Published in final edited form as:

J Acquir Immune Defic Syndr. 2010 December 15; 55(Suppl 2): S116–S121. doi:10.1097/QAI.0b013e3181fbca6e.

Antiretroviral Therapy: A Promising HIV Prevention Strategy?

Wafaa M. El-Sadr, MD, MPH, MPA^{*,†,‡}, Megan Affrunti, MPH, MSW^{*}, Theresa Gamble, PhD[§], and Allison Zerbe, MPH^{*}

^{*}International Center for AIDS Care and Treatment Programs (ICAP), Mailman School of Public Health, New York, NY

[†]College of Physicians and Surgeons, Columbia University, New York, NY

[‡]Harlem Hospital Center, New York, NY

[§]FHI, Durham, NC

Abstract

The use of antiretroviral therapy (ART) has been associated with significant improvement in morbidity and survival of persons living with HIV. In addition, recently, there has also been intense interest in the potential impact of ART on HIV transmission and consequently on the trajectory of the HIV epidemic globally. Evidence from mathematical modeling analyses as well as observational, and ecological studies supports the potential for ART as prevention. However, definitive data from clinical trials are awaited.

In the United States, the feasibility and potential of using ART as a prevention strategy presents particular challenges: the large number of individuals with undiagnosed HIV; the predominance of disenfranchised individuals affected by the epidemic; evidence of delay in engagement in HIV care after diagnosis with attendant late initiation of ART; and difficulties with consistent, long-term adherence to ART as well as concerns regarding long-term risk-behavior change. Thus, for this novel effort to succeed, a multidimensional approach is necessary that must include policy changes, social mobilization, and improved access to clinical and supportive services for persons living with HIV, with a particular focus on the unique needs of at-risk populations, combined with engagement of all cadres of health care providers and community constituencies.

Keywords

HIV treatment; antiretroviral therapy; transmission; prevention

Findings from a mathematical modeling study of the effect of antiretroviral therapy (ART) on HIV incidence and prevalence, reported by Granich et al in early 2009, were met with a mix of excitement and disbelief.¹ Using data from the HIV epidemic in South Africa, this model suggested that with expanded HIV testing and prompt initiation of ART by all those found to be HIV infected, a substantial decrease in incidence of HIV could be achieved in that country.² Skeptics derided the model's optimistic assumptions, which included annual

Correspondence and requests for reprints: Wafaa El-Sadr, MD, MPH, MPA, International Center for AIDS Care and Treatment Programs, Mailman School of Public Health, 722 W 168th St., Room 715, New York, NY 10032 (wme1@columbia.edu), 212/342-0532, 212/342-1824 (fax).

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.

HIV testing for all adults older than 15, immediate ART initiation for the vast numbers of individuals found to be HIV infected, and achievement of high rates of adherence with treatment.³ Further, many questioned the feasibility of achieving such goals in low- and middle-income countries, settings already struggling with efforts to expand HIV testing to their populations and to provide access to antiretroviral drugs for those with advanced HIV disease who are in urgent need of this lifesaving treatment. Nevertheless, the findings from the model generated great interest in exploring the feasibility of this “test and treat” strategy, particularly in view of the limited effectiveness demonstrated by other prevention interventions to date and the lack of progress in controlling the global HIV epidemic.^{3–5}

At the core of the rationale for use of ART for prevention are findings that demonstrate that antiretroviral drugs can lead to suppression of viral replication in the bloodstream as well as in genital tract secretions, with the potential consequence of a decrease in infectiousness.^{6–8} However, the concurrence of suppressed virus in plasma and genital secretions has not been consistently demonstrated, and HIV detection in the genital secretions may be influenced by the presence of concurrent sexually transmitted infections, the genital sampling method, and the timing of specimen collection, particularly in relation to the menstrual cycle.^{9–12}

