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How Cures Can Fail

The Foundation for AIDS Research

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MAKING AIDS HISTORY

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INTRODUCTION

Recent years have seen advocates and researchers forecasting the "end of AIDS" and setting targets for an "AIDS-free generation."[1] To this end, UNAIDS declared in 2014 its ambitious "90-90-90" plan to end the AIDS epidemic by 2020 by maximizing the use of current technology and treatment.[2] These projections are borne of tremendous scientific and medical breakthroughs in the fight against HIV: cutting-edge research promises the development of an eventual cure for HIV, with encouraging research ongoing on reactivating the latent viral reservoir, new cellular and genetic therapies, and early phases of curative vaccination.

However, advocates must guard against declaring that the fight has been won. Indeed, even with a medical curative therapy for HIV, it is imperative that the HIV response be sustained in order to build effective delivery systems and ensure maximum and sustained uptake. Global efforts to eradicate tuberculosis and malaria serve as a warning of how cures can fail. The lessons from these diseases are that cures are not panaceas and that only with a coordinated and enduring commitment can any disease be controlled.

TUBERCULOSIS AND MALARIA

Mycobacterium tuberculosis, a mycobacterial pathogen of the lung, has coexisted with humans for thousands of years.[3] An estimated one-third of the global population is infected with TB, with a majority of individuals maintaining immunological control over the pathogen in a noninfectious and asymptomatic disease state referred to as latent TB. The lifetime estimated risk of developing active disease among those latently infected is 5–10%.[4]

However, despite more than a half-century of readily available treatment for TB, the global burden of disease persists.

Tuberculosis is a treatable and curable disease. In the mid-twentieth century, the four primary antimicrobials used in the treatment of TB were developed. Side effects notwithstanding, treatment causes a rapid reduction in clinical symptoms within only one month and by the end of the course of treatment can achieve complete eradication of the pathogen. However, despite more than a half-century of readily available treatment for TB, the global burden of disease persists. In 1993, the WHO declared TB to be a global emergency. In 2015, TB surpassed HIV to become the leading cause of infectious disease deaths globally, with 1.5 million TB deaths in that year alone.[5]

Malaria, too, is an ancient disease. Four protozoan species of the genus *Plasmodium* parasitize humans *(P. falciparum, P. vivax, P. ovale, and P. malariae)*, each transmitted by anophaline mosquitoes. The epidemiology of malaria is variable, with some geographic areas affected only erratically and others experiencing seasonal, endemic disease. In many areas with endemic malaria, individuals are repeatedly infected throughout their lifetimes. Infection in adults is often asymptomatic, with mortality rates in uncomplicated and treated falciparum malaria of only 0.1%. Malaria in children most commonly causes anemia, and less frequently produces severe symptoms including acute febrile disease, convulsions, comas, neurological damage, and death. Malaria infection in pregnant women is associated with reduced birth weight and increased infant mortality.[6]

The first antimalarial drug, quinine, was discovered in the bark of an Andean tree. By the 1840s, British soldiers stationed in tropical regions combated malaria with daily rations of a "tonic water" consisting of quinine powder, sugar, and soda.[7] In 1934, researchers synthesized chloroquine, a modern antimalarial drug that cured malarial infection with fewer side effects than quinine. Chloroquine remained the most important malaria treatment until the WHO began recommending artemisinin-based combination therapies (ACTs) in 2001. Current treatment lasts for three days and achieves total clearance of the parasite. Much like TB, even with the availability of effective malarial treatment, more than 200 million cases of malaria and 438,000 deaths occurred in 2015.[8] Although malaria mortality decreased globally by 60% between 2000 and 2015, the burden of disease remains high in sub-Saharan Africa, with greater than 35% of all malaria deaths occurring in the Democratic Republic of Congo and Nigeria alone.[8]

HOW CURES CAN FAIL

Given the powerful medical tools available to cure these diseases, why do tuberculosis and malaria persist? The history of these two diseases points to three factors that have hamstrung eradication efforts and continue to enable millions of new infections and deaths each year. All three of these factors are of great importance to HIV

and predict similar challenges that would befall HIV disease control even in the event of a cure.

Diagnosis

Timely and accurate diagnosis is critical in the control of both TB and malaria. In the case of TB, only 63% of cases are diagnosed, leaving an estimated 3.6 million cases undetected and hence untreated in 2014.[5] Malaria case detection is even lower—only 10% of global estimated malaria cases are detected by malaria surveillance systems.[9] Several factors contribute to this low case detection rate.

