From HIV to Tuberculosis and Back Again: A Tale of Activism in 2 Pandemics

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Tuberculosis (TB) and human immunodeficiency virus (HIV) infections are the deadliest chronic infections globally. Although each is deadly alone, they are deadlier together, with TB causing one-quarter of AIDS-related deaths and HIV infecting at least 15% of patients with TB worldwide. Historically, the 2 diseases were treated through specific, vertical programs. Strong activism and massive scientific investment have boosted the global response to AIDS, whereas TB has suffered from weak advocacy and anemic research funding. However, since 2004, there has been increasing collaboration and convergence between programs to control the 2 diseases, driven by the recognition that program cooperation leads to synergistic gains in strengthening responses to the 2 diseases and to health systems in general. Progress to date is incomplete, however, and countries must rededicate themselves to scaling up prevention and treatment programs for TB and HIV infection toward universal access, while pursuing accelerated research efforts to develop effective vaccines, better treatments, and cures for both diseases.

At first glance, the 2 greatest and most deadly infectious pandemics ravaging the world today could not be more different. Tuberculosis (TB) is older than history [1–3]. The first known human immunodeficiency virus (HIV) isolate from a human who died of AIDS dates back to 1959, from Kinshasa, Democratic Republic of the Congo, the year of my birth in San Francisco, California. *Mycobacterium tuberculosis* is a very slow growing bacillus; HIV is a very rapidly growing retrovirus. TB disease can be cured with 4 drugs in 6 months; HIV disease cannot be cured, but lifelong triple-drug therapy offers the hope of a normal lifespan.

A TB vaccine, bacille Calmette-Guérin, has been available since 1921; it is given to ~100 million infants each year and, according to a meta-analysis, may prevent ~30,000 cases of childhood meningitis and 12,000 cases of miliary TB during the first 5 years of life [4]. However, the vaccine does not protect against pulmonary TB or transmission of TB. To date, there is no clear path to a protective HIV vaccine.

TB is not diagnosed in the majority of cases; the most commonly used diagnostic test, sputum smear microscopy, detects <20% of all TB cases, with the lowest rates found among HIV-infected persons and children [5]. HIV infection, by contrast, can be diagnosed within 20 min with use of a rapid antibody test that costs <US $1, is 99% sensitive and specific [6], and can be used at the point of care or in the household.

M. tuberculosis infects ~2 billion persons worldwide. Ninety percent of infected persons never develop clinical disease; however, according to the latest estimates by the World Health Organization (WHO), 9.27 million persons developed clinically active TB in 2007, and 1.8 million died [7]. At least 11 million (and probably more than half) of the 33 million HIV-infected individuals worldwide are already infected with *M. tuberculosis.* In 2008, according to the latest estimates from the WHO, at least 1.4 million (15%) of the 9.4 million cases of active TB disease globally occurred among persons with HIV infection, and 500,000 (27%) of the 1.8 million TB-related deaths occurred among them [7]. In other words, TB was the cause of death for approximately one-quarter of persons infected with HIV who died in 2007, and one-third of the HIV-infected persons who developed clinical TB died—a far cry from the WHO's goal of an 85% cure rate.

HIV, a much newer pathogen than *M. tuberculosis,* currently infects >33 million persons worldwide. Virtually 100% of those infected will eventually develop full-blown AIDS if the infection remains untreated and will die if they do not receive combination antiretroviral therapy (ART). The United Nations Joint Programme on HIV/AIDS (UNAIDS) estimates that ~25

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million persons have died of AIDS in the 3 decades since the epidemic was first noted. According to UNAIDS, in 2007, there were 2.7 million new HIV infections and ~2 million persons died of AIDS [8].

There were some notable anniversaries during 2009. In 2009, I turned 50 years old, and in 2010, I will have been living with HIV infection for 25 years. Because the cause of AIDS, HIV, was discovered rapidly after the epidemic was detected and because of a combination of powerful advocacy and well-funded science, effective treatment became available by the mid-1990s. By 2009, there were >30 approved agents to treat HIV infection, from drug classes with 7 different modes of activity [9]. Thanks to this progress, I am alive and looking forward to several more decades of promoting access to needed treatment and life.

