that the Boston patients experienced reductions in the size of their HIV reservoir of at least 3 logs (1,000-fold), but this was insufficient to lead to a cure. This has potentially sobering implications for current research because in clinical trials of interventions that aim to deplete the HIV reservoir, there has been little or no evidence of even small reductions. Additionally, mathematical modeling indicates that reservoir reductions of 5 logs (100,000-fold) or greater would be needed to achieve long-term remission from HIV replication in the absence of ART in a majority of individuals.

All is not lost, however. Studies of two-pronged strategies designed to awaken the latent HIV reservoir and then target the infected cells for destruction are only just beginning. Examples are clinical trials combining HDAC inhibitors and therapeutic vaccines or bNAbs. There are other approaches that may not necessarily require reservoir reductions, such as gene therapies that aim to protect vulnerable CD4 T cells from HIV and thus promote more effective immune responses against the virus.

While not considered cured, a group of 20 individuals in France—known as the VISCONTI cohort—is displaying prolonged control of HIV replication after being treated with ART soon after becoming infected, then interrupting therapy several years later. Some members of the cohort have now been off ART for a decade and have maintained viral load levels below 50 copies/mm^3. It's not yet known if this control of HIV may come at a cost, such as elevated levels of inflammation, but the cohort does at least offer some reason to believe that—in the absence of a complete cure—long-term suppression of HIV replication without ART may be an attainable goal (and this may have been the type of outcome—sometimes referred to as a "functional cure"—that Bill Gates was thinking of when he made his comments in Davos).

While the cure field is at a relatively early stage, and has not produced any candidates that are likely to start on a path toward licensing in the near future, there is always the potential for surprises. A widely publicized study published recently in the journal *Nature* is an example. A research team led by Michael Farzan at Scripps described a newly created HIV inhibitor named eCD4-Ig that has unprecedented potency against a very diverse array of HIV (and SIV) isolates. When delivered to macaques by an AAV vector (the same approach being studied as a possible means of bNAb delivery), robust protection against infection was documented. The intent is to now evaluate eCD4-Ig for both prevention and treatment.

Bill Gates hopeful reading of the scientific tea leaves is understandable, and likely partly derived from the involvement of his foundation in supporting research in both arenas. But hope does not equate to inevitability and must not lead to complacency. Advances in the vaccine field are underpinned by significant increases in funding over the years; in the mid-1990s, the writer Mark Schoofs penned a piece for the *Village Voice* pointing out that annual HIV vaccine research spending was less than the budget of the flop movie *Waterworld*. Cure research would similarly benefit from increased investment, but the world's leading supporter of scientific research, the National Institutes of Health, has seen funding fail to keep pace with inflation in recent years. This flatlining of funding also creates a grim outlook for young scientists—often the source of new ideas and potential breakthroughs—seeking to pursue a career in HIV.

Beyond funding, the regulatory pathway that candidate HIV vaccines and cures would follow to approval is not entirely clear yet, particularly in the case of partially successful interventions—exactly how good would be good enough for licensing? What criteria would be needed to consider someone cured, and how many years of follow-up would be required?

And, ultimately, an approved vaccine or curative therapy will be useless if the people who need it the most cannot get it, a problem faced already in the case of ART and now being grimly recapitulated with highly efficacious but immorally overpriced hepatitis C cures. All of these issues and uncertainties will require ongoing vigilance and advocacy to ensure their resolution and turn hopes for a vaccine and cure into a reality. •

C U L8ter: Hepatitis C Eradication

Hepatitis C is now curable. Now all we need is surveillance to monitor it, global funding to fight it, and targets set to address it

By Tracy Swan

The first global targets for eliminating hepatitis C virus (HCV) will be set by the World Health Organization later this year. It's about time: although HCV is preventable and curable, it kills 700,000 people annually and continues to spread among millions more. At least 185 million people worldwide have been infected with HCV, although data on the epidemic's scope and spread are sketchy. This inadequate surveillance has made it easy to ignore hepatitis C, and difficult to secure and allocate sufficient resources to save lives.

