SPECIAL ARTICLE

SHATTUCK LECTURE

Chronic Infectious Disease and the Future of Health Care Delivery

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More than four decades after one U.S. Surgeon General reportedly declared it "time to close the book on infectious diseases," drug-resistant pathogens have diminished the effectiveness of once-potent therapies.[1] In the past three decades, newly described pathogens, including the human immunodeficiency virus (HIV), the severe acute respiratory syndrome (SARS) virus, and the H1N1 influenza virus, have caused pandemics, while old scourges from tuberculosis to cholera have persisted or resurged. Simultaneously, rising life expectancy and rapid social change have led to an increasing burden of chronic diseases for which we have effective therapies but inadequate innovation for delivering them efficiently to the neediest people — the so-called know–do, or delivery, gap.

As compared with discovery science and randomized trials, the 20th-century biomedical paradigm viewed care delivery as scientifically uninteresting — too messy for serious scrutiny, like the observational and qualitative methods that elucidate it. Yet understanding how and why care delivery does or does not happen and how to improve it may now represent medicine's most important task.[2]

In settings of poverty, the delivery gap can be a gulf, especially in the case of chronic illness. In the rural villages and small towns in Rwanda, Malawi, and Lesotho, where the nongovernmental organization Partners in Health has worked over the past decade, adherence to daily regimens may seem unlikely. But rapid progress can be made toward closing the gap, as we had learned in rural Haiti. Work with local, national, and international partners to develop health systems able to respond to both acute and chronic disease shows that we can, with adequate resources, improve care delivery, sharply reducing morbidity and mortality. I believe that the lessons from 25 years of responding to the acquired immunodeficiency syndrome (AIDS) and other chronic infections have implications for the chronic afflictions now recognized as leading causes of premature death and disability in places rich and poor (a slide show is available with the full text of this article at NEJM.org).

A slide show of achievements and challenges in addressing chronic infectious diseases is available at NEJM.org

FAILURES OF DELIVERY: A LOOK BACK TO THE YEAR 2000

Although many infectious diseases are acute, most deaths and debility attributed to infections are due to chronic parasitic, mycobacterial, and viral infections. As therapeutic options for these afflictions expanded in well-resourced but low-burden settings, the need for treatment in high-burden, under-resourced settings grew. By 2000, AIDS, tuberculosis, and malaria had killed about 6 million people annually, many of them very poor young adults and children. In 2000, we had no reliable vaccines for these three leading infectious killers. We did, however, have diagnostic tests, including tests for drug resistance, of varying quality; prevention strategies of variable effectiveness; and multidrug regimens that could cure or suppress infection — though the argument that treatment might also serve as prevention was not yet being made or heard.

Six million deaths annually despite the existence of effective therapy: this was a failure of delivery. Many care providers wanted to apply their knowledge to bridging the know–do gap, but there were no funding mechanisms to bridge a gap that spanned both borders and sharp disparities in infection risk, disease progression, and access to care. In 2000, when AIDS surpassed tuberculosis as the leading infectious cause of adult deaths, some argued that without health care providers and infrastructure, it was hopeless or even irresponsible to try to treat AIDS in Africa; others cited potential drug resistance as a reason not to proceed; still others called for research to show that such therapies would prove effective in settings of poverty.[3] AIDS joined diseases (ranging from breast cancer and acute leukemia to diabetes and diseases requiring surgical intervention) held by many to be untreatable in resource-limited settings.

False debates arose after new therapeutic agents for chronic infections were introduced into a world, and a global market, riven by deep disparities.[4] Most debates were about treatment's cost and complexity, viewed as prohibitive; the complexity of prevention, and its relation to ready access to effective therapy, was less often explored. The terms of these debates echoed those of past discussions of tuberculosis treatment.[5] Disease and transmission due to drug-resistant strains of *Mycobacterium tuberculosis* had been documented in the first years of the antibiotic era; even then, it was not obvious that drug development would keep up with mutating pathogens. Partners in Health and its partners in Peru,[6] Russia,[7] Lesotho,[8] Haiti,[9] and Rwanda[10] had treated more than 15,000 patients with highly drug-resistant tuberculosis and worked to improve infection control in these settings. But there were few effective means of, or financing for, delivering therapy to patients with drug-resistant tuberculosis who were living in poverty. We now face the same dilemma in contemplating other chronic infections.

Five salient lessons can be derived from the history of tuberculosis control. First, drug resistance is here to stay, but the rate of its emergence can be slowed. Although supervised therapy with multidrug regimens (and proper management of drug quality and supply, laboratory data, and infection control) might have forestalled the spread of drug-resistant strains of *M. tuberculosis*, their emergence was inevitable: the drugs were developed and brought to market at a time when there was no proper delivery platform for providing combination chemotherapy in ambulatory settings. Nor did researchers, clinicians, or public health authorities understand the complexities of transmission of drug-resistant strains within households or institutions, or strain variation, or tuberculosis immunology, or the likelihood of reinfection before, during, and after treatment. We still do not understand these matters fully. But we know enough to slow the rate of acquired and transmitted drug resistance through prompt action to diagnose drug-resistant tuberculosis, to treat it with the right drugs and using the right system of care, and to improve infection control.[11]

Second, the development of robust delivery platforms will lead to improved clinical outcomes if what is being delivered is clinically effective. Over the past few decades, ineffective or outmoded therapies have been embraced within policy circles on grounds of cost. But it was a clinical error to give patients with multidrug-resistant tuberculosis repeated courses of the drugs to which their infecting strains were resistant, and it was an ethical error to deem those patients "cured" by "standard definitions."[12,13] A clinical strategy ineffective in Boston is not likely to prove effective in Peru or Siberia, whatever its price tag.

