Published in final edited form as:

N Engl J Med. 2013 June 6; 368(23): 2210–2218. doi:10.1056/NEJMra1201533.

The AIDS Pandemic – A Global Health Paradigm

Peter Piot, M.D., Ph.D.¹ and Thomas C. Quinn, M.D.²

¹London School of Hygiene & Tropical Medicine. London, UK

²National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, USA

Historical Perspective

Just over three decades ago, a new outbreak of opportunistic infections and Kaposi's sarcoma was reported in a small number of homosexual men in California and New York^{1,2}. This universally fatal disease was eventually called the acquired immunodeficiency syndrome (AIDS) due to complete loss of CD4+ T-lymphocytes. Within the first year of its description, the disease was also identified in hemophiliacs, injecting drug users, blood transfusion recipients and infants born to affected mothers. Soon thereafter a heterosexual epidemic of AIDS was revealed in Central Africa, preferentially affecting women^{3,4}. Little did we know at that time that this small number of cases would eventually mushroom into tens of millions of affected individuals, becoming one of the greatest pandemics of modern times.

Within two years of the initial reports of AIDS, a retrovirus, later called the human immunodeficiency virus (HIV), was identified as the cause of AIDS⁵. Diagnostic tests were developed to protect the blood supply and to identify those infected. Additional prevention measures were implemented including risk reducing programs, counseling and testing, condom distribution, and needle exchange programs. However, HIV continued to spread, infecting 10 million individuals within the first decade of its recognition.

The second decade of AIDS was marked by further intensification of the epidemic in other areas of the world. The southern cone of Africa experienced an explosive HIV epidemic. Asia and the former Soviet Union, also noted a marked increase in the spread of HIV. However, by the mid-1990s with the discovery of highly active antiretroviral therapy, fatalities in the developed world started to decline. Use of antiretroviral drugs (ARVs) during pregnancy also resulted in a significant decline in mother to child transmission of HIV in high-income countries. However, without access to ARVs, MTCT and mortality in low and middle-income countries continued to increase to 2.4 million deaths, with over 3 million new infections in 2001, with two thirds occurring in sub-Saharan Africa⁶.

Note – See changes in Ref 27 and 29

27. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Updated 2013. Department of Health and Human Services. (Accessed at <http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf>)

29. European Guidelines for treatment of HIV infected adults in Europe: Version 6.1 2012. (Accessed at <http://www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/EacsGuidelines-v6.1-2edition.pdf>)

WHO clinical staging for HIV consists of stage 1--asymptomatic patients and persistent generalized lymphadenopathy; Stage 2--moderate unexplained weight loss, recurrent respiratory infections, herpes zoster, recurrent oral lesions, etc.; Stage 3--severe weight loss (>10% body weight), chronic diarrhea > one month, thrush, severe bacterial infections, tuberculosis within the last 2 years, etc; Stage 4--opportunistic infections consistent with AIDS, HIV wasting syndrome, HIV encephalopathy, etc.

The International Response to AIDS: a Global Health Paradigm

It was not until the third decade of the epidemic that the world's public health officials, community leaders, and politicians united to combat AIDS. In 2001 the UN General Assembly endorsed a historic Declaration of Commitment on HIV/AIDS and renewed this commitment in 2011⁷. These actions resulted in the formation of a Global Fund to fight AIDS, Tuberculosis, and Malaria to finance AIDS activities in developing countries. In 2003 President G.W. Bush announced the President's Emergency Plan for AIDS Relief (PEPFAR), which allocated billions of dollars to countries hardest hit by AIDS.