The best and worst of the situation—dramatic improvements in treatment in the face of a rapidly rising death toll—have ignited a global movement to address hepatitis C. The treatment revolution officially began in 2011, when proof-of-concept for an interferon-free cure was established. Since then, hepatitis C drug development has moved at breakneck speed.

Oral combinations of direct-acting antivirals (DAAs) have cured over 90 percent of people in clinical trials, including people with cirrhosis or HIV/HCV coinfection. These DAAs offer great promise for a global public health approach to hepatitis C: using the same drugs for everyone, for the same length of time.

The response to HCV among women and children has been pitiful. Globally, 1.5 million to 12 million pregnant women have hepatitis C, and the vertical transmission rate ranges from three percent to 10 percent—possibly higher if the mother is also HIV-positive, especially if she is untreated. At present, there is no way to prevent vertical transmission.

As for the safety and efficacy of HCV treatment in children, trials are lagging. However, the first interferon-free pediatric HCV treatment trials are now opening in the United States, the United Kingdom, Australia, New Zealand, Germany, Italy, and the Russian Federation.

Target DAA Regimen Profile Will Be:

safe and tolerable; preferably ribavirin-free (Ribavirin cannot be used in people with unstable heart disease or during pregnancy; it causes birth defects and can be fatal to unborn babies. It also has many side effects, including anemia.);

effective and potent: must cure ≥90 percent;

universal: can be used for all HCV genotypes; for people with HIV/HCV, cirrhosis, and kidney disease; during pregnancy and nursing; and in pediatrics and the elderly;

simple and easily delivered/administered: minimal pre-treatment testing and on-treatment monitoring needed; fixed-duration (preferably ≤12 weeks); once-daily (fixed-dose combination preferred); no food requirement;

affordable; and

stable at different temperatures.

