Published in final edited form as:

Sex Transm Dis. 2011 December ; 38(12): 1089–1093. doi:10.1097/OLQ.0b013e3182387ad6.

2011 Thomas Parran Award Lecture The Thirty-Year War on AIDS: Have We Reached the Tipping Point?

Thomas C. Quinn, M.D., M.Sc.

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 (ASTDA) 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 STDs 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 Erbeling. There are many other colleagues that 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 of the individuals within my laboratory with whom I share this award.

This lecture is dedicated to the memory of two 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 AIDS in Africa, and with others, we built the Infectious Diseases Institute in Kampala, Uganda that is now one of the foremost HIV care and treatment facilities in East Africa. I thank them for their guidance and warm friendship.

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 five previously healthy young men in Los Angeles, California (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 acquired immunodeficiency syndrome (AIDS). Over the ensuing year, similar opportunistic infections were reported in

Correspondence: Thomas C. Quinn, M.D. Division of Infectious Diseases The Johns Hopkins University School of Medicine 855 N. Wolfe St., Suite 530 Baltimore, MD 21205 tquinn@jhmi.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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 primary risk exposure was via heterosexual contact.

Two sentinel reports published one 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 (LAV) or later the human immunodeficiency virus (HIV) was identified as the cause of AIDS(7). Utilizing specimens from our initial investigation in Kinshasa, we found that 94% of our African patients with AIDS were seropositive to LAV/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 over age 40. 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 STDs, and occupational groups such as long-distance truck drivers, military personnel and female sex workers had the highest infection rates. HIV prevalences 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 greater than 10% in the adult population. In seven countries, at least one in four adults were living with HIV(12,13).

Even in the US, sharp increases in the number of new annual AIDS diagnoses and deaths, were reported, reaching highs of 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, respectively(3). Despite this decline in AIDS cases, approximately 45,000–60,000 new infections occur annually(14–16). Today, 53% of new HIV infections are in 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 seven times higher in blacks compared to 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 one or two pills. In 1984–85, 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 antiretroviral drugs had essentially turned the tide 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 US, the President's Emergency Plan for AIDS Relief (PEPFAR) 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, two to three 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 non-sustainability(26,27).

Evolution of Prevention Strategies

Reducing incidence has always been a top priority for most countries, and prevention strategies have evolved over the three 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 three, randomized controlled trials of 10,000 men in South Africa, Kenya, and Uganda(29–31). All three 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 ten-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 U.S. 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). In order 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). While 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 three 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 < 1500 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, 1,763 HIV-discordant couples were randomized to early ARV therapy if CD4 counts were between 350 and 550 cells/mm³ compared to 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 one 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 antiretroviral 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 PrEP

The use of ARVs to prevent acquisition of HIV also witnessed several major successes over the past two years. The first major success was the use of a microbicide containing tenofovir, a nucleotide reverse transcriptase inhibitor. In a randomized trial of 889 women, investigators found that HIV incidence was reduced by 39% in the tenofovir microbicide gel compared to 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 2,499 HIV-seronegative men who have sex with men (MSM) to receive a combination of two ARVs, emtricitabine and tenofovir (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, two 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 three-arm trial of daily oral tenofovir (TDF), emtricitabine/tenofovir (FTC-TDF) and placebo, for the prevention of HIV in HIV discordant partnerships(61). They enrolled 4,758 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 to the placebo. In a separate study conducted in Botswana, 1,200 male and female HIV-negative individuals were enrolled in a double-blinded, placebo-controlled trial of daily oral TDF-FTC vs. a matching placebo(62). In this study the overall efficacy in preventing HIV transmission in the TDF-FTC arm was 62.6%. All three 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 utilizing 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 four years, eight 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 68–76%. 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 pre-exposure prophylaxis 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 utilization, male circumcision for heterosexual men, PrEP for MSM and high-risk heterosexual individuals, and use of microbicides containing ARV compounds should effectively limit HIV's transmission.

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–\$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.