This unprecedented global response to the AIDS pandemic can serve as a paradigm for the response to other global health threats. For example the global AIDS response incorporated a multi-sectoral approach involving public health officials, clinicians, civil society, business and labor, armed forces, law, and politicians working in concert and with financial resources in excess of \$15 billion per year⁸ to achieve a decline in HIV incidence and mortality. As a pandemic, it required a coordinated global response led by UNAIDS since 1996. This transformational response helped redefine what is meant by health diplomacy and a led to a new culture of accountability in international development. Tiered pricing of medicines became commonplace and renewed optimism provided a boost for research on other neglected global health issues. This response to AIDS highlighted the shortage in health care workers, and the weaknesses in availability of essential medications, in primary health care and in our public health systems. Stigma and inequities in care for those affected by HIV focused attention on social and medical equity and human rights.

Whereas it has been argued that health care provision for patients with other conditions may have suffered from "vertical" AIDS programs, in particular because of their recruitment of scarce health care workers⁹, there is also evidence that the AIDS response eventually had multiple collateral benefits including a major increase in attention and funding for global health, particularly for malaria and tuberculosis, and a strengthening of services for maternal and child health in some countries¹⁰⁻¹². Although not perfect, this type of unified and integrated response to AIDS can serve as a model for society's future response to the growing epidemic of chronic diseases, obesity, injuries, and for maternal and child health¹³.

The Fourth Decade of AIDS

UNAIDS estimates that in 2011, 34.2 million people were living with HIV, as compared to 29.1 million in 2001; 2.5 million had become newly infected, a 24% decline as compared to 2001, and 1.7 million died, a decline of 11% as compared to 2001^{8,14}. Similarly, new infections among neonates and infants have decreased from a peak of 570,000 in 2003 to 330,000 in 2011 as a result of interventions to prevent MTCT.

However, these global figures hide a wide diversity. Figure 1 shows adult HIV prevalence levels by country, with sub-Saharan Africa continuing to be the most affected continent, followed by Eastern Europe and the Caribbean¹⁵. A special case is southern Africa, where HIV has become hyper-endemic with adult HIV prevalence rates as high as 31% in Swaziland, 25% in Botswana, and 17% in South Africa, reaching an astonishing 54% among women between 30 and 34 years in Swaziland⁷. Even within a country, differences in HIV prevalence can vary widely by region and risk group. Thus, in 2010 within South Africa, provincial antenatal HIV prevalence ranged from 18.4% in the Northern Cape to 39.5 % in Kwazulu Natal¹⁶. Men who have sex with men (MSM), female sex workers, injecting drug users, truck drivers, fishermen, and military are disproportionately affected around the world¹⁷⁻²².

There is also heterogeneity in epidemiologic trends. Whereas HIV spread is slowing in most regions, HIV incidence continues to increase in Eastern Europe, and several Asian countries¹⁴. There is also a resurgence of HIV infection due to increased risk behaviour among MSM in several European cities, such as a 68% increase in sexual risk behaviour among MSM in Amsterdam²³ in spite of high rates of HIV testing and access to ART. At the same time HIV is spreading to previously unaffected populations, such as IDUs in parts of Africa, and MSM across Asia and Africa, where widespread homophobia drives these men underground.

Progress in Treatment of HIV Infection

With 25 licensed antiretroviral drugs available for HIV treatment, there is a wide choice of effective drugs for treating HIV. With reductions in ARV price, availability of generic ARVs, and international financial aid, the number of people receiving ART has risen from < 200,000 in 2001 to 8 million individuals in low and middle-income countries¹⁴ (Figure 2). As a result of the marked increase in availability of ARVs, the death rate in some of the hardest hit countries has started to decline following mortality reductions in the late nineties in the U.S. and Europe²⁴.

With the life expectancy of an HIV-infected individual under treatment approaching an uninfected individual^{25,26}, there has been an increased emphasis on starting ARV therapy much earlier in the course of infection. The revised 2012 DHHS guidelines recommend ART for all HIV-infected individuals²⁷ (Table 1). These recommendations are based on evidence of ongoing HIV replication on disease progression. Additionally because ART use prevents transmission of HIV in discordant couples²⁸, the guidelines recommend that ART be offered to all HIV infected individuals to reduce the risk for their sexual partners.