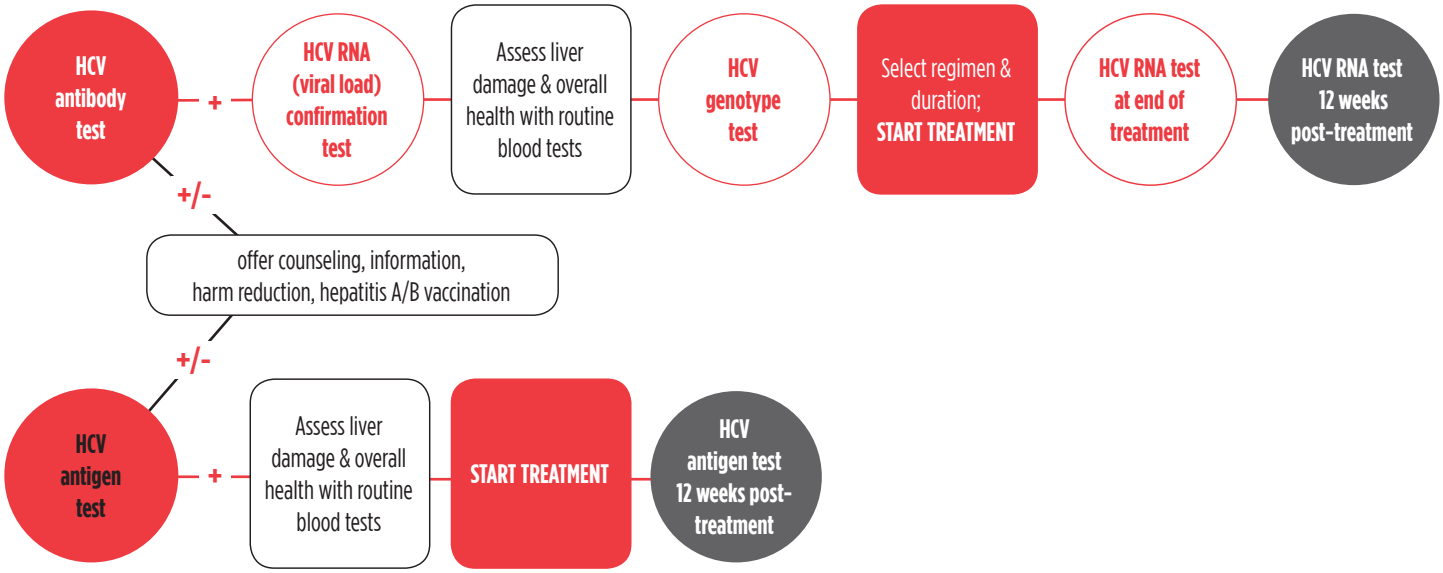
Access, Access, Access

There are several barriers to HCV treatment scale-up—the most significant being high drug prices. In low- and middle-income countries, patent protection allows pharmaceutical companies to control where generic versions of their drugs are sold, through voluntary licensing (VL) agreements.

Many middle-income countries—including China, home to at least 30 million people with hepatitis C—have not been offered VLs, although they bear the brunt of the HCV epidemic. These countries are left to use legal challenges, such as blocking patents, issuing licenses themselves (called compulsory licensing), or purchasing drugs from another country, where affordable generics are available (called parallel importing).

Scaling up HCV treatment is only one piece of the elimination puzzle. Diagnostics must also be simplified. Currently, diagnosing HCV is a complex, expensive, and inconvenient multi-step process. However, it may be possible to streamline HCV diagnostics and pre-treatment assessments in resource-limited settings.

CURRENT HCV DIAGNOSTICS



STREAMLINED HCV DIAGNOSTICS

Evidence to inform and support simplification of HCV diagnostics and monitoring—before, during, and after treatment—continues to evolve, including a handful of important studies featured at the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle.

Unlike the interferon treatment days of yore, it may now be possible to treat hepatitis C without measuring pre-treatment viral load, or monitoring viral load responses during treatment—or at the end of it. Eliminating these tests will simplify treatment in resource-limited settings, ultimately saving time and money for patients and providers.

David Wyles from the University of California at San Diego and colleagues analyzed treatment outcomes among more than 2,000 participants in AbbVie's PEARL, SAPPHIRE, and TURQUOISE trials (of ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin), including people with HIV/HCV or cirrhosis. They found that people were just as likely to be cured, whether it took two, four, six, or eight weeks of treatment to suppress HCV—and regardless of their pre-treatment hepatitis C viral load.

Viral-load test results at week four and at end of treatment (EOT)—a mainstay of HCV treatment monitoring—do not always predict the outcome of HCV treatment. Nearly everyone becomes undetectable within weeks of starting DAAs, but some people relapse within weeks of finishing treatment. In effect, early responses do not predict treatment success, nor do they predict treatment failure with DAA regimens.

Most people with detectable virus at week four will be cured, according to Sreetha Sidarthan from the Institute of Human Virology in Baltimore and colleagues, who analyzed results from the ERADICATE and SYNERGY trials of sofosbuvir-based regimens. Of the 17 people with detectable RNA at week 4 in SYNERGY, 100 percent were cured. In ERADICATE, 32 of 50 people had detectable HCV RNA at week 4; ultimately, 31 of the 32 were cured. EOT testing did not reliably predict cure either.

Researchers have speculated about why HCV may be detectable at the end of treatment in people who are actually cured. One such theory developed by Thi Huyen Tram Nguyen of the French Institute of Health and Medical Research and colleagues suggests that some defective virus lingers after HCV treatment has stopped production of new virus. This virus cannot infect liver cells or reproduce, but persists after treatment is finished, only to die off a few weeks later.

Picking a single HCV regimen that suits all, including people living with HIV, has become easier. In clinical trials, cure rates are just as high for people coinfected with HIV and HCV as for people with HCV alone. An important consideration, however, is drug-drug interactions. Since most HIV-positive people will be using DAAs with HIV treatment, interactions with antiretrovirals (ARVs) need to be managed—or avoided.