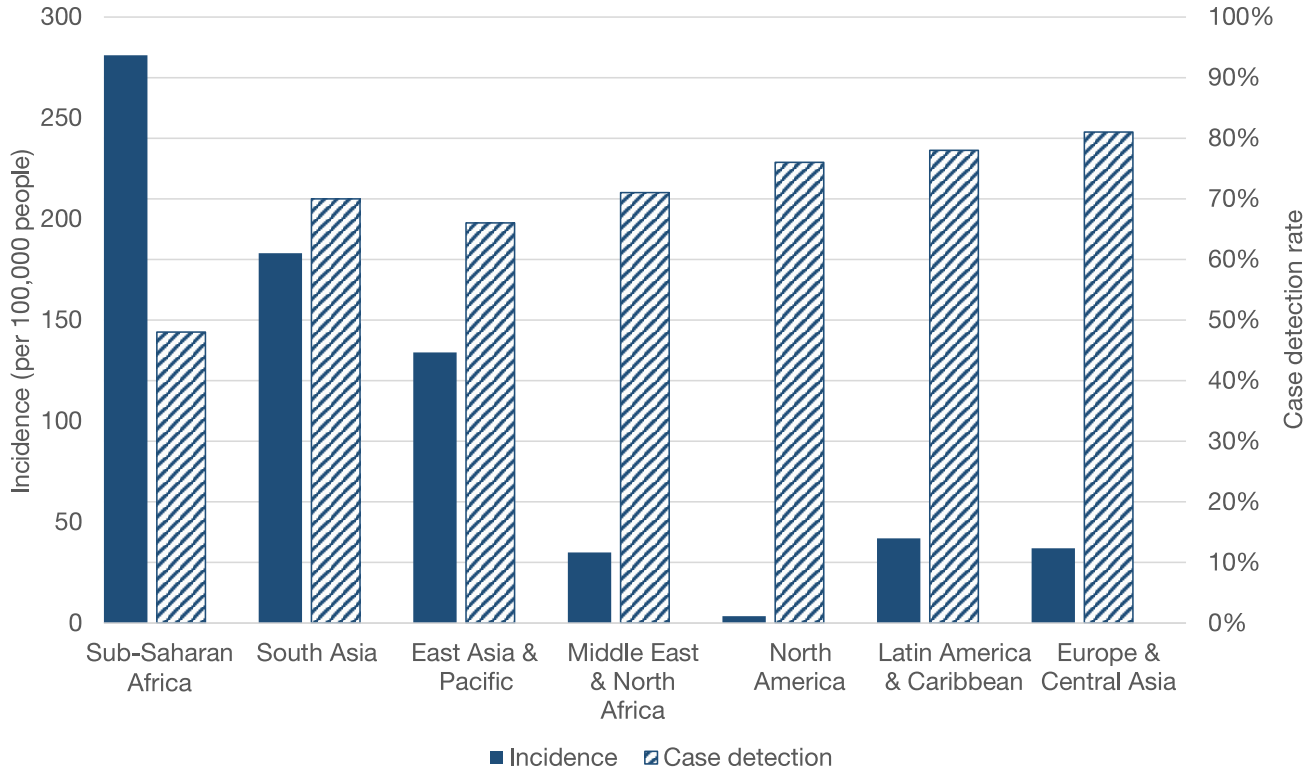
> Only 63% of TB cases are diagnosed, leaving an estimated 3.6 million cases undetected and hence untreated.

First, both tuberculosis and malaria cases are frequently identified by presumptive diagnosis, in which patients are initiated on treatment on the basis of clinical suspicion. In the case of TB, a non-resolving sputum-producing cough or a chest X-ray produces a high degree of clinical suspicion, while in the case of malaria an acute febrile episode in a pediatric patient is the most common indicator of disease.

> In 2015, only 58% of incident TB cases were confirmed by bacteriological test, and nearly one-quarter of presumed malaria cases did not receive a diagnostic test.

This practice of syndromic management is widespread: in 2015, only 58% of incident TB cases were confirmed by bacteriological test, and nearly one-quarter of presumed malaria cases did not receive a diagnostic test.[5,8] Accurate diagnosis is imperative for improving clinical outcomes through disease-appropriate treatment

FIGURE 1: Tuberculosis incidence and case detection in World Bank regions in 2014 (most recent available data)



Source: World Bank (http://data.worldbank.org/)

and for preventing the emergence and spread of treatment-resistant disease, particularly since clinical symptoms are often nonspecific (cough or fever) and the accuracy of presumptive diagnosis is highly variable.

