

# **From HIV to TB and back again: A tale of activism in two pandemics**

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Keynote address

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*Remarks as written but not as delivered*

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At first glance, the two greatest and most deadly infectious pandemics ravaging the world today could not be more different.

TB, as Tony Fauci noted yesterday, is “older than history”; the first known sample of HIV from a human who died of AIDS dates back to 1959, in Kinshasa, DRC, the year I was born in San Francisco, California.

- *MTB* is a very slow growing bacillus; HIV is a very fast growing retrovirus.
- TB disease can be cured with four drugs in six months; HIV disease cannot be cured at all, but lifelong triple therapy offers the hope of a normal lifespan.
- TB has a vaccine which saves the lives of 40,000 babies each year, though 100 million receive it, and it does not protect against adolescent or adult pulmonary TB and onward transmission; HIV does not induce protective immunity and there is as yet no clear path to any kind of vaccine.
- TB is not diagnosed at all in a perhaps a majority of cases, and the most commonly available test, sputum smear microscopy, detects just 19% of annual TB cases; HIV can be diagnosed within 15 minutes with a rapid antibody dipstick test which costs less than \$1, is 99% sensitive and specific, and can be given at point of care or even in the household.
- TB infects ~2 billion people worldwide. 90% of those infected never develop disease, but 9 million people develop TB disease each year, and 2.8 million die of it.
- HIV infects ~33 million people worldwide. Virtually 100% of those infected will eventually develop full-blown AIDS and, if untreated, die. Each year 3 million new HIV infections occur, one million new people are placed on antiretroviral therapy (ART), and 2.8 million people die from AIDS.

- TB infects over 11 million of the world's 33 million people with HIV, causes TB disease in 1.5 million HIV+ people each year, and kills about 500,000 of them, about 20% of all TB deaths.

I have been thinking a lot of anniversaries recently. This year, in November, I will turn 50 – an age I once thought I would never reach.

Thanks to the fruit of science and treatment activism I am alive and looking forward to several more decades of activism and fun.

Next year it will be 25 years since I became infected with HIV.

Fourteen years ago I started treatment with combination of a protease inhibitor and two NRTIs – a mixture of drug classes I'm still on, despite several complete regimen switches due to the development of newer drugs which are safer, equally potent, and much easier to take.

Another anniversary much on my mind has been the 200<sup>th</sup> anniversary of the birth of Charles Darwin, a man in whose shadow anyone fighting or studying infectious diseases must work. At the end of his *Origin of Species* – published 150 years ago in 1859 – he wrote of the “grandeur of this view of life” and how, due to natural selection and survival of the fittest, and that “from so simple a beginning [of life] endless forms most beautiful and most wonderful have been evolved.”

But this view of life also looks at nature as one constant struggle between and within species, and is a dark, almost Hobbesian view of a war of all against all, of nature “red in tooth and claw”.

And I've been thinking of Darwin because his great book came out 100 years before I was born, and because his laws of evolution and natural selection are driving the struggle among humankind and the two pandemics of HIV and TB.

Humanity must be nimble, smart, and work with concerted and sustained attention if we are to outwit, keep ahead of, and ultimately defeat these two pandemics. So far, we can see from the history of TB that early victory may be the preface to decades of neglect and a resurgence during which we are still living.

More people are dying from TB each year today than ever before (partly because the human population is so much bigger).

The same is true of HIV, despite some recent and heroic advances.

Now I am supposed to tell you about some of the supposed lessons of HIV for TB, and perhaps vice versa.

As well as the diseases themselves and their interventions being so different in age and efficacy, the two cultures which have arisen around these diseases are very different as well.

HIV research and advocacy tends to live in a big, somewhat megalomaniacal worldview, with a strong element of bipolar disorder.

We have become accustomed to great breakthroughs, such as HAART, and so every setback, such as the STEP HIV vaccine study, sends the field into a great albeit temporary depression, and everyone vows to go “back to basics” in research.

TB by contrast, again as Tony Fauci noted yesterday, lost more than a generation of research during the years of the great antibiotic bubble when most experts in the rich world felt the disease was vanquished in the north and quietly under control in the south.

As befits an undernourished being, the TB field suffers from stunted growth, emotional deprivation, shrunken ambitions, and a bit of obsessive-compulsive disorder in which TB controllers march around engaging in repetitive behavior and strange internal jargon such as “DOTS coverage”, “70/85 targets”, “HRZE”, or “we have the tools to control TB.”