The 200th anniversary of Charles Darwin's birth occurred in 2009. He is a man in whose shadow anyone fighting or studying infectious diseases must work. At the end of his *Origin of Species,* published in 1859, he wrote,

> There is grandeur in this view of life, with its several powers, having been originally breathed into a few forms or into one; and that whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved. [10, p 490]

When Darwin wrote this, he was not thinking about malign life forms, such as HIV or the mycobacteria, which have destroyed the lives of billions of humans, but he was thinking about the other forms of life that he liked to study, such as barnacles, worms, orchids, pigeons, and, sometimes, humans. However, this view of life also has a dark side—looking at nature as a constant struggle among and within species; it is a grim, Hobbesian view of a war of all against all, of "nature, red in tooth and claw" [11, p 60]. Darwin's great book was published 100 years before I was born, but the laws of evolution and natural selection that he discovered still drive the struggle among us, the human race, and the 2 pandemic microbes. Currently, the pandemics are winning, and debates about the future of global public health and medical care and the merits of horizontal versus vertical health systems continue. Horizontal health systems aim to provide comprehensive primary care, but often at a limited price, and disease-specific, or vertical, systems may focus on a single set of interventions (eg, childhood vaccines) or a set of disease-specific initiatives (eg, HIV infection, TB, and malaria). Humanity must be nimble and smart and work with concerted and sustained attention to keep ahead of and ultimately defeat these 2 pandemics.

One lesson from the history of TB that is pertinent to the struggle against AIDS is that a spate of early victories in TB control—the discovery of the organism through and diagnosis with acid-fast sputum smear microscopy and culture, vaccination with bacille Calmette-Guérin (1921), and chemotherapy (1948–1986)—led to complacency and decades of neglect. During this period, the field of TB science became drained of financing, skipping a whole generation of scientists, and had to be arduously revived when global TB rates resurged in the 1990s. According to the WHO, more persons are living with TB disease than ever before [6].

With regard to HIV infection, the spate of early breakthroughs—the discovery of AIDS (1980), HIV infection (1983), enzyme-linked immunosorbent assay (1985), the first anti-HIV drug zidovudine (1986), quantitative viral RNA testing (1995), and combination ART (1996) and its widespread dissemination around the world from 2003 to present [12]—have neither reversed the epidemic, nor set the stage for its elimination. However, donors, public health figures, and high burden countries appear to be currently expressing doubts about their willingness to continue scale-up of prevention, treatment, and care programs for HIV infection. Therefore, despite all the progress with science and scale-up of treatment, more persons are infected with or die of HIV each year than benefit from currently available prevention or treatment interventions [12].

The TB and AIDS research and treatment fields are also very different from each other. The HIV research field has been well funded, providing young researchers with career opportunities. AIDS researchers and activists have eagerly embraced change and continue to add new tools, assuming that money is no object. The AIDS community can be bipolar, because it is accustomed to great breakthroughs, such as the HIV antibody test (1985), zidovudine (1987), protease inhibitors (1995), viral load testing (1995), highly active antiretroviral therapy (1996), and rapid oral or finger prick diagnostic tests (2004); thus, every step back, such as the recent negative results from the STEP HIV vaccine study [13], may send the entire field into a great, albeit temporary, depression, leading to calls for back-to-basics research [14–19].

TB, by contrast, lost more than a generation of researchers during the years of the great antibiotic bubble, when most experts in the resource-rich countries thought that the disease was vanquished in their countries and under control in the recently liberated resource-poor countries, which had fragile health care systems. During the past 40 years, TB research suffered from stunted growth, emotional deprivation, shrunken ambitions, and slight obsessive compulsive–like disorder, in which TB controllers engaged in repetitive behaviors, speaking an internal jargon not readily understand by others, using terms such as "DOTS coverage" (directly observed therapy, short-course), "70/85 targets" (70% case detection of new smear-positive cases and 85% treatment success by 2005), and "HRZE" (isoniazid, rifampicin, pyrazinamide, and ethambutol).

It was not until TB became associated with the HIV pandemic in New York City in 1989 that authorities began to respond in New York (where the multidrug-resistant TB epidemic was first detected) and

Washington, DC; Bethesda, MD; and Geneva (where public health policy is made). However, the methods that worked in New York City with political will—scaled-up case finding and DOTS, requiring billions of dollars and incredible technical oversight [20]—did not work in the rest of the world during the 1990s, because there was no worldwide comprehensive strategy for dealing with HIV infection. During that period, the head of the WHO Global Programme on AIDS was fired, global responsibility for HIV infection was removed from the WHO [21], and a new group, UNAIDS, was organized to coordinate a multisector response to the AIDS pandemic. Therefore, although the WHO was trying to scale up the fight against TB and rolled out DOTS programs (the 6–8 month curative first-line TB regimen, which became representative of the entire WHO-recommended TB control approach), it ran into an uncontrolled HIV pandemic ravaging the world, particularly sub-Saharan Africa. TB rates increased 5-fold in sub-Saharan Africa during the 1990s because of HIV infection, and the lack of careful systems of treatment and prophylaxis led to the emergence of multidrug-resistant TB (MDR-TB), the rate of which aggressively and exponentially increased in the Russian Federation and, later, in areas of sub-Saharan Africa with the highest burden of HIV infection [22, 23].

