The 30-Year War on AIDS: Have We Reached the Tipping Point?

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It is truly an honor to receive the Thomas Parran Award, and I wish to express my deep thanks and gratitude to the American Sexually Transmitted Diseases Association and the Thomas Parran Award Committee for selecting me to receive this prestigious award. I would like to recognize the support of my colleagues who provided mentorship and guidance to me throughout my career. My lifelong interest in the field of sexually transmitted diseases was essentially forged as an infectious disease fellow under the mentorship of King Holmes. I owe a lifetime of gratitude to King, as well as to many other University of Washington faculty members including Walter Stamm, Larry Corey, Hunter Handsfield, Sheila Lukehart, Jeanne Marrazzo, and Connie Celum. I am also extremely thankful for the support of my colleagues at Johns Hopkins University, including Charlotte Gaydos, Ned Hook, Anne Rompalo, Jon Zenilman, Ron Gray, Maria Wawer, and Emily Erbelding. There are many other colleagues who have advised, counseled, and collaborated with me to whom I owe a great deal of gratitude including Peter Piot, Julie Schachter, Max Chernesky, David Martin, Sevgi Aral, Myron Cohen, Alan Ronald, and countless others. Finally, I wish to thank all the individuals within my laboratory with whom I share this award.

This lecture is dedicated to the memory of 2 individuals who influenced my academic career in significant ways over the years. The first is Walter Stamm, whom I considered a close friend and colleague, and who taught me the intricacies of *Chlamydia trachomatis*. We collaborated on many projects and I learned from him the delicate balancing act of academia and family. I also dedicate this lecture to Merle Sande, who taught me to pursue one's interests with unbridled enthusiasm and commitment. We developed the Academic Alliance for AIDS Care and Prevention in response to the depressing situation of acquired immunodeficiency syndrome (AIDS) in Africa, and with others, we built the Infectious Diseases Institute in Kampala, Uganda that is now one of the foremost human immunodeficiency virus (HIV) care and treatment facilities in East Africa. I thank them for their guidance and warm friendship.

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The Emergence of the AIDS Epidemic (1981–1986)

Thirty years ago on June 5, 1981, the CDC published a report of *Pneumocystis carinii* pneumonia in 5 previously healthy young men in Los Angeles, CA.[1] One month later, a second report indicated that Kaposi's sarcoma, an uncommonly reported malignancy, had been diagnosed in 26 homosexual men (20 in New York City and 6 in California).[2] This identification of opportunistic infections and unusual rare tumors alerted public health officials of a new disease that eventually become known as the AIDS. Over the ensuing year, similar opportunistic infections were reported in persons with hemophilia A, recipients of blood transfusions, injecting drug users, and infants born to women with AIDS.[3] Collectively, it was clear that a putative agent was both sexually and parentally transmitted. In 1982, I joined an investigative team that traveled to Port-au-Prince, Haiti, to investigate the occurrence of AIDS among hospitalized patients in Haiti. By the end of our investigation, it was clear that this disease affected both men and women equally, and that their primarily risk exposure was via heterosexual contact.

Two sentinel reports published 1 year later documented the presence of AIDS in selected urban centers of equatorial Africa.[4,5] Clinically, these cases were recognized by life-threatening enteropathic illnesses, referred to as "Slim's disease," oral esophageal candidiasis, Kaposi's sarcoma, and cryptococcal meningitis. These reports led to a subsequent investigation in 1983 led by Peter Piot, Joe McCormick, and myself to Kinshasa, Zaire (now the Democratic Republic of Congo).[6] We identified 38 patients with clinical AIDS at Mama Yemo Hospital with a male-to-female ratio of 1:1. Opportunistic infections were diagnosed in 84% of the patients; disseminated Kaposi's sarcoma in 16%. A retrospective analysis of medical records identified an increased number of opportunistic infections including central nervous system cryptococcosis and extensive diarrhea with wasting in individuals admitted to the hospital over the previous decade suggesting that the epidemic had been present in Kinshasa since the early 1970s.[6] Our investigation strongly argued that the situation in central Africa represented a new epidemiologic setting for the emergence of this worldwide disease and that as a sexually transmitted disease, it posed a great threat among the heterosexual population.

