Thirty Years of HIV and AIDS: Future Challenges and Opportunities

Carl W. Dieffenbach, PhD, and Anthony S. Fauci, MD

As the third decade since AIDS was first recognized comes to an end, extraordinary advances have occurred in the understanding, treatment, and prevention of HIV infection and AIDS. As a result of these successes, it is now time to focus on future challenges. Paramount among these is reaching the goal of truly controlling and ultimately ending the HIV and AIDS pandemic.

To that end, AIDS researchers and public health personnel worldwide are aggressively pursuing 3 key areas of scientific research. Given the availability of highly effective therapeutic regimens for HIV infection, the first challenge is efficiently identifying a maximum number of HIV-infected persons through voluntary HIV testing and initiating antiretroviral therapy (ART). Second, scientists are trying to develop a cure for HIV infection, which would alleviate the need for lifelong ART. Finally, preventing new cases of HIV infection, which currently number approximately 2.6 million per year globally, is critical to any attempt to end this pandemic. This article addresses each of these challenges and provides directions for the future.

Ann Intern Med. 2011;154:766-771.

For author affiliations, see end of text.

This article was published at www.annals.org on 31 May 2011.

The U.S. medical community became aware of AIDS 30 years ago (1, 2). Since then, the global HIV and AIDS pandemic has caused approximately 60 million infections. Experts estimate that more than 25 million persons have died of AIDS, and more than 33 million currently are living with HIV infection or AIDS (3).

Despite these numbers, progress in basic and clinical research in HIV and AIDS and in the implementation of interventions has been extraordinarily successful. Researchers now understand HIV and its pathogenesis, can rapidly and specifically diagnose HIV infection, and profoundly suppress HIV replication with highly effective antiretroviral therapy (ART) (4–6). Research advances have identified strategies that have nearly eliminated mother–child transmission of HIV infection in many parts of the developed world and reduced the incidence of HIV infection in some developing-world settings (7, 8).

To further control and ultimately end the HIV and AIDS pandemic, we must seriously consider 3 essential research and implementation goals (Table 1) (9, 10). First, we must accelerate the implementation of the many currently available evidence-based HIV treatment and prevention tools. Paramount among these interventions are the delivery of ART to persons who would benefit from such therapy and the establishment and sustained delivery of integrated combination prevention methods that are tailored to the risk factors in various target populations.

Second, research is required to explore innovative approaches to eliminate HIV in infected persons or to control infection without the need for lifelong ART. Researchers should aggressively pursue the goal of a cure for HIV infection.

Third, we must develop new, potent biomedical prevention tools that can be integrated with—and enhance—currently available prevention approaches. Researchers are unlikely to achieve transformative successes in HIV prevention with a unidimensional approach; instead, this will require various versions of combination prevention strategies, depending on the target population (Table 2).

See also:

Web-Only

Conversion of graphics into slides

The Promise and Limitations of ART

One of the most impressive success stories in the translation of basic biomedical research into interventions that positively affect the lives of millions of people has been the delineation of vulnerable targets in the replication cycle of HIV. This achievement has led to the development of highly effective therapies for HIV-infected persons. To understand the enormity of the effect of ART on the lives of HIV-infected persons, it is important to consider that in the early years of the AIDS epidemic before ART was available, the median survival after an AIDS diagnosis was measured in weeks to months and patient care was confined to diagnosing and treating a complex array of opportunistic infections and AIDS-related types of cancer (11–13).

Beginning with the use of zidovudine monotherapy in 1987, 5 classes of antiretroviral drugs have been developed. Combinations of these agents safely and reliably suppress HIV replication in the body below the limits of detection in most HIV-infected persons receiving this therapy. In stark contrast to the early and mid-1980s, if a person aged 20 years is newly infected with HIV today and guideline-recommended therapy is initiated, researchers can predict by using mathematical modeling that this person will live at least an additional 50 years—that is, a close-to-normal life expectancy (14).

Despite these breathtaking advances in therapy for HIV infection, ART has limitations, including the fact that successful treatment of HIV infection requires daily dosing of these agents for the remainder of the patient’s life. This requires health care delivery systems to manage treatment of HIV infection differently from that of typical infec-
tious diseases and more like that of a chronic disease, where long-term follow-up fosters patient adherence. For resource-limited settings and for patients who lack adequate health care coverage, this difference creates a formidable challenge.