HIV treatment activism emerged in the 1980s in New York City, San Francisco, and Paris and later in Rio de Janeiro, Cape Town, Bangkok, and elsewhere through a passionately engaged civil society in the context of the accelerating local epidemics, and activists engaged with political forces in mature or newly emergent democracies to demand money, attention, rights, protection, science, prevention, and treatment. The leaders of these movements were often highly educated and sophisticated and able to command the attention of political elites through marches; public demonstrations; targeting of politicians, academics, or the media (so-called "zaps"); die-ins; or lawsuits, legislation, or media manipulation. Together, these methods constituted an emergent invention of science-informed, community-based treatment activism in the AIDS epidemic [24]. In the United States and in some other resource-rich countries, such as France, this activism created a virtuous cycle, in which after some initial skirmishing and culture clashes, scientists and activists worked together to secure the resources to sponsor the research that led to breakthroughs in diagnosis, prevention, and most dramatically, treatment.

To highlight this phenomenon, I will review a few of the episodes that marked the progress of AIDS treatment activism in the United States during the 1980s and the 1990s and helped to create a new paradigm for responses to epidemics by affected communities. The AIDS Coalition to Unleash Power (ACT UP) demonstrations at the US Food and Drug Administration (FDA) on 11 October 1988 and at the US National Institutes of Health (NIH) on 21 March 1990 led to several very important changes in the way that research was done, including expanded access to experimental drugs; the involvement of activists and HIV-infected persons in every protocol committee, research committee, peer review committee, and data safety monitoring board; and the formation of local, national, and drug company community advisory boards. This treatment activism led to the FDA allowing the use of surrogate markers to approve new drugs to treat HIV infection. Even inadequate early surrogate markers, such as changes in CD4 cell count, were the basis for the approval of all the nucleoside reverse-transcriptase inhibitors in the early 1990s. This, in turn, drew more drug companies into the field, because they could get a new drug approved in $\leqslant$4 years, decreasing the time from the expenditure of ~$800 million to develop a new drug and the realization of profit. Entrance of more companies into the field led to the development of more drugs that could be studied as combinations, ultimately resulting in clinically effective triple-therapy combinations. The addition of viral load measurement technology provided a reliable tool to monitor the efficacy of combination therapy, resulting in the spectacular emergence of highly active antiretroviral therapy in 1996 [25–28]. Within 2 years, rates of AIDS-related death decreased by 67% in the United States and other resource-rich nations [29]. Imagine if surrogate markers were available to measure anti-TB drug activity in real time, rather than requiring long-term trials of hundreds or thousands of patients with clinical end points of relapse, reinfection, or death.

If there was a single pivot around which HIV drug development was accelerated, it was that by which activists, scientists, regulators, and drug companies all communed and said, "We're going to start with inadequate, even mediocre, incomplete surrogate markers, and then we're going to develop better markers on the way," and that created the conditions that led to the combination ART revolution of 1996. It should be emphasized that the ART revolution was preceded by a very dark time in AIDS research—the so-called Berlin years (marking the nadir of AIDS treatment research findings at the 1993 Berlin AIDS Conference). The early years of combination therapy trials were littered with failed approaches; the rate of AIDS-related death increased, and the movement fragmented under the pressure of the high mortality rate. In 1992, when the Treatment Action Group separated from the Treatment and Data Committee of ACT UP/New York, the Treatment Action Group published a report showing that NIH AIDS research was uncoordinated, inefficient, and underfunded [30, 31]. There was a move back to basic science.

At that time, it was not yet clear whether HIV lay indolent in some limited reservoir in the body for $\geqslant$1 decade between acute infection and full-blown AIDS, because the tools for the precise detection and quantification of HIV in the body were still in development. Researchers did not know and could not find where HIV resided and replicated in the body. Despite

>125 years of TB research, there is still far too little information about its in vivo pathogenesis inside the human body.