In variance with the US and European guidelines²⁹, WHO guidelines continue to recommend treating all individuals with CD4 counts > 350 recognizing the limitations of cost and availability in many countries^{30,31}. However, all guidelines strongly recommend ART for individuals regardless of CD4 count with pregnancy, history of an AIDS-defining illness, tuberculosis, and HIV/hepatitis B co-infection, and more recently for HIV-discordant couples³¹ (Table 1).

Despite advances in the accessibility to ARVs, many challenges remain in the provision of HIV care. In the U.S., the CDC estimates that 1.2 million persons are living with HIV, of whom only 28% ultimately had suppressed viral levels³²⁻³⁴ (Figure 3). In one study in Mozambique, of 7,005 identified HIV-infected individuals, only half enrolled in care and only a small percent ultimately started ARVs and maintained adherence rates >90% for more than 180 days³⁵ (Figure 3). This declining cascade in access to treatment is mostly due to an inconsistent pattern of diagnosis, linkage to care, differences in levels of CD4 cell count for initiation, and retention in care. In sub-Saharan Africa the percent of individuals being tested for HIV remains low. The average CD4 cell count at time of ART initiation in low and middle-income countries remains low with a median cell count of 124 cells/mm³^{3,36}. Intensified efforts are needed to identify those infected, initiate therapy, use standardized effective regimens, and encourage adherence and retention. Only with success at each stage in the continuum of care can the ultimate goals of improving health, extending lives, and preventing further HIV transmission be achieved.

Evolution of Prevention Strategies

Reducing incidence has been a top priority for AIDS control. The initial prevention strategy was based on behavioral change: abstinence, be faithful, and use of a condom. This strategy met with only limited success, with Thailand's 100% condom campaign and Uganda's

initial AIDS response being exceptions^{37,38}. There is growing evidence that a relative decline of HIV incidence rates of over 25% between 2000 and 2010 in numerous African countries are the result of behavioural change³⁹. Condom use continues to increase, with several countries including South Africa, India and Botswana, reporting over 75% condom use during last high risk sexual intercourse⁶. However, condom use is still low in many other countries. A cause of concern is that in several African countries such as Uganda, South Africa and Botswana, more men reported multiple partners in 2009 than ten years ago⁷.

Access to sterile injection equipment and substitution therapy, referred to as harm reduction, is highly effective in reducing HIV spread among IDUs⁴⁰. Yet, several countries in Eastern Europe and Asia whose HIV epidemics are driven by injecting drug use continue to use ineffective, punitive approaches, with sustained high HIV incidence as a consequence, also feeding the sexual spread of HIV⁴¹. Structural approaches⁴² such as programs to reduce violence against women⁴³ and cash transfers, i.e., cash payments that can be used for food purchases, transportation, education, health care and other expenses in adolescent school girls in Malawi⁴⁴, should be integrated more in HIV prevention agendas. In addition, laws that drive MSM underground or prohibit harm reduction for IDUs, can be major obstacles to effective HIV prevention¹⁷. That such laws can be reversed was illustrated by India, which decriminalised same sex relations in 2009.

Biomedical Advances in Prevention

Male Circumcision

The first major biomedical breakthrough in prevention was the finding of reduced susceptibility to HIV in circumcised men with an efficacy rate of 50 to 60% in three clinical trials⁴⁵⁻⁴⁷. Five years after the completion of these studies, high rates of community effectiveness (70%) in decreasing HIV incidence have been reported⁴⁸. With an estimated cost per infection averted in the range of \$150 to \$900 over a ten-year period depending on local HIV incidence, male circumcision appears to be one of the most cost-effective prevention interventions, requiring only a one-time intervention⁴⁹.