In the United States, the development and implementation of the National HIV/AIDS Strategy is designed partially to address the structural barriers to optimal care for HIV-infected persons (15). In this context, a portion of the U.S. agenda for implementing AIDS research focuses on defining optimal, cost-effective ways to increase the uptake of HIV testing; maximize the take-up of services; and foster high levels of adherence to treatment regimens. The National HIV/AIDS Strategy also seeks to fully implement the recommendations of the Centers for Disease Control and Prevention on HIV testing (16) and to establish incentives for organizations that conduct testing to provide efficient and effective linkage to care.

A major success in the third decade of the epidemic has been expansion of HIV care and treatment in the developing world. The U.S. President’s Emergency Plan for AIDS Relief (PEPFAR), initiated in 2003 by former President George W. Bush; the multilateral Global Fund to Fight AIDS, Tuberculosis and Malaria; and such nongovernmental organizations as the Bill and Melinda Gates Foundation, the Clinton Foundation, and Médecins Sans Frontières, among others, have transformed the fate of countless HIV-infected persons in the developing world, particularly southern Africa, by providing treatment and care for those who are infected and prevention services for those at risk for infection (8, 17). As of September 2010, PEPFAR alone had provided ART to more than 3.2 million HIV-infected persons; antiretroviral mother–child transmission prophylaxis to more than 600,000 pregnant women with HIV infection; and care to approximately 11 million people, including orphans whose parents died of AIDS (17).

Even with current efforts, approximately 2.5 million persons are infected with HIV each year. For every 2 persons who begin ART, 5 persons become newly infected (8). Worldwide, treatment guidelines have evolved to recommend earlier initiation of ART (that is, at a higher CD4⁺ T-cell count than previously recommended); however, we recognize that only approximately one third of all HIV-infected persons who need ART are receiving it (6). Antiretroviral therapy will remain the cornerstone of the global response to HIV, and we need to find efficient ways to increase the number of persons receiving these life-saving medications.

As we enter the fourth decade of the HIV and AIDS epidemic, the current situation in which large numbers of new infections occur and HIV-infected persons require lifelong therapy is clearly not sustainable. Therefore, research is more important than ever in developing both tools and strategies to obviate the need for lifelong therapy and new and effective prevention methods.

**Curing HIV Infection**

When we are discussing a cure for HIV infection, it is important to begin with a working definition of *cure*. The most straightforward definition is the permanent remission of a disease in the absence of a requirement for therapy. At the 30-year mark in the HIV epidemic, it is critical to acknowledge that there are no documented cases of a true cure induced by ART, even though ART is very effective in suppressing detectable viral replication for extended periods.

It has been claimed that 1 HIV-infected patient was “cured” after receiving a stem cell transplant to treat a complicating case of leukemia. The transplanted cells expressed a genetic defect that did not allow the replication of C-C chemokine receptor 5–dependent HIV, the most common replicating viruses circulating in persons today (18, 19). Although this case does not present a practical approach for treatment of the millions of HIV-infected persons, it does prove in concept that, under certain circumstances, HIV can be controlled in the absence of ART.

**Table 1. Critical Elements to Control and End the HIV and AIDS Pandemic**

| Seek, test, and treat HIV-infected persons |
|-----------------------------------------|
| Cure at least a proportion of existing HIV infections |
| Prevent new HIV infections with comprehensive combination prevention programs |

---

**Table 2. Potential Components of a Combination Prevention Strategy for HIV Infection**

- Proven interventions
  - Screening the blood supply
  - Condoms
  - Education and behavior modification
  - HIV testing and counseling
  - Treatment/prevention of drug and alcohol abuse
  - Providing clean syringes
  - ARVs to prevent mother–child transmission of HIV
  - Postexposure prophylaxis against HIV by using ART
  - Male circumcision

- Interventions under development
  - Vaccines
  - Microbicides for vaginal and rectal use
  - Preexposure prophylaxis against HIV by using ARVs
  - Treatment of other sexually transmitted infections
  - ART for HIV-infected persons
  - Use of the seek, test, link-to-care, and treat strategy for HIV-infected persons

ART = antiretroviral therapy; ARVs = antiretroviral drugs, singly or in combination.