Acknowledgments

This work was supported by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, Bethesda, MD.

References

1. Centers for Disease Control and Prevention. Pneumocystis pneumonia—Los Angeles. MMWR. 1981; 30:250–252. [PubMed: 6265753]
2. Centers for Disease Control and Prevention. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men—New York City and Clifornia. MMWR. 1981; 30:305–308. [PubMed: 6789108]
3. Centers for Disease Control and Prevention. HIV surveillance—United States, 1981–2008. MMWR. 2011; 60:689–693. [PubMed: 21637182]
4. Clumeck N, Mascart-Lemone F, deMaubeuge J, et al. Acquired immune deficiency syndrome in Black Africans. The Lancet. 1983; 1:642.
5. Serwadda D, Mugerwa RD, Sewankambo NK, et al. Slim disease: a new disease in Uganda and its association with HTLV-III infection. The Lancet. 1985; 2:849–852.
6. Piot P, Quinn TC, Taelman H, et al. Acquired immunodeficiency syndrome in a heterosexual population in Zaire. Lancet. 1984; 2:65–69. [PubMed: 6146009]
7. Gallo RC, Montagnier L. The discovery of HIV as the cause of AIDS. N Engl J Med. 2003; 349:2283–2285. [PubMed: 14668451]
8. Brun-Vezinet F, Rouzioux C, Montagnier L. Prevalence of antibodies to lymphadenopathy-associated retrovirus in African patients with AIDS. Science. 1984; 226:453–456. [PubMed: 6238406]
9. Nzilambi N, DeCock KM, Forthal DN, et al. The prevalence of infection with human immunodeficiency virus over a 10-year period in rural Zaire. N Engl J Med. 1988; 318:276–279. [PubMed: 3336420]
10. McCormick JB, Krebs JW, Mitchell SW, et al. Isolation of human immune deficiency virus from African AIDS patients and from persons without AIDS or IgG antibody to human immune deficiency virus. Am J Trop Med Hyg. 1987; 36:102–106. [PubMed: 2949638]
11. Quinn TC, Mann JM, Curran JW, Piot P. AIDS in Africa: an epidemiologic paradigm. Science. 1986; 234:955–963. [PubMed: 3022379]
12. Quinn TC. Global burden of the HIV pandemic. The Lancet. 1996; 348:99–106.
13. UNAIDS. AIDS epidemic update: December 2000. World Health Organization; UNAIDS; Geneva: 2000.
14. Hall HI, Song R, Rhodes P, et al. HIV Incidence Surveillance Group. Estimation of HIV incidence in the United States. JAMA. 2008; 300:520–529. [PubMed: 18677024]
15. Prejean J, Song R, Hernandez A, et al. Estimated HIV Incidence in the United States, 2006–2009. PLoS One. 2011; 6:e17502. [PubMed: 21826193]
16. Centers for Disease Control and Prevention. HIV prevalence estimates—United States, 2006. MMWR. 2008; 57:1073–1076. [PubMed: 18830210]
17. Hall HI, Espinoza L, Benbow N, Hu YW, The Urban Areas HIV Surveillance Workgroup. Epidemiology of HIV infection in large urban areas in the United States. PLoS One. 2010; 5:e12756. [PubMed: 20856793]
18. van Sighern AI, Gras LA, Reiss P, et al. Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. AIDS. 2010; 24:1627–1636.
19. Ray M, Logan R, Sterne JA, et al. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. AIDS. 2010; 24:123–137. [PubMed: 19770621]
20. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet. 2008; 372:293–299. [PubMed: 18657708]
21. Piot P, Coll Seck AM. Internatioanl response to the HIV/AIDS epidemic: planning for success. Bull World Health Organ. 2001; 79:1106–1112. [PubMed: 11799442]
22. Boutayeb A. The impact of HIV/AIDS on human development in African countries. BMC Public Health. Nov 18.2009 9(Suppl 1):S3. [PubMed: 19922687]
23. Committee for the Evaluation of the President's Emergency Plan for AIDS Relief (PEPFAR) Implementation. PEPFAR Implementation: Progress and Promise. In: Sepulveda, J.; Carpenter, C.;