In 1983, a retrovirus referred to initially as the lymphadenopathy-associated virus or later the HIV was identified as the cause of AIDS.[7] Using specimens from our initial investigation in Kinshasa, Zaire, we found that 94% of our African patients with AIDS were seropositive to lymphadenopathy-associated virus/HIV.[8] In addition, a retrospective analysis of sera collected as early as 1976 were also seropositive, documenting the presence of HIV in Africa during the 1970s.[9] We subsequently were able to isolate HIV in our AIDS patients in Zaire and from asymptomatic infected individuals documenting the high rate of infection in Zaire and likely in many other areas of Africa.[10]

By 1984, we formed an international research project referred to as Projet SIDA, initially led by the late Jonathan Mann, who later became the first director of the Global Programme on AIDS at WHO. From these early investigations in Kinshasa, it was evident that HIV/AIDS was an escalating epidemic in central Africa.[11] We found that the male-to-female ratio of cases was 1:1 with age and sex-specific rates slightly greater in females <30 years of age and greater in males aged >40 years. The epidemic was spreading rapidly, being transmitted predominantly by heterosexual contact, parenteral exposure to unscreened blood transfusions, and unsterilized needles, and perinatally from infected mothers to newborns. The seeds for a massive epidemic had been sown and it was increasingly evident that unless a vigorous control program was initiated in the region, the prevailing economic and cultural factors would favor these modes of transmission and the epidemic would expand to the entire continent and beyond.[11]

The Global Expansion of the AIDS Epidemic (1986–1996)

Although we knew the problem was bad in 1986, none of us would have predicted the magnitude of the epidemic today. Over the next 10 years, the epidemic expanded to all areas of the world and over 40 million people became infected.[12] Young men and women, people with sexually transmitted diseases (STDs), and occupational groups such as long-distance truck drivers, military personnel, and female sex workers had the highest infection rates. HIV prevalence of more than 80% was reported for female sex workers in Africa and Asia. Seroprevalence of HIV among pregnant women ranged from 5% to 35% with the highest rates among those in urban centers in East and Central Africa. For 16 countries in Africa, HIV seroprevalences were >10% in the adult population. In 7 countries, at least 1 in 4 adults were living with HIV.[12,13]

Even in the United States, sharp increases in the number of new annual AIDS diagnoses and deaths were reported, reaching to 75,457 in 1992 and 50,628 in 1995, respectively.[3] Following the introduction of highly active antiretroviral (ARV) therapy, AIDS diagnoses and deaths declined substantially from 1996 to 1999, and have essentially remained static since then with an average of 38,279 AIDS diagnoses, and 17,489 deaths per year.[3] Despite this decline in AIDS cases, approximately 45,000 to 60,000 new infections occur annually.[14–16] Today, 53% of new HIV infections are in men who have sex with men (MSM), whereas 31% acquire it by heterosexual contact, and the remainder by injecting drug use or a combination of risk behaviors. Over the past decade, the incident rate of HIV has been 7 times higher in blacks compared with whites. This trend has been particularly accentuated in the District of Columbia, which has one of the highest AIDS case reporting rates at 148.1 per 100,000 population.[16,17]

Turning the Tide: From Basic Biology to Treatment (1996–2000)

Investments in the basic biology of HIV ultimately resulted in the discovery and subsequent licensure of 26 ARV compounds. These compounds include reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, fusion/entry inhibitors, and maturation inhibitors. Combination drugs with longer half-lives have also simplified medication adherence to once or twice a day therapy with 1 or 2 pills. In 1984–1985, the median life survival from diagnosis of AIDS to death was 10 months. With ARV therapy, the life expectancy for a 28-year-old HIV-infected patient following diagnosis is 80 years of age.[18–20] Use of ARV drugs had essentially turned the 3 times daily of the epidemic in terms of survival, life expectation, and quality of life.

The International Response (2000–2011)

While treatment was being expanded and saving lives in the developed world, little was being done in the most affected regions. Because of its widely destabilizing effects superimposed on an already fragile and complex geopolitical system, AIDS became a key issue for human security in sub-Saharan Africa, leading eventually to an HIV resolution by the UN Security Council in 2001.[21,22] This action resulted in the formation of the Global Fund for AIDS, tuberculosis, and malaria to assist developing countries in their efforts to treat infected patients. In the United States, the President's Emergency Plan for AIDS Relief was enacted in 2003 and ushered in billions of dollars of bilateral international assistance to countries hardest hit by HIV/AIDS.[23]

As a result of this coordinated effort and support, 6.6 million people today are receiving ARV therapy and there have been significant declines in HIV-related mortality in sub-Saharan Africa.[24,25] While this is a great success, treatment still only reaches a fraction of those who need it and the costs are not sustainable. Less than 40% of people in need of ARV therapy in low- and middle-income countries are able to access and receive therapy. For every person placed on ARV therapy, 2 to 3 individuals are newly infected with HIV. Projections estimate that 20 million more people will acquire HIV by 2031, which will increase treatment costs up to $35 billion a year, raising the issues of nonsustainability.[26,27]