* Specific combination prevention packages tailored for different populations will require multiple interventions. The set of interventions chosen for a prevention package will be determined by the specific characteristics of the epidemic within the geographic region. Research on how to enhance adherence to each component and on maximal adherence to each element of any combination prevention strategy is critical. All of these strategies have an adherence or behavioral component.
Notwithstanding this unique case, we should consider at least 2 related lines of research when discussing a cure for HIV infection: development of a true sterilizing cure with complete eradication of the virus, and a functional cure, which is a permanent suppression of the virus without significant replication in the absence of ART. The concept of persistence in HIV infection received a molecular and cellular definition when Chun and colleagues (20) demonstrated that resting memory CD4+ cells in HIV-infected persons contained replication-competent HIV that emerged on cellular activation. In 1997, these authors and others showed the central role that these cells play in the persistence of HIV by demonstrating that despite years of effective ART, which consistently suppressed plasma viremia to levels undetectable by standard assays, the replication-competent virus could invariably be isolated from the resting memory T-cell pool of latently infected cells (21–23).

Since the late 1990s, investigators have pursued many strategies to eliminate this persistent reservoir. These strategies have included initiation of ART as early after infection as possible; intensification of ART with up to 5 or 6 different antiretroviral drugs; infusion of cell-activating cytokines, such as interleukin-2, or other means of activating the resting memory cells while the patient is receiving ART so that the activated cells can express the virus and die while ART blocks the released virus from spreading to other cells, thus reducing or eliminating the latent reservoir (24–26). These studies have resulted in variable degrees of reduction in the measurable size of the latently infected resting memory T-cell pool in the blood; however, after ART was empirically discontinued, all participants experienced some rebound of HIV replication (27, 28).

Because previous attempts to purge the persistent HIV reservoir were unsuccessful, we must evaluate a range of approaches that selectively target the integrated provirus or selectively eliminate the resting cell carrying an integrated provirus. To help advance this research, we need simpler and more quantitative measures of the latent HIV reservoir. By using such quantitative tools and coordinating drug discovery and clinical evaluation efforts, we can begin to evaluate therapeutic strategies that target the recalcitrant reservoir.

With regard to the role of the immune system in controlling virus replication after ART is discontinued (that is, a functional cure), there is a significant amount of information available on HIV-infected persons whose immune responses effectively control, but do not clear, their HIV infection. This population, known as “elite controllers,” provides convincing evidence of adequate immunologic control of HIV replication as measured by low to undetectable viral loads and maintenance of high CD4+ T-cell counts (29). Evidence that this elite controller profile is an immune-mediated phenotype is strengthened because many of these patients have specific HLA haplotypes, such as HLA-B*5701 (30, 31).

The challenge to researchers is to determine whether this elite controller phenotype can be induced in persons lacking a favorable HLA profile. To achieve this, investigators are combining and evaluating many strategies, including early treatment of HIV infection to both minimize the size of the viral reservoir and preserve anti-HIV immunity, together with “therapeutic” vaccination to bolster the immune response to a level where adequate control of viral replication is possible. Such strategies, if successful, could establish and maintain effective immunologic control of virus replication in the absence of ART so that HIV infection does not progress and transmission of HIV is highly unlikely. Patients in whom such a regimen could be successfully implemented might avoid the inevitability of lifelong ART.

**PREVENTING HIV INFECTION**

The most compelling goal of the HIV research agenda in the coming years is more effective HIV prevention. Preventing HIV infection is critical to the long-term goal of controlling and ultimately ending the HIV epidemic. Many prevention methods with strong evidence base already exist, such as behavioral and educational approaches, proper use of condoms, needle exchange programs, adult male circumcision, and ART for prevention of mother–child transmission of HIV (7, 32, 33). Yet worldwide, these proven prevention strategies, alone or in combination, are accessible to only a fraction of persons who would benefit from their implementation (32, 34).