- Curran, J.; Holzemer, W.; Smits, H.; Scott, K.; Orzo, M., editors. Institute of Medicine of the National Academies. The National Academies Press; Washington D.C.: 2011.
24. UNAIDS. AIDS at 30: Nations at the Crossroads. UNAIDS; Geneva: 2011.
 25. Joint United Nations Programme on HIV/AIDS. Global report: UNAIDS report on the global AIDS epidemic 2010. UNAIDS; Geneva, Switzerland: 2010.
 26. Shattock RJ, Warren M, McCormack S, Hankins CA. Turning the tide against HIV. *Science*. 333(6038):42–43. [PubMed: 21719662]
 27. Schwartlander B, Stover J, Hallett T, et al. Towards an improved investment approach for an effective response to HIV/AIDS. *Lancet*. 2011; 377:2031–2041. [PubMed: 21641026]
 28. Weiss HA, Halperin D, Bailey RC, Hayes RJ, Schmid G, Hankins CA. Male circumcision for HIV prevention: from evidence to action? *AIDS*. 2008; 22:567–574. [PubMed: 18316997]
 29. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. *PLoS Med*. 2005; 2:e298. [PubMed: 16231970]
 30. Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomized trial. *Lancet*. 2007; 369:657–666. [PubMed: 17321311]
 31. Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomized controlled trial. *Lancet*. 2007; 369:643–656. [PubMed: 17321310]
 32. Kong, X.; Kigozi, G.; Sempija, V., et al. Longer-term effects of male circumcision on HIV incidence and risk behaviors during post-trial surveillance in Rakai, Uganda. 18th Conference on Retroviruses and Opportunistic Infections; Boston. 2011. Abstract
 33. Auvert, B.; Taljaard, D.; Rech, D., et al. Effect of the Orange Farm (South Africa) male circumcision roll-out (ANRS-12126) on the spread of HIV. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention; Rome, Italy. 17–20 July 2011; Abstract WELBC02
 34. Weiss HA, Thomas SL, Munabi SK, Hayes RJ. Male circumcision and the risk of syphilis, chancroid, and genital herpes: a systematic review and meta-analysis. *Sex Transm Infect*. 2006; 82:101–110. [PubMed: 16581731]
 35. Tobian AA, Serwadda D, Quinn TC, et al. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. *N Engl J. Med*. 2009; 360:1298–1309. [PubMed: 19321868]
 36. Gray RH, Serwadda D, Tobian AAR, et al. Effects of genital ulcer disease and herpes simplex virus type 2 on the efficacy of male circumcision for HIV prevention: Analyses from the Rakai trials. *PLoS Med*. 2009; 6:e1000187. [PubMed: 19936044]
 37. Gray RH, Serwadda D, Kong X, et al. Male circumcision decreases acquisition and increases clearance of high-risk human papillomavirus in HIV-negative men: a randomized trial in Rakai, Uganda. *J Infect Dis*. 2010; 201:1455–1462. [PubMed: 20370483]
 38. Tobian AAR, Gray RH, Quinn TC. Male circumcision for the prevention of acquisition and transmission of sexually transmitted infections. The case for neonatal circumcision. *Arch Pediatr Adolesc Med*. 2010; 164:78–84. [PubMed: 20048246]
 39. Gray R, Kigozi G, Serwadda D, et al. The effects of male circumcision on female partners; genital tract symptoms and vaginal infections in a randomized trial in Rakai, Uganda. *Am J Obstet Gynecol*. 2009; 200:42.e1–42.e7. [PubMed: 18976733]
 40. Joint United Nations programme on HIV/AIDS. New data on male circumcision and HIV prevention: policy and programme implications. Joint United Nations Programme on HIV/AIDS; Montreux, Switzerland: 2007.
 41. Gray RH, Li X, Kigozi G, et al. The impact of male circumcision on HIV incidence and cost per infection prevented: a stochastic simulation model from Rakai, Uganda. *AIDS*. 2007; 21:845–850. [PubMed: 17415039]
 42. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. *N Engl J Med*. 1999; 341:394–402. [PubMed: 10432324]
 43. Mofenson LM, Centers for Disease Control and Prevention; U.S. Public Health Task Force. U.S. Public Health Service Task Force recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. *MMWR Recomm Rep*. 2002; 51:1–38. [PubMed: 12489844]