It was not until TB crashed right into the HIV pandemic in 1989 in New York City that authorities began to respond in New York City, in Washington, in Bethesda, or in Geneva. But what worked in NYC, with political will, billions of dollars, and incredible technical oversight, did not work in the rest of the world during the 1990s, because the world was ignoring HIV and there was no global campaign against the disease. You have seen how TB rates rose fivefold in Sub-Saharan Africa during the 1990s, completely due to HIV, and how MDR-TB embarked upon aggressive and exponential growth in the former Soviet States and now around the world.

At the time of the MDR-TB outbreak in NYC, we were not even focused on TB. It seemed that the public health authorities had it well in hand. In fact we were much more focused on another mycobacterial disease, MAC, and were at that time struggling with ACTG investigators like Connie Benson and Dick Chaisson over the optimal design of a MAC prophylaxis trial involving clarithromycin and possibly rifabutin.

Let me spend a couple of minutes describing the conditions out of which HIV treatment activism emerged in the 1980s in NYC and San Francisco, Paris, and later also in Rio de Janeiro, Cape Town, Bangkok and elsewhere. In all these cases a passionately engaged civil society emerged early in the context of the developing local epidemic and engaged with political forces in mature or newly emergent democracies to demand money, attention, rights, protection, science, prevention, and treatment. The leadership of these movements was often highly educated, sophisticated, and able to command the attention of political elites, whether by marches, zaps, die-ins or by lawsuits, legislation, media manipulation, or an emerging invention of the epidemic, science-informed, community-based treatment activism.

In the United States and in some other rich countries such as France, this created a virtuous cycle, where after some initial skirmishing and culture clashes, scientists and activists worked together to secure the resources to sponsor the research which led to breakthroughs in diagnosis, prevention, and most dramatically, treatment.

Let me briefly talk about a few of the episodes which marked the progress of ATA in the US during the 80s and the 90s.

11 Oct 88 “Seize Control of the FDA” which led to expanded access (parallel track) to experimental drugs and to over 35,000 people with AIDS failing AZT to receive ddI (didanosine) between 1989-91 when the drug was approved.

21 May 90 “Storm the NIH” which led the NIAID (Fauci) to order the ACTG and all other AIDS CT networks to include community representatives on all ACTG protocol committees, protocol review teams, Data Safety Monitoring Boards, and to the formation of local and national and drug company Community Advisory Boards.

Following up on these two accomplishments the FDA began to allow in 1991 the approval of ARVs based on changes in surrogate markers, first on the immune system marker CD4 and later on the changes in HIV RNA (viral load).

This made the process of developing and getting a new drug approved much faster and much cheaper. This in turn drew more drug companies into AIDS research. This led to an explosion of new drugs in the mid 1990s and along with the development of quantitative viral load, to the HAART revolution of 1996. AIDS death rates plummeted by 67% in the US + other rich nations.

Imagine if we had surrogate markers which could measure ATT drug efficacy in real time rather than requiring us to rely on LT trials of 00s or 000s of people with clinical endpoints of relapse, reinfection, or death as the only endpoints.

But the HAART breakthrough was preceded by a very dark time in AIDS research. The early years of combo therapy trials were littered with failed approaches. The death count relentlessly climbed. In 1992 we published a report showing that NIH AIDS research was uncoordinated, inefficient, and underfunded. This led to changes put into law by Clinton in 1993 ...

There was a move to “back to basic science”, which TAG in our first year enthusiastically supported (along with wholesale reform of NIH structures).

At that time it was still thought that HIV lay indolent for a decade or more between acute infection and frank AIDS. Researchers did not know and could not find where HIV resided and replicated in the body. We led a call for “in vivo veritas” and for activist involvement in basic science. An example – I underwent three lymph node biopsies in 1992, 96, and 98. The first was published in a case series by Fauci in *Nature* in 1993 (sample from a “32 year old gay white man”) ... showing that HIV resided in the millions in the lymph nodes of infected individuals during the asymptomatic phase.

In fact HIV was never silent, replicating wildly throughout infection, under greater or lesser immune control. This clarified pathogenesis and led to better understanding of viral dynamic and reservoirs.

Imagine if we could understand the in vivo latency of MTB among infected humans, and witness it change, rest, and grow in real time. The technology is emerging to do this, but far too little scientific resources and attention are being given to this vital topic. And human volunteers will need to be willing to undergo possibly dangerous tissue biopsies to answer some of these questions which will not be resolved by ex vivo imaging technology.

Another result of “back to basics” was studies of LTS of HIV infection, which led in the mid 90s to the discovery of HIV coreceptors, of some genetic defects which protected individuals (CCR5delta negative) from HIV infection, and led in a decade to a new class of ARVs, the CCR5 receptor blockers, of which one is now approved and other under study as potential microbicides, PrEP, or ARVs.