The once-daily combination of sofosbuvir and daclatasvir—expected to be approved in the United States later this year—is ARV-friendly. Sofosbuvir can be used with all ARVs except tipranavir/ritonavir. Although daclatasvir dose adjustments are needed with certain ARVs (atazanavir and efavirenz), no change in dosing is needed with other boosted HIV protease inhibitors (darunavir and lopinavir), all nucleoside reverse transcriptase inhibitors, certain non-nucleoside reverse transcriptase inhibitors (nevirapine and rilpivirine), and the integrase inhibitors raltegravir and dolutegravir.

Sofosbuvir and daclatasvir also boast very high cure rates in HIV/HCV-coinfected individuals. In ALLY-2, a phase III evaluation of this regimen, 203 coinfected participants were treated for eight or 12 weeks, according to genotype and treatment history. At CROI, David Wyles and colleagues reported that 97 percent of the 12-week group were cured. In the 8-week group, 76 percent of treatment-naive study participants with HCV genotype 1 were cured.

Daclatasvir and sofosbuvir were safe and effective for HCV genotypes 1, 2, 3, and 4, regardless of treatment experience or liver damage (although cure rates were slightly lower in people with cirrhosis) (see table 1). But more information is needed in non-1 genotypes, especially in people with genotypes 5 and 6, and in people with genotype 3 and cirrhosis—for whom cure rates have reached only 60 percent. Unfortunately, there were only 26 people with non-1 genotypes in ALLY-2; none had G5 or G6. Data on other pangenotypic combinations are expected later this year.

Table 1. Results from ALLY-2

Genotype and Treatment History	Cure Rate
1a, treatment-naive	**96%** (68/71)
1a, treatment-experienced	**97%** (32/33)
1b, treatment-naive or -experienced	**100%** (21/21)
2, treatment-naive or -experienced	**100%** (13/13)
3, treatment-naive or -experienced	**100%** (10/10)
4, treatment-naive or -experienced	**100%** (3/3)

More good news for people with HIV/HCV coinfection came from ION-4, a 335-person trial of co-formulated sofosbuvir and ledipasvir in people with HCV genotypes 1 and 4. Susanna Naggie from Duke University and colleagues reported that 96 percent of study participants were cured after 12 weeks of treatment. Study participants' ARV regimen options were limited to those containing efavirenz, rilpivirine, or raltegravir, plus tenofovir and emtricitabine (because of a known drug interaction between sofosbuvir/ledipasvir and tenofovir, renal function was carefully monitored during this trial).

Treatment history or cirrhosis did not lower cure rates, but race did—unlike trials of sofosbuvir/ledipasvir in HCV monoinfection. Naggie and colleagues noted that all 10 relapses occurred in black participants, and the cure rate was lower (90% vs. 96%). There were no differences in HCV drug levels by race or ARV regimen, or in people who relapsed versus people who were cured. More research will help to explain and, we hope, override the difference in response rate.

On the treatment front, progress against HCV has been astounding. But even the best DAAs—once they are universally affordable—and the simplest diagnostic and monitoring tools aren't enough. Political will and resources will be essential to achieving global hepatitis C elimination targets once they are finally established. The infrastructure to make good on these goals must be created—or expanded. The structural barriers that have allowed this epidemic to flourish—such as criminalization of gay people, people who use drugs, and sex workers—must also be eliminated. •

TB R&D's Shift to the Left

As the Bill & Melinda Gates Foundation realigns its TB vaccine strategy to focus on early-stage candidate development, equitable access priorities must also be established before large-scale trials are conducted

By Mike Frick

The Bill & Melinda Gates Foundation has revised its TB vaccines strategy, calling for a "shift to the left" in TB vaccine research and development (R&D). Accordingly, resources will transfer from a limited number of expensive, late-stage phase IIb/III trials to basic discovery, pre-clinical development, and phase I studies to explore a broader range of vaccine concepts. Missing from this shift, however, are plans for ensuring that new vaccines under development will be equitably available to the communities hit hardest by TB.