44. Guay LA, Musoke P, Felming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *The Lancet*. 1999; 354:795–802.
45. Bedri A, Gudetta B, Isehak A, et al. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet*. 2008; 372:300–313. [PubMed: 18657709]
46. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomized controlled trial. *Lancet*. 1999; 353:773–780. [PubMed: 10459957]
47. World Health Organization. PMTCT strategic vision 2010–2015: preventing mother-to-child transmission of HIV to reach the UNGASS and Millenium Development Goals. http://www.who.int/hiv/pub/mtct/strategic_vision.pdf
48. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med*. 2000; 342:921–929. [PubMed: 10738050]
49. Cohen MS, Gay CL. Treatment to prevent transmission of HIV-1. *Clin Infect Dis*. 2010; 50(Suppl 1):S85–S95. [PubMed: 20397961]
50. Reynolds SJ, Makumbi F, Nakogozzi G, et al. HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy. *AIDS*. 2011; 25:473–477. [PubMed: 21160416]
51. Donnell D, Baeten JM, Kiarie J, et al. Partners in Prevention HSV/HIV Transmission Study Team. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet*. 2010; 375:2092–2098. [PubMed: 20537376]
52. Attia S, Egger M, Muller M, et al. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS*. 2009; 23:1397–1404. [PubMed: 19381076]
53. Angelmyer, A.; Rutherford, GW.; Baggaley, RC., et al. The Cochrane Library, Issue 8. John Wiley & Sons, Ltd.; Chichester, UK: 2011. Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples. Cochrane Review.
54. Del Romero J, Castilla J, Hernando V, et al. Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross-sectional and prospective cohort study. *Brit Med J*. 2010; 340:c2205. [PubMed: 20472675]
55. Cohen MS, Chen YQ, McCauley M. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011 10.1056/NEJMOA11105243.
56. Granich RM, Gilks CF, Dye C, et al. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet*. 2009; 373:48–57. [PubMed: 19038438]
57. Das M, Chu PL, Santos GM, et al. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. *PLoS ONE*. 2010; 5:e11068. [PubMed: 20548786]
58. Montaner JS, Lima VD, Barrios R, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet*. 2010; 376:532–539. [PubMed: 20638713]
59. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. 2010; 329:1168–1174. [PubMed: 20643915]
60. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010; 363:2587–2599. [PubMed: 21091279]
61. Baeten, J.; Celum, C.; on behalf of the Partners PrEP Study Team. Antiretroviral Pre-Exposure Prophylaxis for HIV-1 prevention among heterosexual African men and women: the Partners PrEP Study. 6th International Conference on HIV Pathogenesis, Treatment and Prevention; Rome, Italy. July 17–20, 2011; Abstract Late Breaker
62. Thigpen, MC.; Kebaabetswe, PM.; Smith, DK., et al. Daily oral antiretroviral use for the prevention of HIV infection in heterosexually active young adults in Botswana: results from the

TDF2study. 6th International Conference on HIV Pathogenesis, Treatment, and Prevention; Rome, Italy. July 17–20, 2011; Abstract WELBC01

63. Gladwell, M. *The Tipping Point: How Little Things Can Make a Big Difference*. Little Brown; New York: 2000.
64. Rerks-Ngarm S, Pitissuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med*. 2009; 361:2209–2220. [PubMed: 19843557]
65. Centers for Disease Control and Prevention. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR*. 2006; 55(No. RR-14)