Devising ways of “scaling up” proven, integrated prevention methods would have an important effect on slowing the growth of the HIV epidemic. Implementation of proven HIV prevention strategies needs to be bolstered with the development and validation of additional, effective prevention tools, such as ART-based prevention methods and a safe and effective HIV vaccine. Antiretroviral therapy–based prevention can take many forms. From the perspective of research opportunities, 3 approaches stand out: microbicides, preexposure prophylaxis (PrEP), and treatment as prevention. The use of antiviral agents as prevention is not a new idea, and approaches to prevent mother–child transmission of HIV have been strikingly successful.

Landmark proof-of-concept studies on microbicides and PrEP were published in 2010. The CAPRISA (Centre for the AIDS Programme of Research in South Africa) 004 trial demonstrated that use of 1% tenofovir gel before and after sexual intercourse by heterosexual women was 39% more effective in preventing HIV infection than a placebo gel. Among study participants who reported high adherence to use of the gel, the level of protection against HIV infection increased to 54% (35).

The iPrEx (Pre-exposure Prophylaxis Initiative) trial evaluated daily use of tenofovir plus emtricitabine to prevent HIV infection in men who have sex with men and in transgendered women and was 44% effective (36).
level of protection against HIV infection in participants with high adherence to this regimen increased to 73%. The relationship between adherence to preventive regimens and the efficacy of the interventions in both the CAPRISA and the iPrEx studies underscores the importance of including behavioral interventions and adherence counseling in combination prevention strategies (Table 2).

The VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial is an ongoing phase 2b study evaluating the effectiveness of 1% tenofovir gel or daily use of oral tenofovir or of oral tenofovir plus emtricitabine versus appropriate placebos in preventing HIV infection (37). If successful, this study would provide critical safety and efficacy data to move these approaches toward licensure and implementation. Discussions about devising the strategies for the scale-up, distribution, and rollout of an approved microbicide and PrEP agent have recently begun.

Longer-lasting formulations and novel delivery methods for microbicides and PrEP that are easier to use and subsequently enhance adherence must be developed and proven. Two such approaches currently under evaluation are the use of vaginal rings or implants that release a sufficient amount of active ingredient to provide adequate dosing to prevent HIV transmission for substantial periods. Even with these improved delivery systems, a substantial behavioral research component remains that will be required to optimize the use of these products as they were intended to be used (38).

An example of an integrated prevention strategy is the “seek, test, and treat” approach, which has been widely discussed and modeled. Each model adopts a set of basic assumptions, and the parameters associated with each assumption determine the success or failure of the specific strategy within the model (39–41). We have long believed that these assumptions are testable concepts that must be explored to fully understand the strengths and weaknesses of this approach (42).

For example, how soon after HIV infection should ART be initiated? Current guidelines that recommend starting ART when CD4+ T-cell counts decrease to less than 0.5 × 10^9 cells/L are based on epidemiologic evidence (5). To prove that initiating treatment earlier benefits the patient, the National Institute of Allergy and Infectious Diseases through the International Network for Strategic Initiatives in Global HIV Trials is conducting the START (Strategic Timing of Antiretroviral Treatment) trial. This study will provide a degree of evidence-based clarity to this important question (43).

The development of a safe and effective HIV vaccine has long been a major goal of prevention research. If developed, a vaccine would be the cornerstone of an integrated HIV prevention strategy (Table 2). Over the years, investigators have made numerous attempts to develop an HIV vaccine, including multiple phase 1 and 2 studies of candidate vaccines that proved unsuitable to advance further, 2 failed phase 3 trials of HIV-1 envelope glycoprotein 120 subunit preventive vaccines in men who have sex with men and injection drug users (44, 45), and the Step and Phambili trials of a T-cell–based vaccine. The latter 2 trials failed to show efficacy in reducing viral set-point after infection with HIV and raised concern about enhancing HIV infection in uncircumcised men who received the vaccine and were adenovirus type 5–seropositive (46, 47).

Adding to this challenge is the absence of a well-defined correlate of protective immunity that is associated with natural infection. Because of the consistent failure of attempts to develop a safe and effective HIV vaccine, the Summit on HIV Vaccine Research and Development was held in March 2008 to reevaluate the direction of basic and clinical HIV vaccine research. On the basis of the recommendations of the summit, greater emphasis was placed on basic vaccine discovery with the realization of the need for an appropriate balance of empirical clinical trials that can serve, under certain circumstances, as basic discovery research (48).