Activists led a call for in vivo veritas and for activist involvement in basic science. For example, I underwent 3 lymph node biopsies, in 1992, 1996 (just before starting ART), and 1998 (after 18 months of viral suppression). Information about my first biopsy was published in a case series by Pantaleo et al [32] in 1993 (sample from a "32-year-old gay white man" [obviously, a long time ago]); testing of the biopsy specimen revealed that millions of copies of HIV resided in my lymph nodes during the asymptomatic phase of infection. At that time, my CD4 cell count was 660 cells/mm^4, and I was not yet receiving treatment. Therefore, information about HIV pathogenesis, viral dynamics, and reservoirs was learned by using new tools, such as viral load monitoring and tests that assessed how rapidly HIV replicated and where viral copies were located in the body.

Currently, what is needed in TB research is not just more guinea pigs and mouse and monkey studies. Studies involving humans who are willing to volunteer to undergo possibly dangerous tissue biopsies are needed to answer some of the questions that will not be resolved with ex vivo imaging technology, so that the location of *M. tuberculosis* in the body, the mechanisms of the organism, and the response of the immune system can be determined. This information cannot be obtained through mouse studies of bacille Calmette-Guérin vaccine, because these studies cannot demonstrate the in vivo pathogenesis of *M. tuberculosis* infection in the human host and cannot model the nuances of TB latency and progression.

Another result of back-to-basics HIV research was the studies involving long-term survivors that led to the discovery of the HIV coreceptors (CCR5 and CXCR4) and the development of the CCR5 receptor blockers as a new class of drug approved for HIV treatment and also as potential topical microbicides and pre-exposure prophylaxis [33]. In contrast, the understanding of TB genetics is in its infancy, compared with that of HIV. There are 6 complete *M. tuberculosis* genome sequences, compared with thousands of complete HIV sequences at the Los Alamos database, that are accessible to scientists around the world. A comprehensive global database of TB drug resistance–associated mutations does not exist. Knowledge about these mutations is going to be essential for control of MDR-TB, and there is still no plan to set up a database. A tissue bank does not exist that has samples (blood, sputum, and urine from well-characterized individuals) adequate to develop a TB point-of-care dipstick diagnostic test (S. Laal, personal communication). These are examples of the many resources available for AIDS research that do not exist for TB research, and these resources will be needed if the disease is ever going to be eliminated.

During the 1990s, activists also focused on promoting research on drugs to prevent and treat the major HIV-related opportunistic infections. By the late 1990s, most of these opportunistic infections (eg, *Pneumocystis* pneumonia, disseminated cytomegalovirus disease, toxoplasmosis, fungal infections, Kaposi sarcoma, and non-Hodgkin lymphoma) were controllable. By then, combination ART rendered many of them problems of the past in developed countries. Concerns then switched to the management of antiretroviral drug toxicity, structured treatment interruptions (to reduce drug costs and toxicities), and timing of initiation of ART (a question that remains unanswered).

The Treatment Action Group published the last of a series of reports that focused on opportunistic infections in 1998. At the Bridging the Gap AIDS Conference, Dr. Gerald Friedland of Yale said to me, "You left out one of the biggest—maybe even the biggest—opportunistic infection." I said, "It's too big for us to deal with here; we need to dig more deeply into it before we can become effective advocates against it." That infection was TB, which, as we all know, is not really just an opportunistic infection; it is a coinfection with its own deadly and very lengthy course.

TB came back to haunt activists as soon as US-based activists began to work with the Treatment Action Campaign in South Africa and with the other international treatment access activists, starting at the International AIDS Conference in Durban in 2000. This marked the most important shift in the worldwide treatment activist movement since 1996 and the beginning of the global movement for ART access for all persons infected with HIV. This was succeeded, in rapid turn, by the production of Triomune (a fixed-dose combination of nevirapine, lamivudine, and stavudine; Cipla Pharmaceuticals), which decreased HIV triple therapy costs from $10,000 per person per year to ~$100 per person per year (decreasing HIV drug costs by almost 99%).

Soon after this movement, the Global Fund to Fight AIDS, Tuberculosis, and Malaria (2002), the US President's Emergency Program for AIDS Relief (PEPFAR; 2003), the WHO-led movement to treat 3 million persons with ART by the end of 2005 ("3 × 5"), and the later United Nations–endorsed goal of universal access by 2010 were developed, leading to the unprecedented fact that 4 million persons in resource-poor settings are now receiving combination ART [34]. In the course of advocacy for this global ART scale-up, the expanding global TB pandemic became a major impediment to improved lives for persons infected with HIV around the world. TB rose to become a top priority for the Treatment Action Group's work.