As the largest funder of TB vaccine R&D globally, any move by the Gates Foundation will ripple across the field. Its new strategy recognizes that only candidates with a high probability of success should enter phase II and III trials, which depend on a rational selection process based on rigorous immunology work on a wider field of candidates in phase I. Focusing resources on earlier stages of R&D will enable the investigation of many vaccine concepts with less financial risk attached to any particular failure.

This intention to "shift to the left" comes at a critical juncture in the fight against TB. After years of unambitious targets, in May 2014, the World Health Assembly (WHA) endorsed the World Health Organization's (WHO's) End TB Strategy, with its goal to achieve TB elimination by 2035. The third pillar of the End TB Strategy—"intensified research and innovation"—warns that new tools to fight TB, including new TB vaccines, must be introduced no later than 2025 in order to reach the 2035 elimination target. For TB vaccine R&D to match this pace, the field must head ambitiously in new scientific directions, which makes the turn to basic science and pre-clinical work a welcome development.

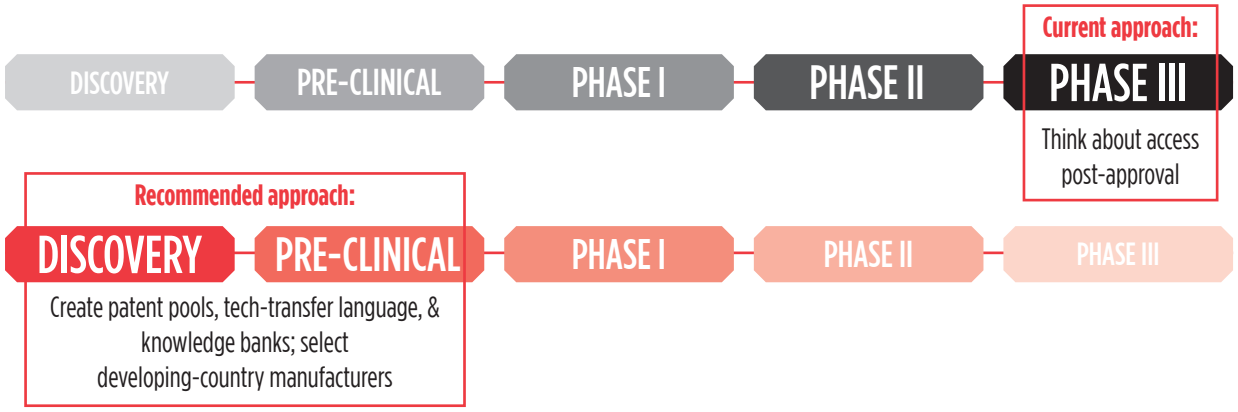
Scientific limitations continue to cast long shadows of doubt over the path TB vaccine R&D has followed since its revitalization 15 years ago. For example, most of the 15 TB vaccine candidates under development target a narrow, overlapping repertoire of *Mycobacterium tuberculosis* (MTB) antigens—meaning that vaccine developers are betting on a limited number of strategies. Also, common measures used to judge vaccine efficacy in clinical trials (i.e., levels of T-cell cytokines like IFNy) appear necessary, but are not sufficient indicators of protective immunity. Additionally, modest levels of protective immunity demonstrated in animal models have not predicted vaccine efficacy in human trials. These issues boil down to an incomplete understanding of how MTB evades, parries, and turns the human immune response to its advantage. Without this knowledge, designing a safe and effective new TB vaccine becomes too daunting a challenge to overcome by following the empirical (trial-and-error) method used to develop most existing vaccines.

Development-as-usual won't cut it, so the Gates Foundation's revised strategy outlines four objectives to guide a new approach: 1) conduct basic science research to understand the natural immune response to infection and disease; 2) develop new vaccine concepts that embrace immunologic diversity; 3) test these concepts through a process of iterative learning; and 4) increase coordination and collaboration. Such a strategy would move the point at which researchers learn whether a vaccine concept will likely work from the most expensive phase of research (i.e., late-stage trials) to pre-clinical development and phase I, where studies are smaller and less costly.