Since the summit, several advances have led to a degree of cautious optimism in the field of HIV vaccine research. For example, important information has emerged about the earliest events in establishing HIV infection. A considerable proportion of sexual transmissions seems to have a single founder virus—a transmitting strain that differs from the divergent strains that evolve over time in persons with HIV infection (49, 50). This insight may lead to new targets for immunogen design.

In addition, investigators have isolated several new, highly potent, broadly neutralizing monoclonal antibodies from patients chronically infected with HIV (51–53). Scientists are working on using crystallographic studies to delineate the precise epitopes to which these broadly reacting neutralizing antibodies bind in order to use structure-based vaccine immunogen design (54–56). Understanding how these antibodies develop and mature in infected persons during natural infection also will be critical to optimize this process in response to a preventive vaccine (51, 53, 56, 57).

In October 2009, a phase 2b clinical trial of a pox virus prime followed by a glycoprotein 120 subunit protein boost (the RV144 vaccine) conducted in 16 000 relatively low-risk participants (predominantly heterosexual men and women) in Thailand showed a modest 31% efficacy in preventing HIV infection (58). This result was the first indication of any degree of efficacy in HIV vaccine trials; therefore, the initial step after completing this study was to identify an immunologic correlate or correlates of protection from this trial. As such, researchers are undertaking a series of case–controlled studies in an attempt to identify such a correlate.

Regardless of whether a correlate of vaccine-induced protection is identified, follow-up on this modest positive signal will require the evaluation of improved vaccine vectors and gene inserts expressing various HIV proteins in higher-risk populations to determine whether the protec-
rative effect of the vaccine can be optimized. We must simultaneously maintain the pipeline of innovative vaccine concepts described earlier in this article to maximize the probability of success.

As we stated, a safe and effective HIV vaccine would be the ideal cornerstone of a potent combination prevention strategy that can draw on a growing list of interventions that have been validated or seem promising in large clinical trials. Adult male circumcision was a major advance in the arena of prevention, with a demonstrated efficacy of at least 55% that has been sustained in follow-up studies (33). Since 2009, we have seen 3 separate positive efficacy signals in large prevention studies, increasing from 31% with the RV144 vaccine to 39% with the CAPRISA 004 microbicide study to 44% with PrEP (35, 36, 58). A safe and effective vaccine would be an important addition to the armamentarium of combination prevention strategies. Such a vaccine optimally would show significant and durable protection from infection against all methods of sexual transmission and, if possible, against bloodborne transmission, as well.

**CONCLUSION**

By focusing on the overarching goal of controlling and ultimately ending the HIV and AIDS pandemic, a scientifically challenging research agenda naturally follows. We have described 3 specific components of the research agenda that are essential to achieving our collective goal (Table 1). By pursuing an aggressive scientific research agenda to develop the necessary interventions, together with a full-scale implementation of effective approaches that use these tools, we can achieve our shared, long-term goal of ultimately ending the HIV and AIDS epidemic.

From the National Institute of Allergy and Infectious Diseases, Bethesda, Maryland.

**Potential Conflicts of Interest:** None disclosed. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-0594.

**Requests for Single Reprints:** Carl W. Dieffenbach, PhD, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 6700 Rockledge Drive, MSC 7620, Bethesda, MD 20892; e-mail, cdieffenba@niaid.nih.gov.

Current author addresses and author contributions are available at www.annals.org.