Third, care for patients who do not require inpatient care should shift from hospitals to clinics and community-based care. We learned this lesson in central Haiti, where we needed the help of community health workers to cure patients of tuberculosis.[14] Of course, resource-poor settings like Haiti also require hospitals and clinics, as well as reference laboratories. But facility-based or community-based care with the wrong therapies (as occurs when multidrug-resistant strains are treated with first-line regimens) should be shifted toward platforms linking rapid diagnosis to effective multidrug regimens delivered with the help of community health workers.

Fourth, therapeutic innovations need to be linked more rapidly to equitable delivery, which requires new financing mechanisms. Newly marketed tuberculosis drugs and diagnostic tests are rarely made widely available where the burden of disease is highest. This neglect applies to most new medical technologies but has graver consequences in the case of airborne

pathogens. Extensively drug-resistant tuberculosis is again a case in point. Bedaquiline, which inhibits the proton pump of mycobacterial ATP synthase, was recently approved in the United States for drug-resistant tuberculosis.[15] But who controls and finances widespread access to bedaquiline (should it prove safe) and other new agents with efficacy against public health threats? The idea that effective therapies for serious communicable diseases could be kept out of the marketplace and held in reserve seems as unlikely from the point of view of those who study the care-seeking behavior of patients and families as it does from the perspective of companies that develop and patent drugs.

Fifth, it is not clear that any disease is helpfully termed "untreatable." This is true of drug-resistant tuberculosis, which serves as a benchmark for medicine today as it did 60 years ago. Just as one can insist overmuch on strict control of medications needed to treat an airborne threat, one can forget that patients and family members will always seek treatment, even for afflictions that experts deem untreatable among the poor. "Untreatable" often really means difficult or costly to treat, just as "resistant" sometimes means resistant to our best efforts to deliver care.

ANTIRETROVIRAL THERAPY BETWEEN DEVELOPMENT AND DELIVERY

The same five lessons apply to HIV disease. Perhaps because more resources have been invested in AIDS, there is some optimism among those combating HIV, a pathogen first described only 30 years ago that within 15 years had surpassed tuberculosis as the world's leading infectious killer of young adults. There have been remarkable developments: the discovery and characterization of both the causative organism and the key steps in its replication and pathogenesis, and thus the points at which both might be blocked; the development of tools to diagnose, stage, and prevent or treat complications of HIV infection; and, astoundingly, the delivery of these advances to millions of the world's poorest and sickest people.[16]

But the decade between development and delivery was a long one if measured in loss of life. As with tuberculosis, there was no magic bullet for HIV disease. When a single agent, such as zidovudine, was used to treat AIDS, resistance ensued quickly; clinical response to the drug was short-lived.[17] As with tuberculosis, it was combination chemotherapy that had a remarkable clinical effect. Mortality from AIDS declined rapidly, if unevenly, when combination antiretroviral therapy (ART) became available in the United States and Europe. Many patients dying from AIDS stopped dying and went home from hospitals to receive ambulatory care; mother-to-child transmission of HIV was slowed and almost stopped. In 1996, a *Newsweek* cover asked, simply (if myopically, given the global pandemic), "The End of AIDS?"[18]

During the mid-1990s, when many patients in Boston's teaching hospitals went home on these regimens, I was completing a fellowship in infectious disease in the Harvard hospitals and traveling back and forth to the small hospital we had built in central Haiti. By 1996, only a decade after the region's first documented case, the facility was full of patients with AIDS. At times, Harvard and Haiti seemed to be in two different worlds. But HIV and other communicable pathogens remind us that we live in one world — hence my skepticism regarding the need to "prove" the effectiveness of ART in rural Haiti. By the late 1990s, ART did not need to be evaluated through randomized, controlled trials in poor settings as much as people dying of AIDS in such places needed access to the only demonstrably effective therapy we had.

The Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections (GHESKIO) and Partners in Health played important roles in expanding access to ART throughout Haiti. The organizations and their U.S. medical-center affiliates also advocated for countering pessimism regarding ART scale-up in Africa.[19,20] Among public health experts accustomed to working within resource-constrained vertical systems, the prevailing view (as recently as 2003) was that it was not feasible, and probably not cost-effective, to deliver ART in poor settings. Some experts pitted prevention against care, arguing that the former was much more cost-effective than the latter, as if either activity could be easily costed and drug prices were set in stone.[21] Others contended that it was a big enough task to diagnose and treat tuberculosis and other opportunistic infections; ART was too complex for weak health systems that

employed few infectious disease experts. Thus arose an invidious distinction between AIDS "care" (do what you can with whatever is on hand, which is not likely to include ART) and "treatment" with ART. Pessimism spread through nongovernmental organizations and public clinics and hospitals serving the African poor. These providers, regardless of motivations or aspirations or talent, were accustomed to scarcity.