Evolution of Prevention Strategies

Reducing incidence has always been a top priority for most countries, and prevention strategies have evolved over the 3 decades. The initial strategy was based on behavioral change: abstinence, be faithful, and use a condom. This strategy met with only limited success, with Thailand's condom campaign being an exception. The second generation of prevention strategies focused on needle exchange programs, which have been highly successful where supported, and more recently male circumcision. Over 30 observational studies suggested that male circumcision was associated with reduced heterosexual HIV acquisition,[28] thereby leading to 3, randomized controlled trials of 10,000 men in South Africa, Kenya, and Uganda.[29–31] All 3 trials demonstrated that male circumcision significantly decreased HIV acquisition by 50% to 60%. Follow-up studies demonstrate durability of effectiveness ranging from 68% to 76%.[32,33] Additional benefits to male circumcision were reduction in a number of STDs, including reduction in genital ulcer disease by 47%, HSV-2 by 28%, pro-inflammatory anaerobes by 72%, and high-risk HPV infections by 35%.[34–38] Similarly, in the female partners of men who were circumcised, genital ulcer disease was reduced by 22%, trichomoniasis by 48%, severe bacterial vaginosis by 61%, and high-risk HPV by 28%.[39]

Cost-effectiveness studies have demonstrated that male circumcision is perhaps one of the most cost-effective means of preventing HIV infection. It is estimated that the cost per infection averted is $150 to $900 over a 10-year period depending on the underlying HIV incidence in the population.[40,41] However, the obstacles to implementing and scaling-up male circumcision have been significant. While some countries have experienced significant successes in rates of male circumcision, such as Kenya, Swaziland, and parts of South Africa, other

countries have been slow in implementing this important HIV prevention modality.

Treatment as Prevention

The third generation of prevention strategies includes use of ARV containing microbicides, treatment, and vaccines. Early treatment studies demonstrated that ARVs could dramatically reduce viral load, and when given to HIV-infected pregnant women and their infants, mother-to-infant transmission was reduced.[42] This intervention was heralded as a major success, and routine screening of pregnant women for HIV infection was recommended followed by ARV treatment during pregnancy and postnatally, along with prophylaxis for the infant.[43] Implementation of these recommendations in the United States and Europe has resulted in a major decline in the number of children infected via perinatal transmission.

Subsequent studies in developing countries demonstrated similar efficacy with less expensive ARVs such as nevirapine alone or in combination with zidovudine.[44–46] By 2010, over 100,000 infant infections have been averted through the scale-up of ARV prophylaxis to HIV-positive pregnant women annually.[24,25] However, as with circumcision, the routine screening of all pregnant women with universal access to ARVs has lagged. Today, only 40% of pregnant women in Sub-Saharan Africa are screened for HIV and offered ARVs if HIV-positive.[25] To provide an impetus to more rapid delivery, The UN General Assembly in May 2011 called for the elimination of HIV perinatal transmission worldwide by 2015.[47] Although this provides a hard target for programs within countries, its success depends on screening of 90% of all pregnant women for HIV with universal access to ARVs, a formidable task for most countries with limited resources.

To determine if HIV viral load was equally responsible for sexual transmission as in perinatal transmission, we identified retrospectively 415 HIV-discordant couples in Rakai.[48] Overall, 90 of the 415 HIV-negative partners seroconverted over 3 years. In a multivariate analysis, each log increment in viral load was associated with a 2.45 risk for transmission. Interestingly, there were no transmissions among partners with serum HIV viral load levels $<$1,500 copies/mL, suggesting that reductions in viral load would be associated with reductions in HIV transmission.

Numerous observational studies subsequently confirmed that effective ARV therapy was associated with reduced sexual transmission.[49–54] In a recent study led by Myron Cohen, 1763 HIV-discordant couples were randomized to early ARV therapy if CD4 counts were between 350 and 550 cells/mm^3 compared with delayed therapy defined as a decline in CD4 cell count below 250 or onset of HIV-related symptoms.[55] A total of 39 HIV transmissions were observed, of which 28 were virologically linked to the infected partner. Of the 28 linked transmissions, only 1 occurred in the early therapy group, demonstrating an efficacy rate of 96%. In addition, subjects receiving early therapy had significantly fewer clinical endpoints such as extrapulmonary tuberculosis or other opportunistic infections.

With a significant reduction in HIV transmission resulting from early initiation of ARV therapy coupled with a significant reduction in HIV clinical events, this study as well as others provide an strong impetus for increased HIV screening of all populations followed by universal access to care and treatment. The concept of HIV treatment as prevention has garnered tremendous interest and hope, and has inspired a series of population-level HIV treatment studies in combination with other prevention strategies.[56–58]

Microbicides and Pre-exposure Prophylaxis

The use of ARVs to prevent acquisition of HIV also witnessed several major successes over the past 2 years. The first major success was the use of a microbicide containing tenofovir (TDF), a nucleotide reverse transcriptase inhibitor. In a randomized trial of 889 women, investigators found that HIV incidence was reduced by 39% in the TDF microbicide gel compared with placebo.[59] In women who used the gel more than 80% of the time, HIV incidence was reduced further with an efficacy rate of 54%. This success in a microbicide containing ARVs, provided yet another success to the HIV prevention agenda, especially for women unable to successfully negotiate mutual monogamy or condom use in their partners.