Second, current diagnostic technologies are inaccurate, slow, and underutilized. In low- and middle-income countries, where 90% of world's TB disease burden is focused, the most common diagnostic tool for TB is sputum smear microscopy. This method is low-cost and produces rapid results; however, its sensitivity varies considerably from 83% to as low as 14%.[10] Additionally, smear microscopy is particularly insensitive among patients with HIV, a critical demographic in the linked HIV-TB epidemic, and is ineffective at diagnosing extrapulmonary TB.[11] To improve the sensitivity of these tests, current WHO guidelines recommend administering serial tests, requiring patients to return to health centers for multiple visits.[12] The travel and opportunity costs borne by patients often produce financial and logistical barriers to accurate diagnosis and contribute to loss to follow-up. Similarly, malaria diagnosis is traditionally via microscopic confirmation of the parasite in blood samples, a practice that is prevalent in endemic settings but is highly sensitive to staff training and slide preparation techniques.[13] In low-resource settings, insufficient staff training, low-quality equipment, and unreliable reagents, electricity, and water make high-quality microscopic diagnoses nearly impossible.[14]

New diagnostic technologies for both diseases hold promise for reducing turnaround time and improving diagnostic accuracy. In 2010, the WHO endorsed the use of Xpert MTB/RIF, a rapid diagnostic test (RDT) for the detection of TB. RDTs to detect malaria parasite using fingerprick blood samples have been available since the 1990s.[15] Several promising new diagnostic technologies are currently in development, including more sensitive, rapid, and portable tests.[16] Nonetheless, although RDTs may improve diagnosis rates, implementation of these technologies has been hindered by problems of capacity, staff training, and supply chain management. Rollout of RDTs must be accompanied by healthcare workforce training and systems for task shifting must be implemented. Without appropriate training, for example, clinicians do not decide which patients should receive RDTs based on standardized guidance and periodically prescribe antimalarial drugs to patients with negative RDT results.[17,18,19]

Additionally, modern testing technologies remain unaffordable for the poorest communities, where even the negotiated cost of the Xpert MTB/RIF test machine in high-burden countries is US$17,000 and the per-test cost is US$9.98.[20] These prices are available only in the public sector; as such, installation and testing costs are significantly higher for private health facilities. Finally, other barriers including cost, stigma, and discrimination hinder testing for TB and malaria; reaching all patients is therefore likely to require active case finding approaches, which demand more coordinated and workforce-intensive strategies beyond diagnostic technology.