We learned the hard way that the treatment–care distinction was fiction. Practitioners in such settings were of course overwhelmed by the collision of the epidemics of tuberculosis and HIV infection and by the ways in which poverty, social insecurity, political turmoil, and labor migration increased the risk of infection, diminished the effectiveness of prevention efforts, and reduced chances of diagnosis and effective care. But even if such social conditions were deemed beyond the ken of clinical practice, lives could clearly be saved through effective delivery of ART.

The treatment–care distinction, and the clinical errors and false debates on which it was based, would probably have become fixed as policy if not for three factors not yet seen in response to drug-resistant tuberculosis: AIDS activism, a large spike in funding for ART rollouts, and steep cost reductions for AIDS diagnostic tests and ART.[22] The debates were sharp in the years between development and delivery. AIDS activists argued that effectively managing a chronic disease would mean needing fewer hospital beds for those sick with its complications. Patients treated effectively would spread the word to others, increasing the reach and effectiveness of AIDS-prevention activities. ART could help break vicious cycles of poverty and disease: patients receiving it could again be economically and socially productive; there would be fewer child-headed households in hard-hit countries. Activists further warned that untreated HIV infection would increase substantially the dimensions and costs of epidemic tuberculosis, including that due to drug-resistant strains. This increase would occur through several mechanisms, including reactivation of latent infection with *M. tuberculosis* as cellular immunity waned, poor infection control, and rampant nosocomial epidemics.

All these claims were based on data, albeit imperfect and incomplete data. Some came from Haiti. GHESKIO, which described Haiti's first AIDS cases in 1982,[23] became a pioneer in operational research seeking to improve the quality of diagnosis and treatment of the country's most common opportunistic infections. At Partners in Health, we tried to follow suit, in part by diagnosing and treating these infections and, in the late 1980s, by introducing zidovudine (and then nevirapine) to prevent mother-to-child transmission of HIV in rural Haiti. But we could not keep up with either AIDS or tuberculosis without ART. In 1995, we reviewed the clinical presentations of 200 consecutive patients seen at our facility in central Haiti. *AIDS Clinical Care* published a pie chart in 1997 showing the diagnoses in these patients (Fig. 1),[24] even though our ability to confirm suspected diagnoses was limited by the lack of laboratory infrastructure and staff. As facility-level and national data from more recent times continue to show, there was and there continues to be lots of tuberculosis.[25] GHESKIO, with better laboratory capacity, reported a preponderance of tuberculosis among urban Hai-

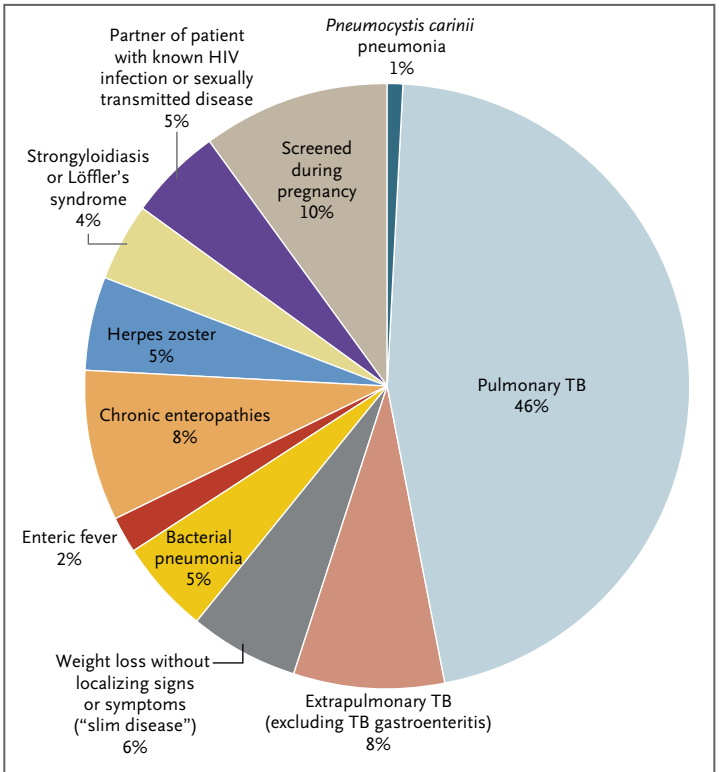

Figure 1. Diagnoses and Clinical Characteristics of 200 Patients Presenting with HIV Infection to Clinique Bon Sauveur in Haiti between 1993 and 1995.

Tuberculosis (TB) was by far the most common presenting disease. Data are from Farmer.[24]

tian patients with AIDS and an increased incidence of tuberculosis among their HIV-negative household contacts[26]; similar reports came in from elsewhere in urban Haiti[27] and from cities throughout sub-Saharan Africa.[28]

We knew how to treat tuberculosis: with community-based delivery of a few pills each day, regular follow-up, and adequate social support. That is, we had a delivery platform. Why not try the same approach for HIV disease, adding a different set of pills to the mix? Although it was difficult, between 1998 and 2003, to find the funds for ART, which then accounted for 80% of program costs, we began enrolling rural Haitian patients in a program hewing to our approach to tuberculosis: ART, free of cost to patients, delivered at home with the help of community health workers and complemented by nutritional and psychosocial support. From the beginning, with the most heavily burdened continent in mind, we called our project "the HIV Equity Initiative" and sought to share our experiences with African colleagues, some of whom came to central Haiti to see for themselves.