Focusing on early science also presents an opportunity to ensure equity in later stages of R&D, and there are specific steps scientists, sponsors, and funders can take to prepare for access on several fronts. Two important areas for action include anticipating intellectual property obstacles and enabling developing-country vaccine manufacturers to enter the market swiftly after vaccine licensing.

Past experience demonstrates that the market entry of multiple vaccine suppliers—including non-originator companies based in middle- and low-income countries—can expand vaccine access in a timely, affordable manner. Typically, more than a decade can elapse between the introduction of a new vaccine in high-income countries

Shifting investment, risk, and access considerations in TB vaccine R&D to the left



and its rollout in low- and middle-income countries. The Global Vaccine Action Plan, endorsed by the WHA in 2012, sets a target for all immunization programs to have sustainable access to recommended vaccine technologies within five years of licensing. In the case of new TB vaccines, any delay past this five-year window would jeopardize the WHO's goal of reaching TB elimination by 2035.

Over the next five years, as TB vaccine R&D embraces the new approach, it should develop the intellectual property governance required to introduce any new TB vaccine in endemic countries in time to fulfill the vision of the WHO's End TB Strategy. Achieving these related goals will require forming patent pools, knowledge banks, and technology transfer platforms. The potential of these structures to expand vaccine access has been outlined by Sara Crager in the July 2014 issue of the *American Journal of Public Health*, but it holds particular relevance for TB vaccine R&D.

Intellectual property protections have introduced an element of prospecting to even basic science research. New TB vaccines may be a decade or more away, but the future is already owned. An ongoing study by the WHO and the World Intellectual Property Organization has observed a sharp rise in the number of patent applications on vaccine technologies over the past 20 years, with over 9,000 filed between 1990 and 2010. Many of these patent applications apply to HIV and TB vaccine technologies and together compose a dense intellectual property landscape that will shape the accessibility of new vaccines.

Patents, however, are not the only obstacles to ensuring equitable access to new TB vaccines. Unlike many drugs, which non-originator companies can produce generically through reverse engineering, vaccines belong to a class of medical products called biologics that have a more complex construction. Consequently, developing-country manufacturers will, in all likelihood, require transfer of technology, industrial know-how, and nonrestrictive intellectual property provisions from originator companies to manufacture a new TB vaccine.

Agreements on patent licensing, technology transfer, and knowledge sharing involve stakeholders with divergent motivations and require time to establish. Under the "shift to the left" approach, as vaccine concepts develop into vaccine candidates, funding could be made contingent on licensing all patents into a patent pool. Templates for technology transfer from vaccine developers to developing-country manufacturers should be developed at this early stage. All of these mechanisms will need to be hosted by an organization that can convene the diverse stakeholders in TB vaccine R&D—originator companies, academic institutions, private and public funders, manufacturers, civil society, and people with TB.

The "shift to the left" envisioned by the Gates Foundation recognizes that the scarcity of resources in TB vaccine R&D—only $95 million spent globally in 2013, according to resource-tracking by TAG—makes it imperative to allow concepts to fail early—before failure becomes expensive. Overcoming intellectual property barriers and developing channels for technology and knowledge transfer would also lower the risk associated with vaccine development for the public and TB-affected communities around the world that will shoulder the majority of R&D costs. Addressing these issues at an early stage of scientific development will be essential for achieving TB elimination by 2035.•

RECENT PUBLICATION & WEBSITE UPDATES

Research Toward a Cure Trials is a continuously updated listing of clinical trials and observational studies related to the research effort to cure HIV infection. Available at: http://www.treatmentactiongroup.org/cure/trials.

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

Activist Strategies for Increasing Access to HCV Treatment in Low- and Middle-Income Countries (Available in English and Russian)
This report presents a number of key strategies through real-world case studies and shows how strategies used to combat the AIDS epidemic can be—and have been—adapted to increase HCV treatment access. Available at: http://www.treatmentactiongroup.org/hcv/publications/activist-strategies-increasing-access-hcv-treatment-low-and-middle-income-countries.

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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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