PrEP

Use of ARVs prior to sex is referred to as pre-exposure prophylaxis. Pre-coital use of 1% Tenofovir gel reduced HIV acquisition by 39% in women and daily oral Tenofovir/Emtricitabine among MSM reduced HIV acquisition by 44%, with greater efficacy observed among individuals who achieved high levels of adherence in both trials^{50,51}. Daily Tenofovir and Tenofovir/Emtricitabine reduced HIV acquisition by 66% and 73%, respectively, among uninfected partners in HIV serodiscordant partnerships, and in young heterosexuals in Botswana⁵². While these studies are encouraging, two studies produced conflicting results finding no efficacy with either oral or gel Tenofovir^{53,54}. The explanation for these discrepant studies may be due to low adherence to the drug regimens, or differences in mucosal penetration. Recently, the FDA approved daily oral Truvada (emtricitabine and tenofovir disoproxil fumarate) for PrEP in combination with safer sex practices to reduce the risk of sexually-acquired HIV infection in adults at high risk.

Treatment as Prevention

Viral load is the single greatest risk factor for all transmission modes⁵⁵, and treatment as prevention is based on the fact that ART can reduce plasma and genital HIV viral load to undetectable levels, thereby reducing infectiousness²⁸. This principle was first proved for prevention of MTCT⁵⁶ and subsequently in preventing sexual transmission by 96% within couples²⁸. This shift from a focus on downstream therapeutic application of ART to a more

upstream preventive benefit of eliminating HIV transmission has inspired optimism for the creation of an “AIDS-free generation”..

Combination Prevention

There is consensus that no single intervention can stop the spread of HIV, and that “combination prevention” is the best approach⁵⁷. Effective biomedical interventions coupled with behavioral and structural approaches may now successfully reduce HIV incidence to very low levels and ultimately control the epidemic. There is also a need to test in community randomized trials how effective treatment as prevention works at the population level; what the optimum program design would be, and in combination with which prevention interventions, and equally important, to ensure good treatment coverage for those in immediate need of clinical treatment.

From both an impact and a cost-effectiveness perspective, HIV prevention efforts should focus more on populations at highest risk for transmission, and should be customized to a wider range of realities than is presently the case. It should be stressed that all components of combination prevention require some form of behaviour intervention, be it to ensure adherence to condom use or ARV-based prevention, or to prevent increased risk behaviour. However, even when optimally applying the most effective HIV interventions, most mathematical models suggest that by 2031 – 50 years after the discovery of AIDS – there may still be as many as one million new infections annually globally^{58,59}. While desperately needed, the search for a vaccine still eludes investigators, although one recent trial in Thailand with a 31% efficacy provided a much needed boost to vaccine research⁶⁰.

The Challenges Ahead

After thirty years in the AIDS epidemic, there are over 34 million people living with HIV, and still 2.5 million new infections and 1.7 million deaths each year, emphasizing that the global response will have to be sustained for at least several decades. There is now an impressive array of evidence-based interventions that can be implemented to treat established infections and prevent new ones. Studies among high-risk populations have shown that HIV prevention can work even in the most challenging settings. Yet, despite this, UNAIDS reports that only 60% of sex workers, 46% of IDUs, and 40% of MSM were reached with HIV prevention programs in 2008⁸ and HIV incidence is rising again in several populations, including in Uganda^{8,14}.

In 2011, less than 25% of all HIV infected individuals had access to, or were virologically suppressed with ARV treatment¹⁴. To ensure ART access, many lower-income countries are still dependent almost entirely on international aid, which has declined in recent years. As we witness the increase in chronic care and chronic diseases in people with HIV as a result of treatment and increased life expectancy, innovative solutions of care delivery must be developed, including task shifting and integrated service delivery in the community.

In conclusion, enormous progress has been made in the global AIDS response, but these achievements are fragile because of the enormous challenge of sustaining political, programmatic and technical commitment, and national and international funding. A certain level of AIDS “fatigue” coincides with the unprecedented opportunities of new tools to control AIDS. In this new era prevention and care will need to be targeted strategically and creative combinations of behavioral, biomedical, and structural interventions implemented widely^{58,59}. These programs will require universal access, wide scale implementation, careful monitoring and evaluation, financial and technical resources, and robust commitment. Only then may we begin to see a substantial impact on the spread of HIV globally.