This modest initiative further emphasized equity by reserving scarce-because-expensive ART for the sickest patients (as assessed by CD4 count, weight, and other basic clinical and laboratory measures). When active tuberculosis was documented, we treated it first — not because we believed that ART should be delayed or that we could not get around drug–drug interactions such as that between rifampin and nevirapine, or because we feared severe immune reconstitution syndrome, which we diagnosed rarely. Nor did we believe that delaying ART would be shown to be prudent by proposed clinical trials of the timing of initiation of ART in patients with active tuberculosis and advanced HIV disease. It was clear before ART was developed that the lower the CD4 count, the greater the risk of dissemination of tuberculosis and the higher the mortality; it was well known shortly after the development of ART that nothing else could reliably reconstitute cellular immunity destroyed by HIV. We delayed ART in our coinfected patients because we could not get the drugs and knew that treating active tuberculosis might buy them time.

An evaluation of early outcomes did not surprise us but stiffened our resolve to advance the equity agenda and echo calls for similar initiatives in Africa, where life expectancy was dropping, tuberculosis was surging, and HIV prevalence was high. When we compared the central-Haiti ART group with patients who received therapy for opportunistic infections alone, it was clear that patients with late-stage HIV disease who received ART did much better — whether we examined mortality, weight gain, hospital admissions, new opportunistic infections, or markers of return to function — than those who received everything but ART, even though the latter group had higher CD4 counts. Mortality among the first 100 patients who received the full package of community-based ART was zero in the first 4 years after enrollment; it was 10 to 20% among those who received aggressive and free care for their opportunistic infections. Good home-based follow-up, again with the help of community health workers, accounted for a halving of mortality among patients not yet receiving ART.[29]

We published descriptions of this community-based approach to AIDS treatment in rural Haiti in 2001, as debates about AIDS in Africa reached a fever pitch.[30,31] But the argument that treatment of opportunistic infections alone would suffice in the poor world was never buttressed by any data. It was egregiously false in places where the leading such infection was tuberculosis. Experience in an informal settlement on the outskirts of Cape Town, South Africa, offers a case in point: in Khayelitsha district, 24.9% of women seeking prenatal care in 2001 were found to be HIV-infected; tuberculosis incidence in the district was pegged at 1062 cases per 100,000 residents.[32,33] Nor were arguments that ART was too difficult to implement ever shored up by data. In May 2001, Doctors without Borders, working within public-sector clinics, initiated a community-based ART program in Khayelitsha. By the end of July 2003, they had enrolled 600 patients in care and were registering results similar to ours.[34] ART programs were also launched in 2001 in urban areas of Botswana, Uganda, and Senegal. Each was deemed feasible and successful. For patients reached by such pilot projects, the delivery gap had been bridged. But even by conservative estimates, at least 10 million people in Africa alone needed ART. What were the chances, many asked in 2001, of scale-up of such efforts?

THE DELIVERY DECADE: BRINGING ART TO SCALE

The global AIDS debate, in the years between development and delivery, was really about funding; claims that treating a chronic infection with a multidrug regimen was impossible in poor settings were invalid. And in 2002, the Global Fund to Fight AIDS, Tuberculosis, and Malaria and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) changed the equation not only for millions of people dying of untreated HIV disease but also for global health. Once there was funding for ART, there was a great rush — even before national plans for rollout of care were elaborated — to diagnose HIV disease, enroll patients, and thus bridge the know–do gap. In 2003, Harvard's Jim Yong Kim, then the director of Partners in Health and one of the architects of the HIV Equity Initiative in rural Haiti, joined the World Health Organization (WHO) to lead the "3 by 5" Initiative, which proposed to begin ART in 3 million Africans with AIDS by 2005.[35]

What has happened in the decade since funding for scaling up ART became available? Once Haiti had received funding for integrated AIDS prevention and treatment from the Global Fund in 2003, Partners in Health and GHESKIO, working with public health authorities and other groups, rapidly increased enrollment in central Haiti, where community health workers and nurses played key delivery roles, and in the Port-au-Prince area.[36,37] PEPFAR began supporting treatment rollout in Haiti the following year. In the ensuing decade, despite political unrest and several major natural disasters, scale-up continued throughout the country; Haiti met its first Global Fund targets early.[38] Marked declines in mortality from AIDS and tuberculosis were registered throughout the decade and throughout the country, as the cost of ART dropped precipitously. Such funding was also used to halt HIV transmission through blood transfusion, slow mother-to-child transmission, and support myriad other prevention activities. In central Haiti, Global Fund (and, later, PEPFAR) resources were deployed in all-but-abandoned public facilities to improve not only care for AIDS and tuberculosis but also primary care.[39]

Although tardy diagnosis and loss to follow-up after screening were considerable in Haiti, these problems were addressed more effectively there than in most other poor countries, often through help with patients' transportation costs and food insecurity; adherence rates were high by international comparison, especially when community health workers were involved.[40] Even the 2010 earthquake, which destroyed much of urban Haiti's health infrastructure and killed as many as 200,000 people, did not reverse these gains; within a few months after the quake, more than 90% of surviving patients receiving ART were accounted for.[41] Nor did a massive cholera epidemic, which also began in 2010, stop Haiti's progress on AIDS. According to July 2013 data from Haiti's national Monitoring, Evaluation, and Surveillance Interface, a collaboration between the Haitian Ministry of Health and the U.S. Centers for Disease Control and Prevention and its