Lessons for HIV

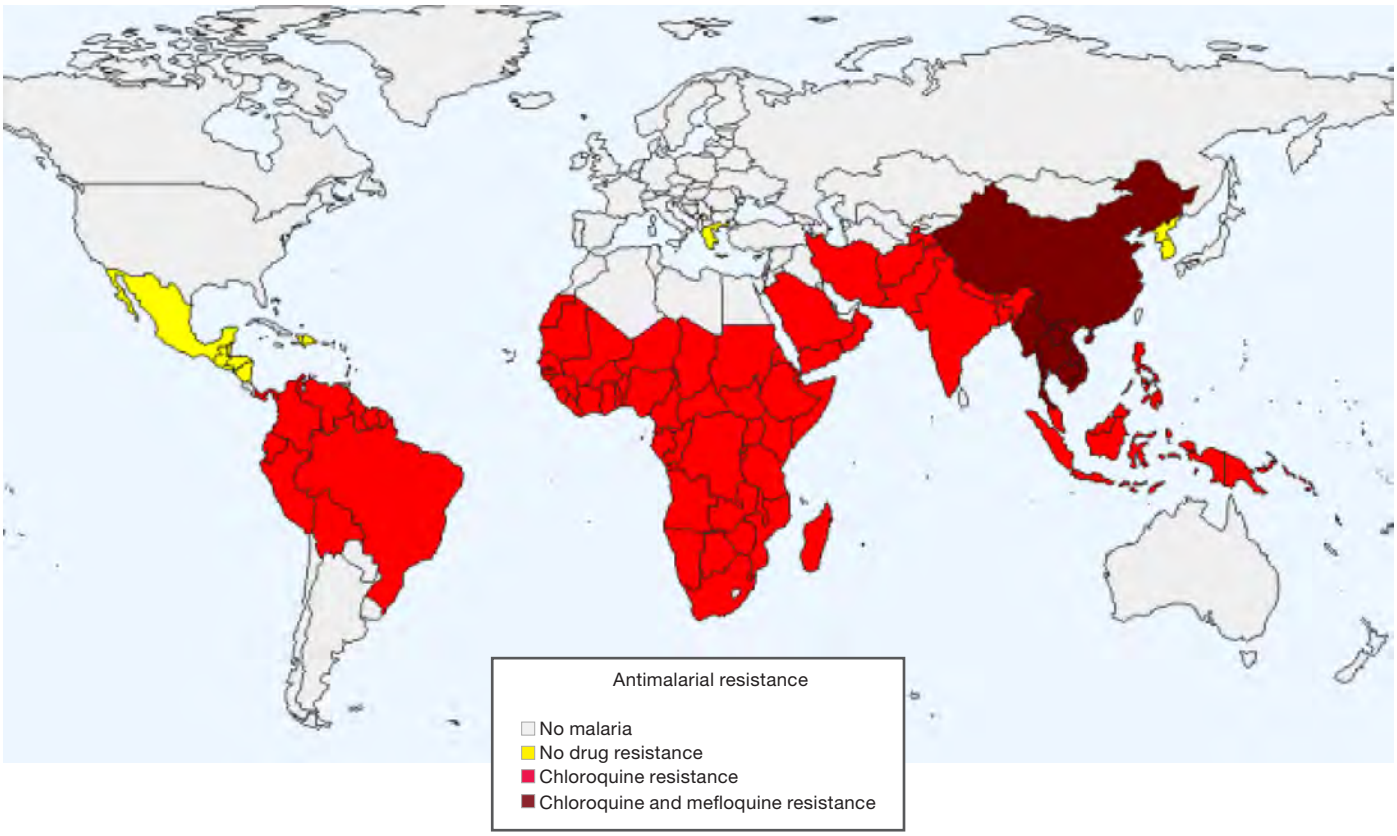
The introduction of rapid, point-of-care (POC) HIV testing technology has led to significant improvements in HIV diagnosis, allowing for greater accessibility to testing and quicker results.[21] Nonetheless, case finding will remain a critical challenge for HIV in the foreseeable future, particularly given that half of all people living with HIV are undiagnosed.[22] As with TB and malaria, rapid HIV testing must be accompanied by appropriate training for healthcare workers on interpreting test results, providing appropriate pre- and post-test counseling, and linking patients to further care.

> Individuals with late HIV diagnoses are 11 times more likely to die within one year of diagnosis than those diagnosed shortly after exposure.

Diagnosing and treating all HIV patients will require ongoing investment in novel diagnostic tools since the most widely used antibody-based tests are not accurate until up to three months after initial HIV infection. This constraint is of particular concern given that the highest infectiousness is in this time frame and individuals with late diagnoses (CD4 <350) are 11 times more likely to die within one year of diagnosis than those diagnosed shortly after exposure.[22]

Most importantly, diagnosing and treating all HIV patients can only occur with increased uptake of existing and new testing technologies. This will require overcoming barriers such as stigmatization from patients' partners, families, communities, and healthcare providers, fears of a positive diagnosis and lifelong treatment, costs to both patients and the health systems, and logistical hurdles borne by patients such as transportation time

FIGURE 2: Countries with malaria transmission and antimalarial resistance



Source: CDC (https://www.cdc.gov/malaria/travelers/country_table/a.html)

to testing facilities. Several innovative case-finding approaches should continue to be explored and expanded, including community-based outreach, opt-out voluntary testing strategies, and at home self-testing. Testing strategies must be accompanied by linkages to care, since current strategies suffer from very high losses to follow-up after diagnosis.[23] Increasing testing and linkage among adolescents will be especially crucial in Sub-Saharan Africa, where new infections are highly concentrated among young women and adolescent girls.