References

1. CDC. Pneumocystis pneumonia--Los Angeles. Morb Mortal Wkly Rep. 1981; 30:250-2.
2. CDC. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men--New York City and California. Morb Mortal Wkly Rep. 1981; 30:305-8.
3. Piot P, Quinn TC, Taelman H, et al. Acquired immunodeficiency syndrome in a heterosexual population in Zaire. Lancet. 1984; ii:65-69. [PubMed: 6146009]
4. Quinn TC, Mann JM, Curran JW, Piot P. AIDS in Africa: an epidemiologic paradigm. Science. 1986; 234:955-63. [PubMed: 3022379]
5. Gallo RC, Montagnier L. The discovery of HIV as the cause of AIDS. The New England Journal of Medicine. 2003; 349:2283-5. [PubMed: 14668451]
6. Piot P, Bartos M, Ghys PD, Walker N, Schwartlander B. The global impact of HIV/AIDS. Nature. 2001; 410:968-73. [PubMed: 11309626]
7. UNAIDS. World AIDS Day Report 2011: How to get to zero: Faster. Smarter. Better. Joint United Nations Programme on HIV/AIDS (UNAIDS); Geneva, Switzerland: 2011.
8. UNAIDS. Global AIDS Response Progress Reporting 2012. Joint United Nations Programme on HIV/AIDS (UNAIDS); Geneva, Switzerland: 2012.
9. Shiffman J. Has donor prioritization of HIV/AIDS displaced aid for other health issues? Health policy and planning. 2008; 23:95-100. [PubMed: 18156161]
10. El-Sadr WM, Abrams EJ. Scale-up of HIV care and treatment: can it transform healthcare services in resource-limited settings? AIDS. 2007; 21(Suppl 5):S65-70. [PubMed: 18090271]
11. Rasschaert F, Pirard M, Philips MP, et al. Positive spill-over effects of ART scale up on wider health systems development: evidence from Ethiopia and Malawi. Journal of the International AIDS Society. 2011; 14(Suppl 1):S3. [PubMed: 21967809]
12. Harries AD, Zachariah R, Jahn A, Schouten EJ, Kamoto K. Scaling up antiretroviral therapy in Malawi-implications for managing other chronic diseases in resource-limited countries. J Acquir Immune Defic Syndr. 2009; 52(Suppl 1):S14-6. [PubMed: 19858929]
13. Lamptey P, Merson M, Piot P, Reddy KS, Dirks R. Informing the 2011 UN Session on Noncommunicable Diseases: applying lessons from the AIDS response. PLoS medicine. 2011; 8:e1001086. [PubMed: 21909245]
14. UNAIDS. Global Report: UNAIDS Report on the Global AIDS Epidemic 2012. Joint United Nations Programme on HIV/AIDS (UNAIDS); Geneva, Switzerland: p. 2012
15. [Accessed Nov 20, 2012, 2012] AIDSinfo Epidemiological Status UNAIDS. 2012. at <http://www.unaids.org/en/dataanalysis/datatools/aidsinfo/>.
16. National Department of Health. The 2010 national antenatal HIV and syphilis prevalence survey in South Africa. Pretoria: 2011.
17. Beyrer C, Baral S, F VG. The global epidemiology of HIV infection among men who have sex with men. Lancet. 2012; 380:367-77. [PubMed: 22819660]
18. Baral S, Beyrer C, Muessig K, et al. Burden of HIV among female sex workers in low-income and middle-income countries: a systematic review and meta-analysis. The Lancet infectious diseases. 2012; 12:538-49. [PubMed: 22424777]
19. Mathers BM, Degenhardt L, Phillips B, et al. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. Lancet. 2008; 372:1733-45. [PubMed: 18817968]
20. MacPherson EE, Sadalaki J, Njoloma M, et al. Transactional sex and HIV: understanding the gendered structural drivers of HIV in fishing communities in Southern Malawi. Journal of the International AIDS Society. 2012; 15(Suppl 1):1-9. [PubMed: 22713352]
21. Pandey A, Benara SK, Roy N, et al. Risk behaviour, sexually transmitted infections and HIV among long-distance truck drivers: a cross-sectional survey along national highways in India. AIDS. 2008; 22(Suppl 5):S81-90. [PubMed: 19098482]
22. Abebe Y, Schaap A, Mamo G, et al. HIV prevalence in 72,000 urban and rural male army recruits, Ethiopia, 1999-2000. Ethiopian medical journal. 2003; 41(Suppl 1):25-30. [PubMed: 15227877]