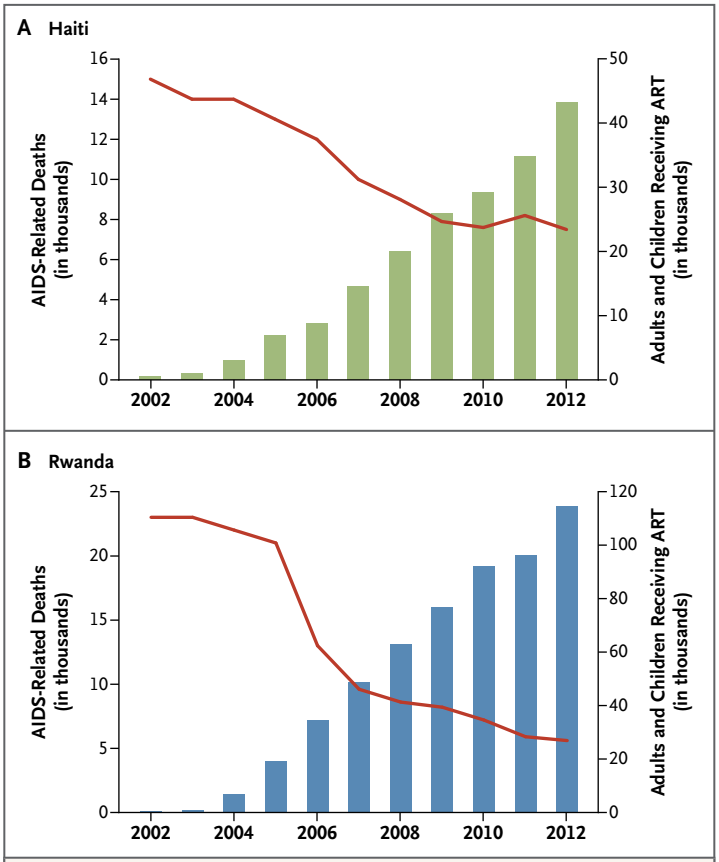

Figure 2. Community Response to HIV Infection in Haiti and Rwanda.
In both countries, the number of AIDS-related deaths (red line) fell as the number of people, both children and adults, who received antiretroviral therapy (ART) increased. Data are from the Joint United Nations Program on HIV/AIDS (UNAIDS).[42]

Figure 3. One of the First Patients Enrolled in a Community-Based HIV and Tuberculosis Treatment Program in Rural Southeastern Rwanda, before and after Initiation of Therapy for Both Diseases.

partners, Haiti had achieved universal ART coverage according to the WHO 2010 guidelines, defined as access to care for more than 80% of patients with a CD4 count of less than 350 cells per cubic millimeter (Fig. 2).[42,43]

Of course, we know this enrollment criterion was much too timid. In June 2013, the WHO released revised guidelines recommending that ART be initiated in all patients with a CD4 count of less than 500 cells per cubic millimeter.[44] In the rural and urban settings in which Partners in Health and GHESKIO work, 53% of patients with newly diagnosed HIV infection in 2012 had a CD4 count of less than 350 cells per cubic millimeter, and 18% had a CD4 count of 350 to 500 cells per cubic millimeter: nearly three fourths of patients with newly diagnosed infection will meet the criterion for ART.[45] There are competing priorities for scarce resources, but earlier treatment will save lives and help to further contract the Haitian epidemic, already shown to be shrinking: HIV prevalence, pegged at 6.2% in 1993, was estimated to have declined to 2.2% by 2012.[46,47]

Rwanda's success has been even more dramatic. Clinical results were often, again, striking (Fig. 3). Of the first 1061 patients enrolled in community-based care in rural southeastern Rwanda, more than 92% were still in care after 2 years of daily therapy.[48] National scale-up proceeded rapidly: between 2002 and 2012, nearly 100,000 Rwandan patients were receiving ART. By 2009, Rwanda was one of only two African countries to achieve universal ART access; the other was far wealthier Botswana (Fig. 4).[42,49,50]

Even at a national scale, the quality of care has remained high: as of April 2009, it was estimated that 83% of those receiving ART had viral suppression.[51] During the past decade, deaths attributed to AIDS dropped by more than 80%; those due to tuberculosis and malaria have also declined steeply, with Rwanda now ranked as the world's leader in the rate of reduction of case-fatality rates for these diseases. As in central Haiti, AIDS programs (and their funding) have been used to build and strengthen health systems. But regional advances in Rwanda have been more swiftly translated into national poli-