Our HIV treatment activist group started its TB and HIV workshops at the International Union Against Tuberculosis and Lung Diseases Conference in Montreal in November 2002, and it was very lonely work. The only other activists of note who were clearly working on TB and HIV infection that year were Winstone Zulu of Zambia and Ezio Távora dos Santos Filho of Brazil.

Unlike the AIDS field when activists had to "seize control of the FDA" and

"storm the NIH," the TB field did not yield to storming, because the culture was so different from that of the HIV field from which I came. Indeed, the discovery of activists and their incorporation in the Global Stop TB Partnership has been unprecedented by the ease with which it was accomplished and by the welcoming embrace with which we were met by the Partnership from the first time that we began to participate. I believe that, by 2000, the Global Stop TB Partnership recognized that they needed to summon some activism to more effectively achieve their mission, and they looked to the AIDS movement with hopes that they could mount such activism themselves or at least borrow some of our intensity and momentum. In September 2003, I was asked back to Switzerland to join a small group of experts who met over 3 days to draft the outline of what became the WHO Recommended TB/HIV Collaborative Activities, published by the WHO in 2004 [35] and currently being implemented worldwide in both TB and HIV programs.

The turning point in the recognition of the inextricable connections between the TB and HIV pandemics occurred in 2004. The Treatment Action Group received its first grant from the Bill & Melinda Gates Foundation to support its TB and HIV Project in July 2004 at the Bangkok AIDS Conference, where the highlight was Nelson Mandela's speech on how "we can't fight AIDS unless we do much more to fight TB as well" [36].

In September, supported by the TB/HIV Working Group of the Stop TB Partnership, Haileyesus Getahun of the WHO and I invited a corps of determined, dedicated, and fierce activists to the TB/HIV Working Group Meeting in Addis Ababa, Ethiopia. Eric Goemaere (Médecins sans Frontières/Khayelitsha Site B) called for an all-out assault on DOTS as a strategy ineffective in a high HIV epidemic situation. Zackie Achmat (Treatment Action Campaign) counseled for intelligent integration and transformation from within (ie, build on DOTS). WHO doctors from the HIV department attacked their colleagues in the Stop TB Partnership and charged that the whole DOTS approach was obscurantist, out of date, paternalistic, and ineffective. The TB establishment—never strong, but always solid—began to fracture under the strain of internal doubt, external evidence, and the unrestrained ambitions of the HIV scale-up movement toward 3 × 5 and Universal Access.

In November 2005, the new TB and HIV activists at the Stop TB Partnership meetings in Versailles and Paris called for "a revolution in TB diagnosis, prevention, treatment and care" [37]. We demanded from Marcos Espinal, head of the Stop TB Partnership, that activists be placed in every body of the Stop TB Partnership, including its Working Groups and Coordinating Board. Much to our surprise, he immediately agreed to do so.

In 2005, we demanded that UNAIDS hire an expert on TB and HIV infection and elevate the diseases among their priorities, and we were impressed when they immediately agreed to do so. The new UNAIDS Executive Director Michel Sidibé has described decreasing the number of persons with HIV infection who die of TB as one of his top priorities [38]. In addition, in 2005, we demanded that the "Global Plan to Stop TB: 2006–2015" include achievement of universal access targets for the HIV and TB collaborative activities by 2010, in line with HIV universal access; this was also accepted [39].

In 2007, we demanded that the Stop TB Partnership rewrite its plan and that the WHO revise its guidelines to rapidly expand resources to control MDR-TB after the outbreak of extensively drug-resistant TB in Tugela Ferry, KwaZulu-Natal, South Africa. They immediately did so [40].

The situation has been different at the country level. Many national TB program managers did not want to meet the activists, no matter how well trained. The national TB program managers did not talk to the AIDS program managers. Activists were not welcome. The tools used by many national programs to control TB, particularly smear microscopy, did not work well for persons infected with HIV; thus, dually infected persons were considered to be "problematic."

We initially thought that TB research was in good shape, but closer scrutiny found this was not the case. Thus, we decided to follow the money. We discovered that for $1 spent on HIV research, $.05 was spent on TB research [41]. Although HIV drugs make up a market of ⩾$8 billion per year, TB drugs make up a market of <$600 million per year. No new class of drugs to treat TB had been approved since the 1960s. TB was the ultimate neglected tropical disease.