Drug resistance

The history of both TB and malaria is plagued by the struggle against drug resistance. Resistance to all first-line TB drugs was reported shortly after their introduction.[24-25] Between the 1950s and 1980s, clinicians refined the recommended therapy for TB to include a phased, multidrug combination therapy that produced better clinical outcomes while lessening the selective pressures that enabled the emergence of drug-resistant TB strains.[26]

However, several factors contribute to the continuing emergence of drug-resistant tuberculosis. Treatment for TB is long, lasting six months for drug-sensitive patients and up to two years for drug-resistant TB. Furthermore, although symptoms will typically subside within several weeks of treatment, the complete elimination of the pathogen only occurs after the full course of treatment. Since TB medications sometimes produce serious side effects, including permanent hearing loss and psychosis, patients are prone to discontinuing treatment early and thus contributing to a rebound of drug-resistant disease. Finally, patients are typically observed when taking each medication dose by a clinical or community healthcare worker, under the directly observed treatment, short-course, strategy (DOTS) promoted by the WHO to combat drug resistance. The evidence for this strategy is mixed and, since travel and opportunity costs are often borne by patients in these programs, it may paradoxically contribute to loss to follow-up or poor adherence.[27-28] Successful treatment is additionally hindered by distrustful and stigmatizing language toward patients (phrases

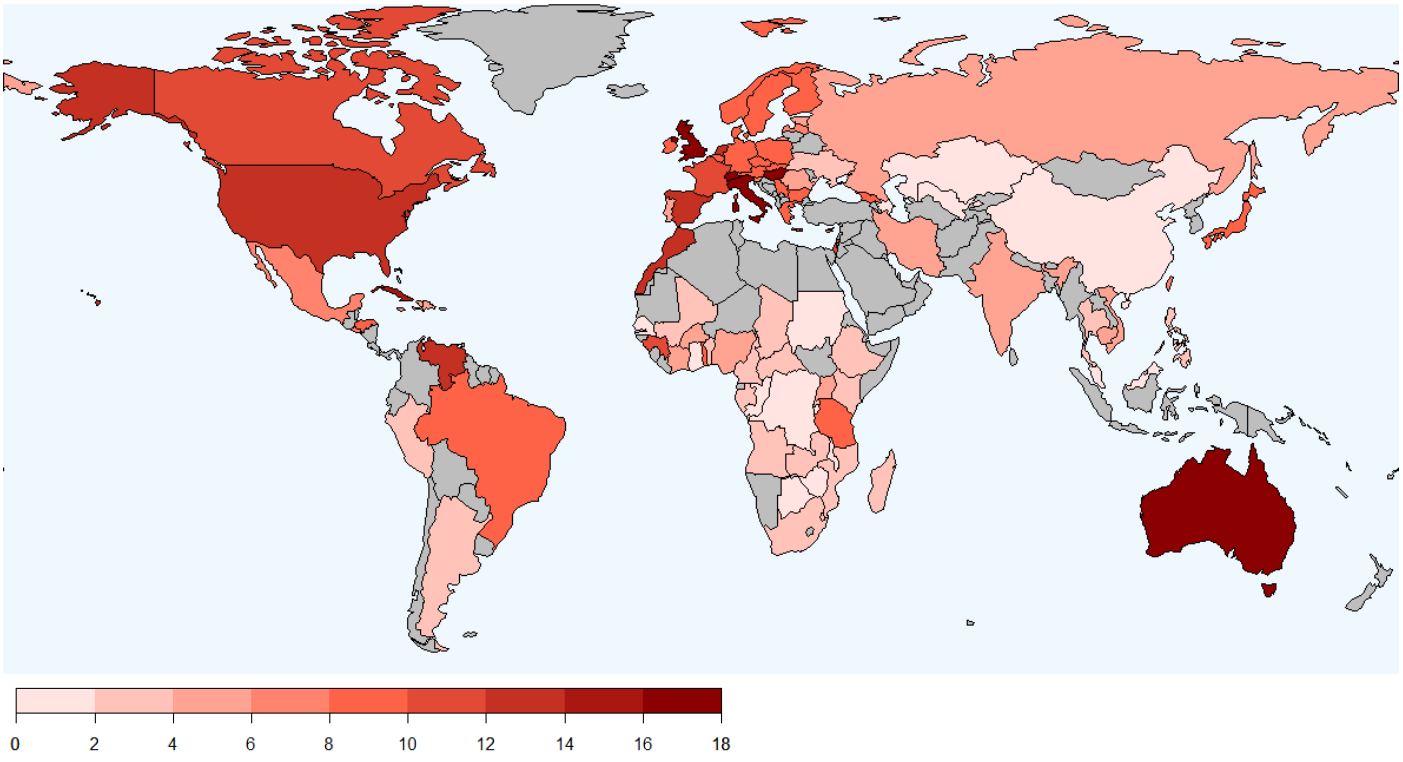
like “treatment defaulter” or “non-compliant” that assign blame) and systematic failures to increase treatment literacy after diagnosis.