Again TB genetics is in its infancy compared with HIV. We have 6 complete MTB sequences. We have 000s of complete HIV sequences. We do not even have a comprehensive global DB of TB DR associated mutations – knowledge which will be essential to bring MDRTB under control.

Throughout the 90s we also focused on pushing research on drugs to prevent and treat the major OI's. By the late 90s most – PCP, CMV, toxo, fungal infections, even KS and NHL – were controllable. By then HAART rendered much of them a concern of the past, in the rich world. Concerns now switched to ARV toxicity, structured treatment interruptions, and when to start (WTS) a question we are still waiting for answers about.

But the most important switch which occurred after 1996 was the worldwide movement for ARV access for all, beginning with the Durban conference in 2000; the production by Cipla of Triomune in 2001 which brought HIV drug combo costs down by 99%, the foundation of the GFATM and establishment of PEPFAR and the WHO led movement for 3x5 and later universal access, leading to the now unprecedented fact that 4M people around the world in RPS are receiving ART.

In the course of advocacy for this scale up we ran smack into the expanding global TB pandemic.

TAG held the first TB/HIV workshop for activists at the IUATLD world conference on lung health in Montreal during November 2002. It was lonely work. The only other activists of note interested in TB/HIV that year were Winstone Zulu of Zambia and Ezio Santos Filho of Brazil.

From that year on, we began holding annual TB/HIV activist workshops at the Union conferences. I should note that from the very first workshop the Union has generously waived registration fees for TB and TB/HIV activists, enabling many more of us to attend and participate in these annual meetings.

Nevertheless I must note that we early TB/HIV activists recoiled from the formaldehyde-enshrouded world of TB science in the early part of this decade, so different from the vibrant and ever forward thrusting vitality of HIV science.

I took a further tentative step forward in the world of TB science and policy when I attended the 3<sup>rd</sup> meeting of the TB/HIV Working Group of the Stop TB Partnership, which was held in Montreux, Switzerland, in June 2003. Not a single other activist, infected or affected community person was to be seen despite the presence of several hundred researchers and implementers. Despite being new to this milieu, I stood up to denounce the lack of activist or community involvement in the Stop TB Partnership and demanded that this oversight be quickly addressed. At lunch, a young Ethiopian physician recently recruited by the Stop TB Department of the World Health Organization (WHO), Haileyesus Getahun introduced himself to me and described the work he had done with TB patients in rural northern Ethiopia in the late 1990s, reorganizing the care and treatment program to form TB clubs of people with TB from the same geographic area so that they could provide each other with treatment and adherence support. Treatment success rates rose from 45% to over 80% and the TB clubs expanded when former patients now cured of TB asked to stay involved by participating in community based case finding and support. This work showed that even at a grassroots level in a very poor and dispersed rural community in a resource-poor setting, affected communities and patient support groups could be mobilized against the disease.

In September 2003 I was asked back to Switzerland to join a small group of experts who met over three days to draft the outline of what became the WHO recommended TB/HIV collaborative activities, published by WHO in 2004 and currently being implemented all over the world within both TB and HIV programs.

2004 was the turning point. Supported by the TB/HIV Working Group of the Stop TB Partnership, Haileyesus Getahun of WHO and I invited a corps of determined, dedicated, and fierce activists to the TBHIV meeting in Addis. Eric Goemaere (MSF) called for an all-out assault on DOTS as a strategy ineffective in a high HIV epidemic situation. Zackie Achmat counseled for intelligent integration and transformation from within (build on DOTS). Charlie Gilks (WHO HIV Dept) savagely attacked the whole DOTS approach for being 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 of obvious inadequacy, and the unrestrained ambitions of the HIV scale up movement towards 3x5 + Universal Access. Mario Raviglione has played a progressive leadership to evolve the DOTS Strategy to the Stop TB Strategy.

In July 2004 at Bangkok with Nelson Mandela on the rostrum we received our first Gates grant to build a more sustained effort.

In November 2004 the new TBHIV activists in Versailles and Paris called for “a revolution in TB diagnosis, prevention, treatment and care.

We demanded from Marcos Espinal, head of the Stop TB Partnership, that activists be placed on every body of the STBP. Much to our shock, he immediately agreed to do so.

In 2005 we demanded that UNAIDS hire an expert on TBHIV and elevate it among their priorities, and much to our shock they immediately agreed to do so.

Also in 2005 we demanded that GPSTB include achievement of UA targets for MTB by 2010 in line with UA for HIV; this too was accepted.