The annual number of deaths from TB and HIV infection are very similar, but the market sizes are totally disproportionate, as are the sizes of the research budgets. Therefore, we undertook the work of renewal of all research for TB, not just research for TB and HIV coinfection. At the time, there were virtually no TB monoinfection activists doing this work, and most of the other AIDS activists were busy with other aspects of HIV research.

TB activists were assailed from new and unexpected quarters. There was talk that HIV research was too lavishly funded and that the response to TB, which was finally getting attention, was tarred with the same brush of being a vertical program that could undermine health systems, which were, somehow, wonderful before the scale-up of DOTS in the 1990s and the scale-up of HIV treatment in the 2000s.

Some of these concerns were familiar. Structural readjustments and the Washington consensus and sector-wide approaches in the 1980s led to the dismantlement of TB programs in countries, such as Tanzania and Zambia, just as HIV infection was becoming more prevalent [42]. In that decade, donors tied grants and loans to countries only if they cut their public sector spending, including health spending. This led to the dismantlement of TB programs in many countries [43].

Currently, continued momentum toward universal access to prevention, treat-

ment, and care for HIV infection, TB, and malaria is threatened by a political backlash and an economic crisis. The US Government has spent >$787 billion on rescuing its own economy, but international development and health assistance for the period 2009–2010 have been essentially flat.

The Republic of Uganda is running out of funds to pay for ART, but President Yoweri Museveni just spent $48 million on a new private jet [44]. Despite Zimbabwe's raging cholera epidemic, chronically high rates of HIV and TB coinfection, and politically induced violence and routine abuses of human rights, President Robert Mugabe's 85th birthday was marked with a US $250,000 celebration [45].

President Obama's budget for 2010 pits disease versus disease; the NIH budget, which is virtually flatlined [46], fails to fully fund PEPFAR programs at the authorized level of $9.6 billion and uses ~$700 million from the PEPFAR budget for maternal and child health programs [47]. There is absolutely no question that much more funding is urgently needed for maternal and child health programs, but there is no reason to pit dying, low-income individuals against each other for pieces of an inadequate pie [48], when the obvious solution is to continue scaling up both sets of urgently necessary global health initiatives.

One of my proudest anniversaries in 2009 was to note how much progress has been made in the 5 years since the publication of the collaborative TB and HIV activities document that I helped to write with Haileyesus Getahun and others [35]. The most emblematic features of health system strengthening are the TB and HIV collaborative activities, the global laboratory initiative, the strengthening of MDR-TB treatment, the move to universal access to TB culture and drug-susceptibility testing, and the ongoing roll-out of rapid culture and line probe tests for drug-resistant TB while we wait for the elusive TB point-of-care dipstick.

Workers in the HIV and TB field are at the vanguard of health systems strengthening. Do not let global health or national leaders describe the work as being "vertical" or "undermining health systems." These efforts are at the vanguard of the health system strengthening, which will be essential to achieve universal access and primary health care for all persons.

The 5th International AIDS Society Conference on HIV Pathogenesis, Prevention, and Treatment, held in Cape Town, South Africa, in July 2009, demonstrated how much unprecedented progress has been made in Africa and elsewhere since the Durban AIDS Conference in 2000. One paper from Gugulethu (a township outside Cape Town) showed that, from 2003 through 2007, during the scale-up of ART, the incidence of TB decreased by almost 80% in only 4 years. This was the first demonstration that ART scale-up could have a population-level affect, reducing TB levels to those last seen in 1990 [49].

Now is the time to redouble our activism to overcome HIV infection and TB. It is time to unite and join in a more general struggle for primary and comprehensive health care for all persons, including prevention, treatment, and care for HIV infection, TB, and malaria, and to redouble research efforts to discover better tools and drugs—most urgently, a point-of-care TB diagnostic, cures for drug-resistant TB and HIV infection, and safe and effective vaccines for TB and HIV infection.

Finally, the emerging science of optimizing health care delivery is essential to understanding how to sustain and continue to scale up the necessary responses to HIV infection, TB, and other global infectious disease threats, or we will succumb, once again, to the microbes, which continue to outpace humanity's best efforts. Scientists and activists will have to form even stronger and more durable alliances, mobilize resources, and convince the leaders of today and tomorrow that we need to work together to save lives, avoid unnecessary deaths, and make these pandemics diseases of history and not scourges of the future [50].