**References**

1. **Centers for Disease Control (CDC).** Pneumocystis pneumonia—Los Angeles. MMWR Morb Mortal Wkly Rep. 1981;30:250-2. [PMID: 6265753]
2. **Centers for Disease Control (CDC).** Kaposis's sarcoma and Pneumocystis pneumonia among homosexual men—New York City and California. MMWR Morb Mortal Wkly Rep. 1981;30:305-8. [PMID: 6789108]
3. **Joint United Nations Programme on HIV/AIDS.** World Health Organization. AIDS Epidemic Update 2009. Geneva: Joint United Nations Programme on HIV/AIDS; 2009. Accessed at http://data.unaids.org/pub/Report/2009/ jc1700_epi_update_2009_en.pdf on 27 April 2011.
4. **Gallo RC, Montagnier L.** The discovery of HIV as the cause of AIDS. N Engl J Med. 2003;349:2283-5. [PMID: 14668451]
5. **DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents.** Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Bethesda, MD: Department of Health and Human Services; 2011. Accessed at www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf on 24 February 2011.
6. **World Health Organization.** Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach. 2010 Revision. Geneva: World Health Organization; 2010. Accessed at http://whqlibdoc .who.int/publications/2010/9789241599764_eng.pdf on 24 February 2011.
7. **Mofenson LM.** Prevention in neglected subpopulations: prevention of mother-to-child transmission of HIV infection. Clin Infect Dis. 2010;50 Suppl 3:S130-48. [PMID: 20397941]
8. **Joint United Nations Programme on HIV/AIDS.** Global Report: UNAIDS Report on the Global AIDS Epidemic 2010. Geneva: Joint United Nations Programme on HIV/AIDS; 2010. Accessed at www.unaids.org/globalreport/documents/201010123_GlobalReport_full_en.pdf on 25 April 2011.
9. **Fauci AS, Follers GK.** Investing to meet the scientific challenge of HIV/AIDS. Health Aff (Milwood). 2009;28:1629-41. [PMID: 19887404]
10. **Follers GK, Fauci AS.** Controlling and ultimately ending the HIV/AIDS pandemic: a feasible goal [Editorial]. JAMA. 2010;304:350-1. [PMID: 20639573]
11. **Rothenberg R, Woelfel M, Stonesturner R, Milberg J, Parker R, Truman B.** Survival with the acquired immunodeficiency syndrome. Experience with 5833 cases in New York City. N Engl J Med. 1987;317:1297-302. [PMID: 3500409]
12. **Centers for Disease Control (CDC).** A cluster of Kaposi’s sarcoma and Pneumocystis carinii pneumonia among homosexual male residents of Los Angeles and Orange Counties, California. MMWR Morb Mortal Wkly Rep. 1982;31:305-7. [PMID: 6811844]
13. **Hernes KB, Cheung T, Greene JB, Prose NS, Marcus A, Ballard H, et al.** Kaposi’s sarcoma in homosexual men—a report of eight cases. Lancet. 1981;2:598-600. [PMID: 6116083]
14. **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. [PMID: 18657708]
15. **The White House Office of National AIDS Policy.** National HIV/AIDS Strategy for the United States. July 2010. Accessed at www.aids.gov/federal-resources/policies/national-hiv-aids-strategy/nhas.pdf on 27 April 2011.
16. **Branson BM, Handsfield HH, Lampe MA, Janssen RS, Taylor AW, Lyss SB, et al.** Centers for Disease Control and Prevention (CDC). Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep. 2006;55:1-17. [PMID: 16988643]
17. **United States President’s Emergency Plan for AIDS Relief.** Latest results. Accessed at www.pepfar.gov/results/index.htm on 27 April 2011.
18. **Hütter G, Nowak D, Morsmeyer M, Ganepola S, Müssig A, Allers K, et al.** Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. N Engl J Med. 2009;360:692-8. [PMID: 19213682]
19. **Allers K, Hütter G, Hofmann J, Loddenkemper C, Rieger K, Thiel E, et al.** Evidence for the cure of HIV infection by CCR5Delta32/Delta32 stem cell transplantation. Blood. 2011;117:2791-9. [PMID: 21148083]
20. **Chun TW, Finzi D, Margolick J, Chadwick K, Schwartz D, Siliciano RF.** In vivo fate of HIV-1-infected T cells: quantitative analysis of the transition to stable latency. Nat Med. 1995;1:1284-90. [PMID: 7489410]
21. **Finzi D, Hermankova M, Pierson T, Carruth LM, Buck C, Chaisson RE, et al.** Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. Science. 1997;278:1295-300. [PMID: 9360027]
22. **Chun TW, Stonyver L, Mizell SB, Ehler LA, Mican JA, Baseler M, et al.** Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy. Proc Natl Acad Sci U S A. 1997;94:13193-7. [PMID: 9371822]
23. **Wong JK, Hazrahe M, Günthard HF, Havlir DV, Ignacio CC, Spina CA, et al.** Evidence of replication-competent HIV despite prolonged suppression of plasma viremia. Science. 1997;278:1291-5. [PMID: 9360026]
24. **Chun TW, Davey RT Jr, Engel D, Lane HC, Fauci AS.** Re-emergence of HIV after stopping therapy. Nature. 1999;401:874-5. [PMID: 10553003]
25. **Strain MC, Little SJ, Daar ES, Havlir DV, Günthard HF, Lam RT, et al.** Effect of treatment, during primary infection, on establishment and clearance of cellular reservoirs of HIV-1. J Infect Dis. 2005;191:1410-8. [PMID: 15809898]
26. Richman DD, Margolis DM, Delaney M, Greene WC, Hazuda D, Pomerantz RJ. The challenge of finding a cure for HIV infection. Science. 2009;323:1304-7. [PMID: 19265012]