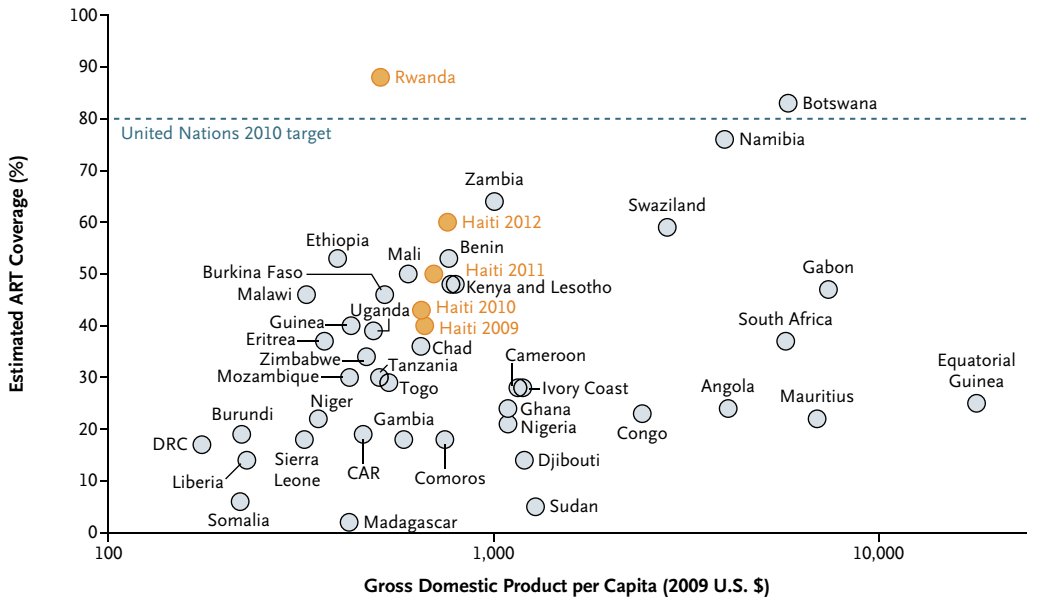

Figure 4. Estimated ART Coverage in Various Sub-Saharan African Countries in 2009, According to Gross Domestic Product.

Estimated ART coverage is based on the estimated numbers of eligible patients receiving ART according to the World Health Organization (WHO) 2010 guidelines. The United Nations target was 80% coverage by 2010; only Rwanda and Botswana achieved this goal. Data for Haiti from 2009 to 2012 are also shown. Rwanda and Haiti, two resource-limited countries that have made dramatic progress in the fight against AIDS, are highlighted. The axis for gross domestic product is plotted on a log scale. CAR denotes Central African Republic, and DRC Democratic Republic of Congo. Data are from UNAIDS,[42] the WHO,[49] and the World Bank.[50]

cy: more than 93% of Rwandan infants are inoculated against 11 vaccine-preventable illnesses, up from 25% against 5 diseases in the year after the 1994 genocide. A national rollout of vaccination to prevent infection with human papillomavirus has been linked to new programs to integrate cervical-cancer prevention, diagnosis, and care.[52] Rwandan authorities have pushed forward an agenda that includes increased resources for a delivery platform able to integrate prevention of and care for chronic and noncommunicable diseases.[53] Electronic medical records[54] and community-based health insurance[55] have been introduced throughout Rwanda. The results of a "health systems–strengthening" approach to AIDS, tuberculosis, and malaria have been stunning: death during childbirth has decreased by more than 60% over the past decade; deaths registered among children under 5 years of age, even more sharply (Fig. 5).[56] Life expectancy has doubled since the early 1990s. These are some of the steepest declines in mortality ever documented anywhere (Fig. 6).[56-58]

As in Haiti and Rwanda, so too in South Africa, Kenya, Tanzania, Uganda, Mozambique, and across the continent: more than 7.1 million Africans — nearly half of those who would most benefit from it — are now receiving ART[59]; an estimated 700,000 deaths and more than 200,000 perinatal infections were averted in 2010 alone.[60] Evidence is mounting that effective therapy has reduced HIV-transmission rates, by one estimate as much as 96%.[61] The per-patient cost of ART has continued to drop as true demand, based on burden of disease rather than ability to pay, is acknowledged.[62,63] By most accounts, ART's per-patient cost has declined by well over 90%.[64] So too has the cost of laboratory tests and personnel, a decline hastened by task shifting from physicians and nurses to community health workers in regular contact with patients in or close to their homes. Thus did new funding mechanisms such as the Global Fund and PEPFAR render visible millions of people who had never had access to modern medical care (see interactive graphic, available at NEJM.org). If eligibility for ART follows new guidelines recommending ear-

An interactive graphic showing AIDS-related mortality in sub-Saharan Africa is available at NEJM.org