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References

1. Salo WL, Aufderheide AC, Buikstra J, Holcomb TA. Identification of *Mycobacterium tuberculosis* DNA in a pre-Columbian Peruvian mummy. Proc Natl Acad Sci U S A **1994**; 91(6):2091–2094.
2. Nerlich AG, Haas CJ, Zink A, Szeimies U, Hagedorn HG. Molecular evidence for tuberculosis in an ancient Egyptian mummy. Lancet **1997**; 349(9067):1760–1763.
3. Donoghue HD, Spigelman M, Greenblatt CL, et al. Tuberculosis: from prehistory to Robert Koch, as revealed by ancient DNA. Lancet Infect Dis **2004**; 4(9):584–592.
4. Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. Lancet **2006**; 367(9517):1173–1180.
5. World Health Organization (WHO) Special Programme for Research and Training in Tropical Diseases (TDR), Foundation for Innovative New Diagnostics (FIND). Diagnosis for tuberculosis: global demand and market potential. Geneva: World Health Organization, **2006**.
6. U.S. Centers for Disease Control. FDA-approved rapid HIV antibody screening tests. 4 February **2008**. http://www.cdc.gov/hiv/topics/testing/rapid/rt-comparison.htm. Accessed 4 October 2009.
7. World Health Organization. Global tuberculosis control: a short update to the 2009 report. Geneva: World Health Organization, **2009**. http://whqlibdoc.who.int/publications/2009/9789241598866_eng.pdf. Accessed 26 March 2010.
8. UNAIDS. 2008 Report on the global AIDS epidemic. July **2008**. http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/2008_Global_report.asp. Accessed 28 August 2009.
9. US Food and Drug Administration. Antiretroviral drugs used in the treatment of HIV infection. http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm076940.htm. Accessed 28 August 2009.