> Today, malaria resistant to at least one antimalarial drug is present in most countries with endemic disease.

Drug resistance in malaria is driven by historical efforts to eradicate the disease. In 1955, encouraged by the recent development of DDT, a long-acting insecticide, the WHO declared a Global Malaria Eradication Program (GMEP) with the aim of eradicating malaria through universal indoor residual spraying with DDT. This effort occurred in tandem with an explosion in the use of DDT in agriculture and the implementation of mass administration of chloroquine in high-burden countries; in several countries in Southeast Asia, miners were given medicated table salt, a practice that contributed to widespread but often subcurative coverage of the drug.[29] In response to these selective pressures, DDT-resistant mosquitoes and chloroquine-resistant Plasmodium emerged quickly in South America, Southeast Asia, India, and Africa. Due to the combination of widespread drug resistance, technical and political failures, and the lack of sustained funding from donor countries, in 1976 the WHO abandoned its eradication campaign.[30] Today, malaria resistant to at least one antimalarial drug is present in most countries with endemic disease.[31,32]

In the case of both TB and malaria, inappropriate diagnosis contributed to the emergence of drug resistance. Presumptive diagnosis in both diseases leads to both the administration of inappropriate drug regimens to patients with drug-resistant disease or providing drugs to patients suffering from an entirely different disease. This is of particular concern in the case of malaria, in which patients can self-diagnose and purchase antimalarials from pharmacies or from street vendors (which may be counterfeited or diluted to subcurative potencies) without any clinical diagnosis. In addition, identifying drug-resistant tuberculosis is hindered by long turnaround times of diagnostic tests; typically, drug resistance is

FIGURE 3: Global HIV drug resistance rates (%) in ARV-naïve populations



Values are country medians from analysis by Rhee 2015 *PLOS Medicine* (https://hivdb.stanford.edu/page/surveillance-map/).
Grey areas indicate missing data.

identified by culturing sputum samples, a process that can take two months to produce definitive results. In the interval between diagnosis and receiving results of drug resistance tests, clinicians may initiate patients on an inappropriate treatment regimen, contributing both to poor patient outcomes and the development of disease that is resistant to multiple drugs. Although the Xpert MTB/RIF test does identify rifampicin-resistant TB, identifying the full spectrum of resistance continues to rely on culture tests.

Lessons for HIV

Drug resistance is a nearly inevitable byproduct of treating any disease. By virtue of its rapid replication, HIV is particularly adept at mutating and thereby developing resistance to treatment. Monotherapy treatment regimens used early in the epidemic produced drug resistance rates in some population groups as high as 57%, leading to the adoption of more effective combination therapies with reduced selective pressure on viral strains.[33] Today, HIV drug resistance rates in low- and middle-income countries are lower than in high-income countries, although they are expected to increase with expanded access to treatment.[34] In East and Southern Africa, HIV drug resistance rates range from 5% to 20% and have increased markedly in the years since antiretroviral therapy was introduced.[35] Drug resistance is especially of concern in the wake of the WHO's updated recommendation to treat all patients, regardless of disease stage, since asymptomatic patients are at increased risk of poor treatment adherence and thus of contributing to the emergence of drug-resistant disease.

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Drug-resistant HIV is typically identified by treatment failure, presenting as viral rebound and CD4+ cell decline, but in low- and middle-income countries it is not identified at the time of diagnosis due to technical and financial constraints. Maintaining the efficacy of current drugs, or any future cure, will require the implementation of diagnostic and monitoring strategies to quickly identify each patient's drug resistance profile at the time of treatment initiation. As demonstrated by TB, curative treatments must be easy to take and cause only minimal side effects, and the course of treatment must be short. Treatment for HIV has to its benefit a history of better patient communication and involvement and, unlike TB, does not suffer from the negative experiences associated with supervised treatment.[36] Finally, ensuring treatment adherence will require strengthening supply chain management to eliminate drug stock-outs and combat drug counterfeiting, as well as developing effective strategies for ensuring treatment compliance.