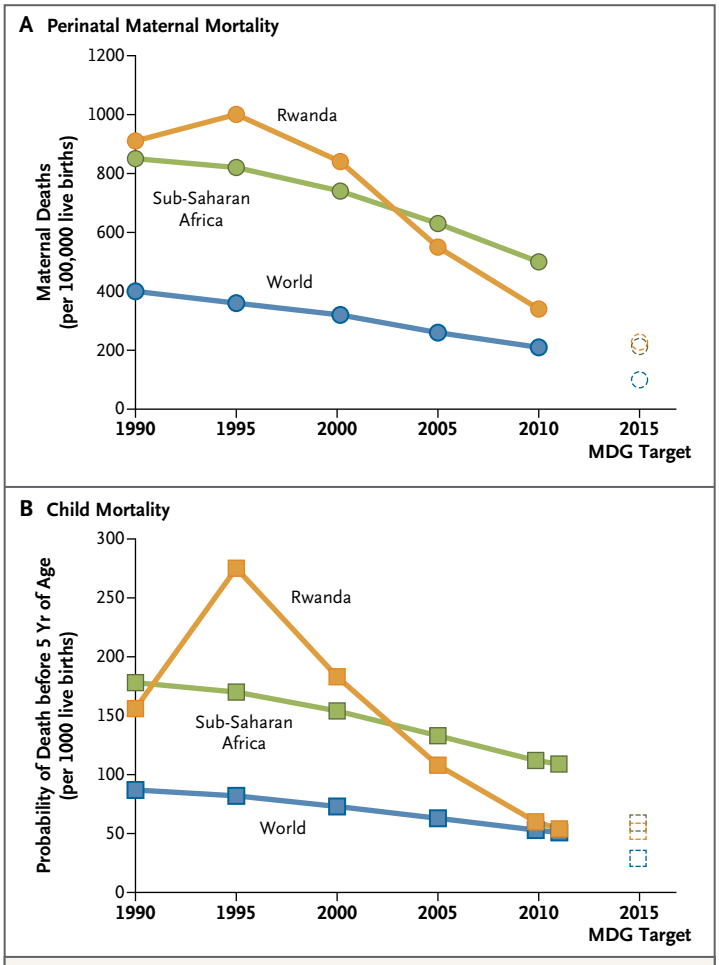

Figure 5. Perinatal Maternal Mortality and Child Mortality in Rwanda from 1990 to 2010 or 2011.

Shown for comparison are perinatal maternal mortality and child mortality for the entire world and for sub-Saharan Africa. MDG denotes United Nations Millennium Development Goals. Data are from Farmer et al.[56]

lier treatment, twice as many people living with HIV infection in Africa — 13 million — will require care.

What about claims that poor people will not be able to "comply" with ART? Early reviews of ART programs in sub-Saharan Africa suggested that adherence rates were higher than those in North America.[65] But one of the biggest problems with large treatment programs in Africa and elsewhere has been loss to follow-up, which increases mortality, transmission rates, and drug resistance — with obvious implications for treatment success as well as for costs, since second-line drugs cost more. In the most important early effort in Kenya, the fraction of patients lost to follow-up went from under 2% in the first cohort to as high as 25% in subsequent ones, as the number of patients enrolled in each cohort went from a few dozen to tens of thousands.[66,67] Shifting tasks to community health workers will help: most HIV care is still offered in cities, but many people needing care in Africa live in rural areas, some of them labor migrants in cities and mining towns who return home sick to regions with few doctors or nurses and little modern infrastructure. Care will increasingly need to be mobile, as patients are.

What about drug resistance? Drug-resistant HIV emerged as ART was deployed in a way that echoed the sequence of events and complexities seen in efforts to treat tuberculosis. And since transmission of HIV has not been stopped, we know that drug-resistant HIV, like tuberculosis, can spread. In some U.S. cities, as many of 16% of new infections are caused by drug-resistant strains of HIV.[68] Anxiety about such strains is briefly allayed, in wealthy countries, when new and effective agents are introduced: in 2006, when most U.S. patients who had already received treatment carried drug-resistant strains of HIV, a second-generation protease inhibitor (darunavir, boosted by a second drug, ritonavir) was shown to be effective and have few side effects. The millions who now receive first-line ART will also survive to need these agents — and the laboratory capacity required to diagnose treatment failure.[69]

Tuberculosis and AIDS offer two very different stories about funding and translation of discoveries into large-scale delivery.[70] But there are many reasons to combine these narratives, which are rooted in epidemiology and pathophysiology. Among patients with active tuberculosis and advanced HIV infection, even brief delays in ART initiation are associated with increased mortality.[71,72] It is not clear that randomized, controlled trials are necessary to show that yet again — one reason why some ethicists criticized a South African trial comparing delayed ART with concurrent initiation of combination chemotherapy for both diseases.[73,74] The debate underscores the question of where research resources should be invested: some of these trials cost tens of millions of dollars, largely because of the study designs that are privileged.[75] Our colleagues used rigorous observational methods to reach the same conclu-

sions in Rwanda,[76] in a study costing well under $50,000.

Resources are needed to capitalize on research that has already revealed ways to lessen the impact of epidemics that have long since collided: for example, designing or retrofitting facilities to minimize the risks of exposure to airborne pathogens, most notably tuberculosis, for patients and staff, especially those with HIV infection.[77,78] Reducing the risk of nosocomial epidemics is another reason that community-based care for AIDS and tuberculosis is important to patients and providers.

CONCLUSIONS: FROM PESSIMISM TO OPTIMISM

All five lessons from tuberculosis treatment apply to HIV disease. Many diseases affecting the world's poor are treatable, including those that are considered untreatable because of delivery, rather than clinical, failures. The belief that it was too costly to treat paralyzed action in Africa for a decade after ART was proved effective. But such defeatist discussions occurred even in affluent countries: 8 months after *Newsweek* asked whether ART heralded the end of AIDS, it ran an article about barriers to care for poor Americans with AIDS under the title "Too Poor to Treat."[79] These people were not receiving treatment not because they had drug-resistant HIV strains, but because our health care delivery system could not reliably reach the poorest or otherwise marginalized patients, a deficit compounded by the requirement for lifelong treatment.