10. Darwin C. On the origin of species by means of natural selection, or the preservation of favoured races in the struggle for life. London: John Murray, **1859**. http://darwin-online.org.uk/content/frameset?itemID=F373&viewtype=side&pageseq=1. Accessed 28 August 2009.
11. Lord Tennyson A. In Memoriam A.H.H. 1849. Canto 56. New York, Blanche McManus Mansfiled, **1900**.
12. World Health Organization. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector: progress report 2009, p 54. Geneva: World Health Organization, **2009**. http://www.who.int/hiv/pub/tuapr_2009_en.pdf. Accessed 26 March 2010.
13. Buchbinder SP, Mehrotra DV, Duerr A, et al.; Step Study Protocol Team. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. Lancet **2008**; 372(9653):1881–1893.
14. Fields BN. AIDS: time to turn to basic science. Nature **1994**; 369(6476):95–96.
15. Cohen J. Retrovirus meeting: back-to-basics push as HIV prevention struggles. Science **2008**; 319(5865):888.
16. Senior K. Back to basics for HIV vaccine research. Lancet Infect Dis **2008**; 8(8):467.
17. Broliden K, Haase AT, Ahuja SK, Shearer GM, Andersson J. Back to basics: mucosal immunity and novel HIV vaccine concepts. J Intern Med **2009**; 265(1):5–17.
18. Back to basics [editorial]. Nature Med **2009**; 15(8):821.
19. Gonsalves G. Basic research on HIV infection: a report from the front. Treatment Action Group (TAG). In: Program ans abstracts of the 10th International Conference on AIDS (Yokohama, Japan). August **1994**. Abstract 227A.
20. Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City—turning the tide. N Engl J Med **1995**; 333(4): 229–233.
21. Merson MH, O'Malley J, Serwadda D, Apisuk C. The history and challenge of HIV prevention. Lancet **2008**; 372(9637):475–488.
22. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet **2006**; 368(9547):1575–1580.
23. Abdool Karim SS, Churchyard GJ, Abdool Karim Q, Lawn SD. Health in South Africa 3: HIV infection and tuberculosis: an urgent need to escalate the public health response. Lancet **2009**; 374:921–333.
24. Achmat Z. Science and social justice: the lessons of HIV/AIDS activism in the struggle to eradicate tuberculosis. Int J Tuberc Lung Dis **2006**; 10(12):1312–1317.
25. Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature **1995**; 373(6510):123–126.
26. Saag MS, Holodniy M, Kuritzkes DR, et al. HIV viral load markers in clinical practice. Nature Med **1996**; 2:625–629.
27. Gulick RM, Mellors JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. N Engl J Med **1997**; 337(11):734–739.
28. Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. The Advanced HIV Disease Ritonavir Study Group. Lancet **1998**; 351(9102):543–549.
29. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med **1998**; 338(13): 853–860.
30. Gonsalves G, Harrington M. AIDS research at the NIH: a critical review. Treatment Action Group (TAG). In: Program and abstracts of the VIII International Conference on AIDS (Amsterdam). 20 July 1992.
31. Harrington M, Gonsalves GS. AIDS research at the National Institutes of Health: a critical review revisited—ten years of advocacy for NIH reform. Int Conf AIDS 2002. Abstract TuPeE5075. http://gateway.nlm.nih.gov/MeetingAbstracts/ma?f=102259289.html. Accessed 28 August 2009.
32. Pantaleo G, Graziosi C, Demarest JF, et al. HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. Nature **1993**; 362(6418):355–358.
33. Wood A, Armour D. The discovery of the CCR5 receptor antagonist, UK-427,857, a new agent for the treatment of HIV infection and AIDS. Prog Med Chem **2005**; 43:239–271.
34. UNAIDS. HIV treatment data update—July 2009. http://www.unaids.org/en/KnowledgeCentre/Resources/FeatureStories/archive/2009/20090723_AIDS_treatment_Data_UPD_2009.asp. Accessed 28 August 2009.
35. World Health Organization. Interim policy on collaborative TB/HIV activities. Geneva: World Health Organization, 2004. http://www.who.int/tb/publications/tbhiv_interim_policy/en/. Accessed 28 August 2009.
36. Check E. Mandela launches fight against HIV and TB: $100 million is to go to projects in poor countries. Nature News Media 15 July 2004. http://www.nature.com/news/2004/040712/full/news040712-15.html. Accessed 7 Aoril 2010.
37. Treatment Action Group. Towards a revolution in tuberculosis (TB) prevention, care and treatment: statement of individuals from communities affected by tuberculosis (TB). New York: Treatment Action Group, 2005. http://www.treatmentactiongroup.org/publication.aspx?id=3556&terms=revolution. Accessed 26 March 2010.
38. Sidibé M. Letter to Partners. 10 February 2009. http://www.unaids.org/en/AboutUNAIDS/Leadership/EXD/Partner-letter/20090210_page1.asp. Accessed 28 August 2009.
39. Stop TB Partnership. The Global Plan to Stop TB: 2006–2015. Geneva: World Health Organization, **2006**.
40. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008. Geneva: World Health Organization, **2008**. http://www.who.int/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html. Accessed 28 August 2009.
41. Feuer C. Tuberculosis research and development: a critical analysis of funding trends, 2005–2006: an update. Treatment Action Group. New York, July 2008. http://www.treatmentactiongroup.org/publication.aspx?id=2486. Accessed 28 August 2009.
42. Agarwal N. Tuberculosis research and development: a critical analysis of funding trends, 2005–2007: an update. Treatment Action Group. New York, May 2009. http://www.treatmentactiongroup.org/publication.aspx?id=3058. Accessed 28 August 2009.
43. Bosman MC. Health sector reform and tuberculosis control: the case of Zambia. Int J Tuberc Lung Dis **2000**; 4(7):606–614.
44. Namutebi J. Uganda: MPs approve new jet for Museveni. New Vision, Kampala, 18 December 2007. http://allafrica.com/stories/200712190006.html;. Accessed 28 August 2009.
45. Pretty Ncube. Mugabe celebrates his 85th birthday in Chinhoyi. Harare Tribune. 28 February 2009. Zimbabwe Human Rights NGO forum. Political Violence REport: June 2009. ZimOnline. http://www.zimonline.co.za/Article.aspx?Articleid=5026. Accessed 7 April 2010.
46. Guterman L. Flat-lined: how flat NIH funding undermines research on HIV, TB and viral hepatitis. Treatment Action Group. New York, **2009**. http://www.treatmentactiongroup.org/publication.aspx?id=3052. Accessed 28 August 2009.
47. Treatment Action Group. Obama's global, domestic, HIV research budgets leave a trail of shredded promises in their wake. New York, 7 May **2009**. http://www.treatmentactiongroup.org/base.aspx?id=3030&terms=Obama. Accessed 28 August 2009.
48. Denny CC, Emanuel EJ. US health aid beyond PEPFAR: the mother & child campaign. JAMA **2008**; 300(17):2048–2051.
49. Middelkoop K, Wood R, Myer L, Whitelaw A, Kaplan G, McIntyire J, Bekker L-G. Widespread ART is associated with decline in TB prevalence. In: Program ans abstracts of the 5th IAS Conference on HIV Pathogenesis, Prevention, and Treatment (Cape Town, South Africa). 19–22 July 2009. Abstract WELBB105.
50. Geffen N. Beyond HAART: scientists and activists need to work together. Lancet **2009**; 374: 860–861.