27. Chun TW, Engel D, Mizell SB, Hallahlan CW, Fischette M, Park S, et al. Effect of interleukin-2 on the pool of latently infected, resting CD4+ T cells in HIV-1-infected patients receiving highly active anti-retroviral therapy. Nat Med. 1999;5:651-5. [PMID: 10371503]

28. Margolis DM. Eradication therapies for HIV infection: time to begin again. AIDS Res Hum Retroviruses. 2011;27:347-53. [PMID: 21314240]

29. Walker BD. Elite control of HIV Infection: implications for vaccines and treatment. Top HIV Med. 2007;15:134-6. [PMID: 17720999]

30. Rodés C, Toro C, Pazinos E, Poveda E, Martinez-Padial M, Benito JM, et al. Differences in disease progression in a cohort of long-term non-progressors after more than 16 years of HIV-1 infection. AIDS. 2004;18:1109-16. [PMID: 15166526]

31. Costello C, Tang J, Rivers C, Karita E, Meizen-Derr J, Allen S, et al. HLA-B*5703 independently associated with slower HIV-1 disease progression in Rwandan women [Letter]. AIDS. 1999;13:1990-1. [PMID: 10513667]

32. Pandian NS, Bove A, Balkus J, Serwadda D, Cates W Jr. Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward. Lancet. 2008;372:585-99. [PMID: 18687456]

33. Bailey RC, Moses S, Parker CB, Agot K, MacLean I, Krieger JN, et al. The protective effect of adult male circumcision against HIV acquisition is sustained for at least 54 months: results from the Kisumu, Kenya trial. Presented at the XVIII International AIDS Conference, Vienna, Austria, 18–23 July 2010. Abstract FRLBC101.

34. Stover J, Walker N, Garnett GP, Salomon JA, Stannecki KA, Ghys PD, et al. Can we reverse the HIV/AIDS pandemic with an expanded response? Lancet. 2002;360:73-7. [PMID: 12114060]

35. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al; CAPRISA 04 Trial Group. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010;329:1168-74. [PMID: 20643915]

36. Grant RM, Lama JR, Anderson PL, McMahan V, LiuAY, Vargas L, et al; iPrEx Study Team. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363:2587-99. [PMID: 21091279]

37. Safety and Effectiveness of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate, and Emtricitabine/Tenofovir Disoproxil Fumarate Tablets in Preventing HIV in Women. Clinical trial. Accessed at http://clinicaltrials.gov/ct2/show/NCT00975679 on 27 April 2011.

38. Rotheram-Borus MJ, Swendeman D, Chovnick G. The past, present, and future of HIV prevention: integrating behavioral, biological, and structural intervention strategies for the next generation of HIV prevention. Annu Rev Clin Psychol. 2009;5:143-67. [PMID: 19327028]

39. Lima VD, Johnston K, Hogg RS, Levy AR, Harrigan PR, Anema A, et al. Expanded access to highly active antiretroviral therapy: a potentially powerful strategy to curb the growth of the HIV epidemic. J Infect Dis. 2008;198:59-67. [PMID: 18498241]

40. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009;373:48-57. [PMID: 19038438]

41. Wagner BG, Kahn JS, Blower S. Should we try to eliminate HIV epidemics by using a ‘Test and Treat’ strategy? [Editorial]. AIDS. 2010;24:775-6. [PMID: 20177359]

42. Dieffenbach CW, Fauci AS. Universal voluntary testing and treatment for prevention of HIV transmission. JAMA. 2009;301:2380-2. [PMID: 19509386]

43. Strategic Timing of Antiretroviral Treatment (START). Clinical trial. Accessed at http://clinicaltrials.gov/ct2/show/NCT00867048 on 27 April 2011.