23. Bezemer D, de Wolf F, Boerlijst MC, et al. A resurgent HIV-1 epidemic among men who have sex with men in the era of potent antiretroviral therapy. *AIDS*. 2008; 22:1071–7. [PubMed: 18520351]
24. Bendavid E, Holmes C, Bhattacharya J, G Miller. HIV development assistance and adult mortality in Africa. *JAMA : the journal of the American Medical Association*. 2012; 307:2060–7. [PubMed: 22665105]
25. 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; 372:293–9. [PubMed: 18657708]
26. Mills EJ, Barnighausen T, Negin J. HIV and aging--preparing for the challenges ahead. *The New England journal of medicine*. 2012; 366:1270–3. [PubMed: 22475591]
27. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services; Updated 2013 Accessed at <http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf>
28. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *The New England journal of medicine*. 2011; 365:493–505. [PubMed: 21767103]
29. European Guidelines for treatment of HIV infected adults in Europe: Version 6.1 2012. Accessed at <http://www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/EacsGuidelines-v6.1-2edition.pdf>
30. WHO. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. Geneva, Switzerland: 2010. 2010 rev. http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf 2010. Report No.: ISBN 978 92 4 159976 4
31. WHO. Guidance on Couples HIV Testing and Counselling Including Antiretroviral Therapy For Treatment and Prevention in Serodiscordant Couples. UNAIDS; Geneva, Switzerland: 2012.
32. CDC. HIV surveillance--United States, 1981–2008. *MMWR Morbidity and mortality weekly report*. 2011; 60:689–93. [PubMed: 21637182]
33. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2011; 52:793–800. [PubMed: 21367734]
34. Hall, HI.; Frazier, EL.; Rhodes, P., et al. Continuum of HIV care: differences in care and treatment by sex and race/ethnicity in the USA; Abstract FRLBX05 International AIDS Conference; Washington, DC. July 17–22, 2012;
35. Micek MA, Gimbel-Sherr K, Baptista AJ, et al. Loss to follow-up of adults in public HIV care systems in central Mozambique: identifying obstacles to treatment. *J Acquir Immune Defic Syndr*. 2009; 52:397–405. [PubMed: 19550350]
36. Gupta A, Nadkarni G, Yang WT, et al. Early mortality in adults initiating antiretroviral therapy (ART) in low- and middle-income countries (LMIC): a systematic review and meta-analysis. *PloS one*. 2011; 6:e28691. [PubMed: 22220193]
37. Stoneburner RL, Low-Beer D. Population-level HIV declines and behavioral risk avoidance in Uganda. *Science*. 2004; 304:714–8. [PubMed: 15118157]
38. UNAIDS. Case Study. Joint United National Programme on HIV/AIDS; Geneva, Switzerland: Geneva: 2000. Evaluation of the 100% condom programme in Thailand.
39. Ghys PD, Gouws E, Lyster R, et al. Trends in HIV prevalence and sexual behaviour among young people aged 15–24 years in countries most affected by HIV. *Sexually transmitted infections*. 2010; 86(Suppl 2):ii72–ii83. [PubMed: 21106519]
40. Beasley, R. Brief Report. Institute of Medicine of the National Academies; Washington, DC: Jan. 2010 Reducing Harm. 2010
41. Beyrer C, Malinowska-Sempruch K, Kamarulzaman A, Kazatchkine M, Sidibe M, Strathdee SA. Time to act: a call for comprehensive responses to HIV in people who use drugs. *Lancet*. 2010; 376:551–63. [PubMed: 20650515]
42. Gupta GR, Parkhurst JO, Ogden JA, Aggleton P, Mahal A. Structural approaches to HIV prevention. *Lancet*. 2008; 372:764–75. [PubMed: 18687460]