In a study examining oral pre-exposure prophylaxis (PrEP) to prevent HIV, Grant et al conducted a randomized trial of 2499 HIV-seronegative MSM to receive a combination of 2 ARVs, emtricitabine and TDF (FTC-TDF) or placebo once daily.[60] One hundred men became infected during the follow-up period (36 in the FTC-TDF and 64 in the placebo group), indicating a 44% reduction in the incidence of HIV. For men who adhered to the medication for more than 90% of the days, there was a 73% reduction in HIV acquisition.

On July 13, 2011, 2 new randomized clinical trials were announced demonstrating the efficacy of oral PrEP to prevent HIV acquisition in high-risk men and women in Africa. The Partners PrEP study was a randomized double-blind placebo-controlled 3-arm trial of daily oral TDF, FTC-TDF, and placebo, for the prevention of HIV in HIV discordant partnerships.[61] They enrolled 4758 HIV-serodiscordant couples in Kenya and Uganda and observed an efficacy rate of 62% in the TDF arm and a 73% efficacy in the FTC-TDF arm compared with the placebo. In a separate study conducted in Botswana, 1200 male and female HIV-negative individuals were enrolled in a double-masked, placebo-controlled trial of daily oral TDF-FTC versus a matching placebo.[62] In this study, the overall efficacy in preventing HIV transmission in the TDF-FTC arm was 62.6%. All 3 studies demonstrated that oral use of ARVs (either TDF or TDF-FTC) was effective and safe for prevention of HIV infection among MSM, and heterosexual men and women. Lack of adherence appears to be the limiting factor, but when viewed collectively, all these studies using ARVs opened a new era of HIV prevention.

Have We Reached the Tipping Point?

Gladwell defines the tipping point as "the moment of critical mass, the threshold, the boiling point. . . that influences change."[63] When it comes to the 30-year dissemination of HIV, it is evident that this virus has delivered a severe blow to human society, resulting in over 40 million fatalities and 33 million people living with HIV.[25] Although there were several successes in the prevention of HIV over the years, still 2.5 million people become newly infected each year, illustrating our inability to reduce its spread. However, within the last 4 years, 8 well-conducted randomized clinical trials have demonstrated that HIV transmission and acquisition can be prevented by a variety of biomedical interventions. A single one-time intervention of male circumcision appears to have a durable protective effect for both HIV and STDs in heterosexual men in the range of 68 to 76%. Use of ARVs for prevention of mother-to-child transmission has an effectiveness of $>$95%; administration of ARVs to HIV-discordant couples has an efficacy of 96%; and PrEP to MSM or to high-risk partners in a discordant couple or men and women in Africa ranges from 42% to 73%. For women, microbicides containing ARVs have

now been shown to have an efficacy of 54% if adherent at least 80% of the time. Finally, although not covered in this presentation, there is a glimmer of hope from the recent vaccine trial in Thailand demonstrating a 31% efficacy.[64]

Thus, I believe we have reached a "tipping point" in that we now have highly effective means to reduce HIV incidence and reduce the overall impact of the AIDS pandemic in our society. Recommendations by CDC, WHO, and UNAIDS as well as in-country programs have all stressed the importance of routine HIV screening followed by access to care.[65] Once individuals know their HIV status, there are several interventions that should be implemented. Among HIV-positives, early institution of ARV therapy should reduce subsequent transmissions. For those that are HIV negative, access to intensive counseling, condom use, male circumcision for heterosexual men, PrEP for MSM and high-risk heterosexual individuals, and use of microbicides containing ARV compounds should effectively limit transmission of HIV.

The greatest limiting factor to this scenario is the lack of financial resources to implement these strategies. The UN has set goals for 2015 to scale up treatment to 15 million people, to prevent 12 million new infections, to prevent 7.4 million deaths, and to eliminate perinatal and injecting drug use transmission.[27,28] The overall estimated cost for this campaign is $22 billion per year, although the current international contributions to HIV treatment and prevention are approximately half that amount. The alternative for inaction is that by 2031 there will be 50 to 60 million people living with HIV, and the cost of caring for only a small proportion of those individuals will range between $35 to $40 billion per year. It is therefore cost-effective to invest in these interventions now to limit the further expansion of HIV. Thus, we have reached the tipping point in our history of HIV/AIDS where we can really make a difference and can effectively reduce the global impact of HIV. The question is not whether we know how to do it, but whether we have the will and the resources to do it.

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