Research and Development

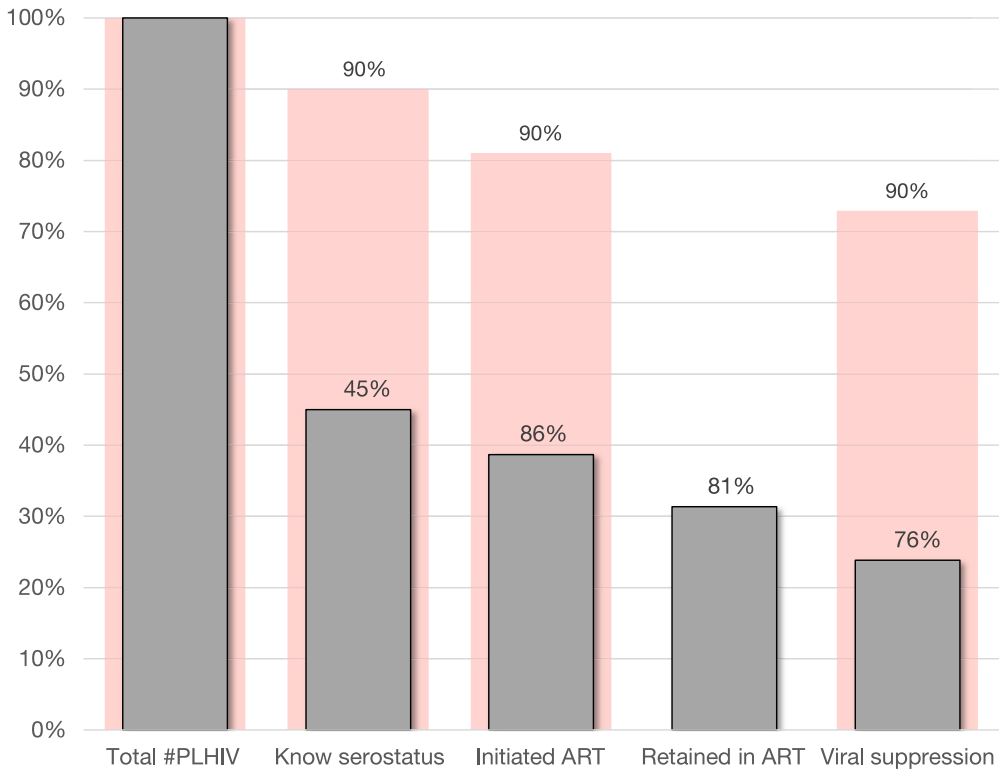
The distribution of curative treatments without a sustained commitment to research and development (R&D) undermines any disease control effort. The predictable emergence of drug resistance necessitates ongoing development of new treatments; however, both tuberculosis and malaria have seen serious R&D shortfalls. Global spending on TB R&D is at its lowest level since 2008 and has decreased for the past two years; investments from 2011 to 2015 amounted to just one-third of the spending recommended by the Global Plan to Stop TB.[37] Bedaquiline was the first anti-tuberculosis drug to be approved by the FDA in 40 years, and today there are only five tuberculosis drugs in trials that are often delayed for years.[38,39]

> Global spending on TB R&D is at its lowest level since 2008 and has decreased for the past two years.

Malaria treatment has thus far kept ahead of drug resistance, in part due to treatment guidelines that recommend combinations of chloroquine, sulfadoxine/pyrimethamine, mefloquine, and artemisinin that vary by each geographic region's resistance profile. However, the emergence of resistance to artemisinin in 2009 has raised concerns about conserving the ability to treat malaria and has emphasized the need for ongoing drug development.[32] Similarly, the development of more accurate RDTs for malaria is underfunded; by one estimate, current R&D investment in diagnostics amounts to less than a quarter of the estimated research need.[40]

Developing drugs for TB and malaria, two classic "diseases of poverty," is less lucrative for biotechnology and pharmaceutical companies than developing medicines and technologies for diseases affecting high-income countries. Although the market for diagnostic technologies and pharmaceutical products for TB and malaria is greater than 200 million individuals per year,

FIGURE 4: Continuum of care in sub-Saharan Africa overlaid over 90-90-90 targets



Source: UNAIDS Gap Report and WHO (http://www.who.int/hiv/pub/guidelines/arv2013/operational/retention/en/)

these individuals are predominantly in low- and middle-income countries with limited purchasing power. As such, the majority of R&D for both TB and malaria is financed by a small number of governments and philanthropic organizations.[41,42] In an effort to incentivize investments in TB and malaria R&D, advocates have proposed a variety of strategies including prizes, grants, advanced purchase commitments, "pay-as-you-go" strategies, and reform of international patent law.[43]

Lessons for HIV

HIV has benefited from a strong international financial commitment, receiving a disproportionately large share of donor funding for communicable diseases.[44] However, global spending on prevention

> Global spending on HIV prevention R&D has been flat for the past decade.