43. Jan S, Ferrari G, Watts CH, et al. Economic evaluation of a combined microfinance and gender training intervention for the prevention of intimate partner violence in rural South Africa. *Health policy and planning*. 2011; 26:366–72. [PubMed: 20974751]
44. Baird SJ, Garfein RS, McIntosh CT, Ozler B. Effect of a cash transfer programme for schooling on prevalence of HIV and herpes simplex type 2 in Malawi: a cluster randomised trial. *Lancet*. 2012; 379:1320–9. [PubMed: 22341825]
45. 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; 21:845–50. [PubMed: 17415039]
46. 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 medicine*. 2005; 2:e298. [PubMed: 16231970]
47. Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet*. 2007; 369:643–56. [PubMed: 17321310]
48. Gray R, Kigozi G, Kong X, et al. The effectiveness of male circumcision for HIV prevention and effects on risk behaviors in a posttrial follow-up study. *AIDS*. 2012; 26:609–15. [PubMed: 22210632]
49. Tobian AA, Serwadda D, Quinn TC, et al. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. *The New England journal of medicine*. 2009; 360:1298–309. [PubMed: 19321868]
50. 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; 329:1168–74. [PubMed: 20643915]
51. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *The New England journal of medicine*. 2010; 363:2587–99. [PubMed: 21091279]
52. Thigpen M, Kebaabetswe P, Paxton L, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *New England Journal of Medicine*. 2012; 367:423–34. [PubMed: 22784038]
53. Baeten J, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV-1 prevention in heterosexual men and women. *New England Journal of Medicine*. 2012; 367:399–410. [PubMed: 22784037]
54. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among african women. *New England Journal of Medicine*. 2012; 367:411–22. [PubMed: 22784040]
55. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *The New England journal of medicine*. 2000; 342:921–9. [PubMed: 10738050]
56. Garcia PM, Kalish LA, Pitt J, et al. Women and Infants Transmission Study Group. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. *The New England journal of medicine*. 1999; 341:394–402. [PubMed: 10432324]
57. Piot P, Bartos M, Larson H, Zewdie D, Mane P. Coming to terms with complexity: a call to action for HIV prevention. *Lancet*. 2008; 372:845–59. [PubMed: 18687458]
58. Quinn, T.; Serwadda, D. Brief Report. Institute of Medicine of the National Academies; Washington, DC: Nov. 2010 Preparing for the Future of HIV/AIDS in Africa: A Shared Responsibility. 2010
59. AIDS, 2031, Consortium. *AIDS: Taking a Long-Term View*. 1st ed.. FT Press; Upper Saddle River, New Jersey: 2010.
60. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *The New England Journal of Medicine*. 2009; 361:2209–20. [PubMed: 19843557]

Figure 1.
World map with HIV prevalence by country (Data from UNAIDS¹⁵).

Figure 2. Number of people receiving antiretroviral therapy in low- and middle-income countries, by region, 2002-2011. (Data from UNAIDS¹⁴).

Figure 3.

HIV Treatment cascade in the US and Mozambique from time of diagnosis to retention and adherence to antiretroviral therapy. Data for the US are derived from Gardner et al³³ and data for Mozambique are estimated from Micek et al³⁵. Data for adherence to ART for the US represent the % of individuals virally suppressed, while for Mozambique, the data represent the % adherent to ART by questionnaire and pill count and retained in care for more than one year as viral levels were not obtained.