In 2007 we demanded that STB rewrite its MDR plan after the Tugela Ferry outbreak; they immediately did so.

Where was the need for demonstrations? It appeared that at the global level the STBP was most welcoming of activism.

But the situation was much worse at country level. NTP and NACP managers did not collaborate; activists were not welcome at NTPs, and the tools in use did not work in people with HIV.

We had to get more involved in research. As we did 20y earlier with HIV, we followed the money. We found that for every dollar spent on HIV R&D, five cents are spent on TB. While HIV drugs make up a market of over \$8B /y ear, TB drugs make up a market of less than \$600M. No new class of drugs had been approved since the 1960s. You know the story.

So we had to undertake the work of renewal of ALL TB R&D, not just TBHIV R&D. And there were still far too few activists working in the field (many others are busy with other aspects of HIV).

Now we are assailed from new and unexpected quarters. There is talk that HIV is too "lavishly" funded, and the response to TB – finally getting attention – is tarred with the same brush of being a "vertical" program which "undermines health systems". We have been here before with the structural readjustment and Washington consensus and sector-wide approaches (SWAPs) in the 1980s which led to the dismantlement of TB programs in countries such as Tanzania and Zambia just when HIV was taking off.

Now continued momentum towards UA is threatened by a political backlash and an economic crisis.

Now we can see the disparities of leaders in countries rich and poor:

- The USG has invested more in saving AIG (237 billion + counting) than in international development assistance since 1960.
- Uganda is running out of \$ to pay for ARVs but President Yoweri Museveni just spent \$48M on a new private jet.

- Zimbabwe is an international basket case with a raging cholera epidemic as well as chronic high rates of HIV and TB coinfection, as well as politically induced violence and routine abuses of human rights, a travesty of democracy whose President Robert Mugabe, fresh from violently suppressing a democratic opposition which clearly won a stolen election, recently spent \$250,000 U.S. (not Zimbabwe) dollars to celebrate his 85<sup>th</sup> birthday.
- The new White House senior advisor on global health, Zeke Emmanuel, whose brother Rahm is President Obama's chief of staff, told a group of visiting AIDS doctors that international AIDS programs are currently receiving far too much "lavish" support from the U.S. government, and that it is more cost effective and thus more ethical to save a baby from diarrhea than to stave a baby from AIDS.
- President Obama's budget for 2010 pits disease vs disease in the NIH budget which is virtually flatlined, fails to fully fund PEPFAR programs at the authorized level of \$9.6 billion, and scoops some \$700M from the PEPFAR budget for maternal child health programs. There is no absolutely no question that much more funding is urgently needed for maternal child health programs, but there is no reason to pit dying poor people against each other for pieces of an inadequate pie when the obvious solution is to continue scaling up both sets of urgently necessary global health initiatives.
- Last month in Seattle at the Pacific Health Summit, WHO Director General Margaret Chan disgracefully described TB control as a failure due to a lack of advocacy. I think she was blaming the victim. If one branch works at WHO it is Stop TB. If your own leader abandons you and accuses you of failure, it is a form of bureaucratic abuse. She is tolerating a civil war within WHO and global health which is weakening the organization and slowing progress on global health. This cannot be allowed to continue.
- If I have learned one thing from TB/HIV activism – and one of my proudest anniversaries of this year is to note how much progress has been made by so many on the collaborative TB/HIV activities which I helped to write with HG and others in 2003 and which were published just five years ago. If anything is health system strengthening, it is TB/HIV collaborative activities, it is the global laboratory initiative, it is strengthening MDR treatment and moving to universal access to TB culture and drug susceptibility testing (DST), and the ongoing rollout of rapid culture and line probe tests for DR TB while we wait for the elusive TB point-of-care dipstick.
- We are at the vanguard of HSS strengthening. Do not let global health or national leaders accuse you of being "vertical" or "undermining health systems". You are at the vanguard of the health system strengthening which will be essential to achieve universal access and primary health care for all.



In conclusion now is not the time to stop our activism. It is time to unite and join in a more general struggle for primary and comprehensive health care for all including prevention, treatment, and care for HIV, TB, and malaria, and to redouble our research efforts to discover better tools, most urgently a TB diagnostic and an HIV vaccine.

Finally I would like to recur to a comment Liz Corbett made yesterday which is that we must devote the same intelligent intensity to studying health care delivery as we do to developing slick new tools. This emerging science of health care delivery is actually essential to understanding how to sustain and continue to scale up our responses to HIV, TB, and other global ID threats, or else we will succumb once again to the microbes, which are continuing 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 pandemic diseases of history and not scourges of the future. Thank you.

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