44. Pittisutthithum P, Gilbert G, Gurwitz M, Heyward W, Martin M, van Griensven F, et al; Bangkok Vaccine Evaluation Group. Randomized, double-blind, placebo-controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV-1 vaccine among injection drug users in Bangkok, Thailand. J Infect Dis. 2006;194:1661-71. [PMID: 17109337]

45. Flynn NM, Forthal DN, Harro CD, Judson FN, Mayer KH, Para MF; rgp120 HIV Vaccine Study Group. Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. J Infect Dis. 2005;191:654-65. [PMID: 15688278]

46. Buchbinder SP, Mehurola DV, Duerer A, Fitzgerald DW, Mogg R, Li D, et al; Step Study Protocol Team. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. Lancet. 2008;372:1881-93. [PMID: 19012954]

47. Gray G, Allen M, Churchyard G, Beldker L, Nhabelengu M, Misiana K, et al. Interim efficacy analysis of HVTN 503/Shambili: A phase IIb test of concept trial of the MRK Ad5 HIV-1 Gag/Pol/Nef vaccine conducted in HIV-1 uninfected adults in South Africa. Presented at AIDS Vaccine 2009, Paris, France, 19–22 October 2009. Abstract S01-04.

48. Fauci AS, Johnston MI, Dieneffach CW, Burton DR, Hammer SM, Hoxie JA, et al. HIV vaccine research: the way forward. Science. 2008;321:530-2. [PMID: 18653883]

49. Keele BF, Giorgi EE, Salazar-Gonzalez JF, Decker JM, Pham KT, Salazar MG, et al. Identification and characterization of transmitted and early founder viruses in primary HIV-1 infection. Proc Natl Acad Sci U S A. 2008;105:7552-7. [PMID: 18496057]

50. Derdeyn CA, Decker JM, Bibollet-Ruche F, Mokili JL, Muldoon M, Denham SA, et al. Envelope-constrained neutralization-sensitive HIV-1 after heterosexual transmission. Science. 2004;303:2019-22. [PMID: 15044802]

51. Walker LM, Phogat SK, Chan-Hui PY, Wagner D, Phung P, Goss JL, et al; Protocol G Principal Investigators. Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target. Science. 2009;326:285-9. [PMID: 19729618]

52. Wu X, Yang ZY, Li Y, Hogerborp CM, Schief WR, Seaman MS, et al. Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. Science. 2010;329:856-61. [PMID: 20616233]

53. Pietzsch J, Scheid JF, Mouquet H, Klein F, Seaman MS, Janikovic M, et al. Human anti-HIV-neutralizing antibodies frequently target a conserved epitope essential for viral fitness. J Exp Med. 2010;207:1995-2002. [PMID: 20679402]

54. Pejchal R, Walker LM, Stanfield RL, Phogat SK, Koff WC, Poignard P, et al. Structure and function of broadly reactive antibody PG16 reveal an H3 subdomain that mediates potent neutralization of HIV-1. Proc Natl Acad Sci U S A. 2010;107:11483-8. [PMID: 20534513]

55. Zhou T, Georgiev I, Wu X, Yang ZY, Dai K, Finzi A, et al. Structural basis for broad and potent neutralization of HIV-1 by antibody VRC01. Science. 2010;329:811-7. [PMID: 20616231]

56. Montero M, van Houten NE, Wang X, Scott JK. The membrane-proximal external region of the human immunodeficiency virus type 1 envelope: dominant site of antibody neutralization and target for vaccine design. Microbiol Mol Biol Rev. 2008;72:54-84. [PMID: 18322034]

57. Mouquet H, Scheid JF, Zoller MJ, Krogsgaard M, Ott RG, Shukair S, et al. Polyreactivity increases the apparent affinity of anti-HIV antibodies by heterologous complement activation. Nature. 2010;467:591-5. [PMID: 20882016]

58. Horaks-Ngarm S, Pittisutthithum P, Ntayaphanan S, Kaelwang K, Chui J, Paris R, et al; MOPH-TAVEG Investigators. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med. 2009;361:2209-20. [PMID: 19843557]