Table 1
Guidelines for Initiation of Antiretroviral Drugs in HIV-infected Adults

Clinical Condition and/or CD4 Count	Recommendations to Start Treatment		
	DHHS 2013 ^{27, A}	EACS 2012 ²⁹	WHO 2010 ^{30,31}
CD4 count 350 cells/mm ³	Yes (AI)	Yes	Yes
CD4 count > 350-500 cells/mm ³	Yes (AII)	Asymptomatic: Consider Symptomatic: Yes	Stage 1 or 2: Defer Stage 3 or 4: Yes
CD4 count 500 cells/mm ³	Yes (BIII)	Asymptomatic: Defer Symptomatic: Yes	Stage 1 or 2: Defer Stage 3 or 4: Yes
Pregnancy	Yes (AI)	Yes	Yes
History of AIDS-defining illness	Yes (AI)	Yes	Yes
HIV-associated nephropathy	Yes (AII)	Yes	Yes
Tuberculosis coinfection	Yes (AII)	Yes	Yes
HBV coinfection	Yes (AII)	Yes, when treatment is indicated for HBV. Defer if HBV does not require treatment and CD4 is >500; consider if CD4 is 350-500	Yes, when treatment is indicated for HBV
HCV coinfection	Yes (BII)	Yes if CD4 < 500; Defer/Consider if CD4 > 500	Not specified
Risk for Transmission			
Perinatal Transmission	Yes (AI)	Yes	Yes
Heterosexual Transmission	Yes (AI)	Strongly Consider	Yes
Other Sexual Transmission Risk Groups	Yes (AIII)	Strongly Consider	Not specified
Preferred Combination Regimens			
Patients receiving first line therapy	TDF/FTC [*] + one of the following: EFV (AI) ATV/r (AI) DRV/r (AI) RAL (AI)	(TDF/FTC [*]) or (ABC/3TC) + one of the following: NVP EFV Ripivirine ATV/r DRV/r LPV/r RAL	(AZT or TDF)+(3TC or FTC)+(EFV or NVP)
HIV/TB	Regimens as noted above ^B	TDF/FTC [*] /EFV ^B Alternative is TDF/FTC [*] +PI/r with rifabutin	(AZT or TDF)+(3TC or FTC)+ EFV ^B
HIV/HBV	TDF/FTC [*] + EFV (AI) or other regimens as noted	TDF/FTC [*] /EFV or other regimens as noted above	TDF/FTC [*] /EFV

Clinical Condition and/or CD4 Count	Recommendations to Start Treatment		
	above		
Pregnancy	AZT/3TC plus ATV/r or LPV/r (A1). See perinatal treatment guidelines for more details	AZT/3TC + (LPV/r, SQV/r or ATV/r)	AZT/3TC/NVP

Rating of Recommendations: A = Strong; B = Moderate; C=Optional

Rating of Evidence: I= data from randomized controlled trials; II=data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III=expert opinion
 Abbreviations: DHHS—Department of Health and Human Services; EACS—European AIDS Clinical Society; WHO—World Health Organization; AZT—zidovudine; ABC—abacavir; 3TC—lamivudine; FTC—emtricitabine; TDF—tenofovir DF; NVP—nevirapine; EFV—efavirenz; RAL—raltegravir; /r—ritonavir-boosted; LPV/r—lopinavir/ritonavir; ATV/r—ritonavir-boosted atazanavir; DRV/r—ritonavir-boosted darunavir

* 3TC can be used instead of FTC, or visa versa

^A A list of panel recommended alternative and acceptable regimens can be found in all of the three guidelines listed above.. Based on individual patient characteristics and needs, in some instances an alternative regimen may actually be preferred for a patient. Selection of a regimen should be individualized on the basis of virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results and comorbid conditions.

^B In patients with HIV and tuberculosis (TB), ART should be started within 2 weeks of starting TB treatment if CD4 count <50 cells/mm3 (A1). For CD4 counts>50 cells/mm3, ART can be delayed beyond 2 weeks but the strength of the recommendation varies on CD4 counts with time delay in initiation of ARV increasing with increasing CD4 counts. ARV dosing should be adjusted when used in combination with rifampin or rifabutin