The know–do gap is readily visible in the United States, where resources are plentiful but clinical outcomes are uneven and health disparities persist. Experience in delivering care for patients with AIDS in places like Haiti and Rwanda might plausibly inform the needed transformation of U.S. health care, since much of the problem here concerns chronic disease.[80,81] Our system does a poor job of linking hospital-based care to that delivered in clinics, homes, or workplaces.[82] Care delivered with the help of community health workers, and attuned to the social needs of patients, is meant to do just that.[83]

Bridging the delivery gap is important for the future of clinical medicine and public health globally. The success of global AIDS efforts offers one reason for optimism about future endeavors to improve care for other diseases. We are likely to face precisely the same delivery challenges whenever new diagnostic tests and therapeutic agents are developed for any chronic communicable infection. If only we could develop the right community-based and equitable delivery platforms in advance, we could spare our patients a lot of suffering, and ourselves a lot of headaches and acrimony. That is what we should be doing now for chronic hepatitis C virus (HCV) infection, which is thought to affect 180 million people globally and is a primary indication for liver transplantation in resource-rich countries. Diagnosis — advanced by greater understanding of HCV pathogenesis — will probably shift, for many patients, from liver biopsy to noninvasive assays of liver function, identification of HCV genotype, and measurements of viral load. Two new protease inhibitors, telaprevir and boceprevir, and the nucleotide inhibitor sofosbuvir (expected to be approved by the Food and Drug Administration in December 2013) might double the cure rates seen with the current standard of care in wealthy countries, peginterferon and ribavirin.[84] The likelihood of cure will be greater when treatment is delivered

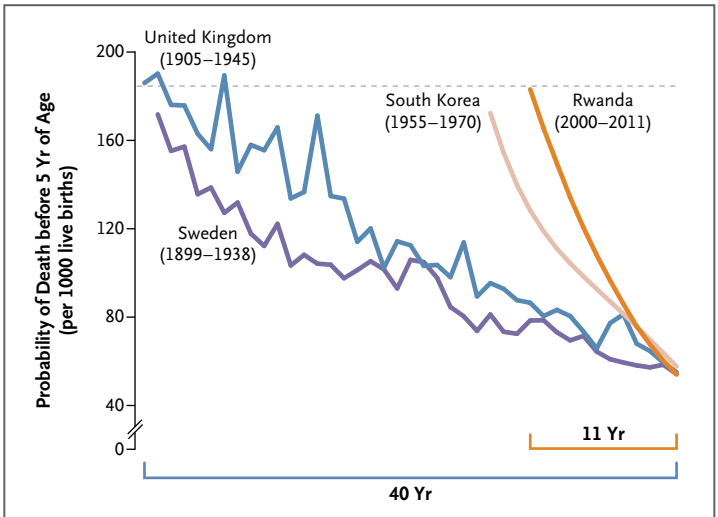

Figure 6. Probability of Death before 5 Years of Age during Various Periods in the United Kingdom, Sweden, South Korea, and Rwanda.

The data are presented to show a common ending point, although the calendar date for the ending point ranges from 1938 for Sweden to 2011 for Rwanda. The dashed line indicates the approximate probability of death before 5 years of age in the United Kingdom in 1905 and in Rwanda in 2000. The scale for the horizontal axis varies as shown. Data are from the United Nations Children's Fund[57] and the Gapminder Foundation.[58]

through community-based platforms that improve adherence by enhancing convenience for patients, including those with addiction and other coexisting disease.

All five lessons of chronic disease management also apply to HCV infection and to most of the 20 or so pathogens that cause infections considered to be "neglected tropical diseases." No one would argue either that these chronic infections are not public health problems disproportionately affecting the poor and marginalized or that we do not generally have the tools to diagnose and treat them. Above all, we fail to bring new deliverables to people who need them most because demand is constructed largely around the notion of markets. There are too few equity plans to link demand to burden of disease. When treatments are easily administered, convenient, and likely to result in cure or excellent clinical response, there will be great demand for them. But when such need is seen as demand only if there is an established market for these innovations, it is fair to talk about market failure, as we have in contemplating the diagnostic tests and drugs required to treat drug-resistant tuberculosis.[85] The same failures will now ensue, or already have, without an equity plan to deliver new agents for chronic HCV infection. Telaprevir and boceprevir have not been widely used since their introduction in 2011, because a multidrug regimen including telaprevir or boceprevir can cost more than $67,000.[84] Sofosbuvir may initially be priced at up to $90,000 per 12-week course.[86]

ART's high costs were also invoked to stop the conversation about its rollout in the poorer reaches of Africa. With the rollout, however, came a precipitous drop — more than 90% — in cost.[87] How PEPFAR and the Global Fund came into being is known; why they led to the delivery decade, linking burden of disease to demand, remains a subject of debate.

Similarly effective advocacy has not yet emerged for patients with tuberculosis, malaria, chronic hepatitis C, cholera, or "neglected tropical diseases." The same holds true for other chronic diseases, from diabetes to epilepsy to major mental illness and many cardiovascular diseases — and for many acute conditions, from trauma to obstructed labor (and most other conditions requiring surgical intervention), and most cancers. The development of new therapeutic agents has outpaced our investments in robust delivery platforms tailored to meet demand. Only by building health systems that provide high-quality care for all, especially the most vulnerable, can we catch up with the preventive, diagnostic, and therapeutic revolution. What we need now are revolutionary improvements in the delivery of prevention, diagnosis, and care.

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