R&D has been flat for the past decade, driven primarily by declining investments by the United States and European governments.[45] Similarly, funding for HIV vaccine research has not increased in the last seven years and only half as many philanthropic organizations donated to vaccine R&D in 2014 as in 2010.[46] In the absence of a curative treatment, it is evident that a commitment to R&D funding must be maintained; moreover, the examples of TB and malaria indicate the importance of ongoing research even in the post-cure era.

HOW HIV IS DIFFERENT

In many respects, HIV is fundamentally distinct from other infectious diseases like TB and malaria, both to its benefit and disadvantage. For one, HIV disease control initiatives in some populations have been much more successful than any strategies for TB or malaria. For example, the aggressive effort to end vertical transmission of HIV has resulted in notable gains in preventing mother-to-child transmission and in diagnosing pregnant women. However, this history of "vertical" HIV programming, in which stand-alone facilities are established to target only one disease or population, has in effect created entire health systems that are insulated from national health programs—a structure that is not only unsustainable but also may contribute to the erosion of health

services throughout the country by draining human and other resources from the health system and distorting national planning policies away from improved coordination.[47,48,49] Integrating HIV programs with other health services is an important strategy to improve case finding and linkages to care.

Additionally, the HIV community has benefited from strong advocacy in the United States from the beginning of the epidemic, in contrast to TB or malaria. These efforts have resulted in greater awareness of HIV, dramatic increases in government funding, changes in the ways drugs are approved, and impacts on patient engagement with the government and healthcare system.[50] Advocacy has been particularly important for reducing stigma and supporting people living with HIV, a disease with much higher prevalence among "key populations" like men who have sex with men, commercial sex workers, transgender women, and people who inject drugs. This epidemiological distribution is distinct from that of TB and malaria, two diseases that are to a much lesser degree concentrated in subpopulations.

RECOMMENDATIONS

Despite the differences between these three diseases, three recommendations are taken from the examples of TB and malaria.

1. Increase support for implementation research to ensure engagement along care continuum

In HIV, as with TB and malaria, treating patients is dependent on identifying those who are HIV positive, initiating treatment, and ensuring adherence to therapy. The loss of patients at various points along the HIV treatment cascade is well described.[22,51] In sub-Saharan Africa, for example, only 45% of HIV-positive individuals know their status. Of those with known status, only 45% of treatment ineligible patients remain in pre-ART care. Of treatment eligible patients, only 86% begin antiretroviral treatment and only three-quarters of these remain in care after three years. Regardless of current treatment efficacy or any future development of a cure, patient outcomes cannot be improved unless diagnosis and retention in care are dramatically improved. Indeed, early vaccine prototypes are unlikely to be effective against all viral subtypes, necessitating both appropriate rollout of new treatments while continuing to engage all patients in care. This will require increasing support for implementation research to develop evidence-driven, patient-centered, and cost-effective strategies to improve patient outcomes.

In sub-Saharan Africa, for example, only 45% of HIV-positive individuals know their status.

2. Increase R&D funding aimed at developing new treatments and diagnostic technology

Drug resistance will continue to reduce the efficacy of current antiretroviral drugs and could also undermine the effectiveness of a future cure. Ongoing R&D for new pharmaceutical treatments is imperative. New POC testing technology must be developed to allow for accurate diagnosis immediately after infection. Affordable and rapid testing for drug resistance must accompany all diagnoses to minimize the emergence of treatment-resistant viral strains. Governments and funders must both increase funding for research and consider novel mechanisms to incentivize private sector drug development.

3. Sustain political commitment to HIV

Achieving an end of HIV will require a sustained political and financial commitment from donor governments, multilateral and philanthropic organizations, and pharmaceutical organizations. HIV programming must be integrated with existing national health programs to ensure their sustainability, particularly as donor governments under economic pressure shift their focus to other national priorities. Even after developing a cure, an enduring dedication to enabling and financing effective rollout, long-term implementation, and continuing research will remain vital.

CONCLUSION

There is no known cure for HIV, although current treatments can allow people living with HIV to lead normal and healthy lives. However, the HIV community must guard against prematurely declaring the "end of HIV." The lessons from TB and malaria are self-evident: The development of effective medical interventions—indeed, even cures—is only one step in the control of disease. Ending HIV will require a continuing commitment to research, case finding, and patient-centered, cost-effective, and sustainable programs.

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