The use of ART in HIV-infected patients as a strategy for HIV prevention is not a novel idea. Several publications from as early as 2000 have suggested this possibility.^{8,13} In addition, other mathematical models have examined the issue, some using less optimistic assumptions than those used by Granich et al, resulting in a less dramatic effect on HIV incidence.^{14–16} Accumulating evidence from observational and ecological studies provides additional support for possible effectiveness of treatment for prevention. A study in Uganda found that the risk of HIV transmission was 0.9 per 1000 person-years with the use of ART compared to 45.7 per 1000 person-years without.¹⁷ An analysis of linked HIV transmission in HIV discordant heterosexual couples from sub-Saharan Africa demonstrated that use of ART by the HIV-infected partners was associated with a 92% decrease in HIV transmission.¹⁸ However, conflicting findings were reported from a study of discordant couples in China, where use of ART was not associated with a statistically significant decrease in HIV transmission to the HIV-uninfected partner, raising concerns that suboptimal long-term adherence could compromise ART’s benefit in decreasing infectiousness.¹⁹

In terms of ecological evidence in support of the potential effect of ART on HIV transmission, in one study, a decrease in median community viral load in San Francisco was reported to be associated with a decrease in new HIV infections.²⁰ Similarly, data from British Columbia, Canada, indicated that an increase in the proportion of HIV-infected individuals with undetectable viral loads was associated with a decrease in number of new HIV infections.²¹ Similarly, in a study from Taiwan, a decrease in HIV transmission by 53% was noted after establishment of a national program for provision of free ART to all HIV-infected individuals in that country.²²

Findings from such observational and ecological data, however, must be interpreted with caution due to possible selection biases. For example, individuals who initiate ART versus those who do not may differ in certain characteristics (eg, sexual risk taking). Moreover, ecological studies cannot account for viral load levels among individuals unaware of their HIV diagnosis in any given community; this will affect the imputations used to take into account missing viral load measurements. Thus, it is important to appreciate that definitive data supporting the long-term impact of ART on HIV incidence are not yet available which await the results of randomized clinical trials, including HPTN 052, an ongoing study evaluating the effect of immediate versus deferred ART on transmission of HIV to the uninfected member of the discordant couple.²³

The HIV epidemic in the United States is an entrenched one, with about 56,000 new infections occurring per year over the past decade and no evidence to date of a decrease in the annual number of new infections.²⁴ Although screening the blood supply, promoting the use of condoms and the expansion of syringe access and exchange, limiting the number of partners, and serosorting, as well as interventions for prevention of mother-to-child transmission, have shown positive effects in reducing transmission in the United States, particularly in the early years of the epidemic, the unchanged magnitude of new infections in the past decade clearly motivates the need for innovative prevention strategies, including an exploration of the test and treat approach. However, certain characteristics of the HIV epidemic need to be taken into account when such a strategy is considered, and several challenges must be confronted if the promise of ART for prevention can be realized in the United States. These characteristics include the large numbers of individuals who (1) are unaware of their HIV infection; (2) are diagnosed late with HIV infection; (3) delay or face barriers to accessing care and initiate ART at late-stage HIV disease; (4) have suboptimal adherence to ART over time; and (5) continue to engage in HIV transmission risk behaviors. Figure 1 illustrates these challenges and highlights many of the behavioral, economic, societal, and policy issues that impede individuals from achieving milestones that are critical to the success of the ART-for-prevention approach.

Lack of Awareness of HIV Status

Identifying all individuals with HIV infection in a community is the foundation of effective use of ART for prevention. However, US data indicate that of the estimated 1 million individuals living with HIV, 21% are unaware of their HIV status.²⁵ Evidence suggests that these individuals are responsible for more than 50% of new sexually transmitted infections and are 2.5 times more likely to transmit HIV than individuals who are aware of their HIV infection.²⁶ Of further concern is the fact that the proportion of individuals unaware of their HIV infection is even higher among blacks, a group at particular risk for HIV in the United States. In a study conducted among men who have sex with men (MSM), 77% of those found to be HIV infected were unaware of their HIV status; of this group, 91% were black and 60% white.²⁷

A further challenge to identification of individuals with HIV in the United States is the localized nature of the HIV epidemic, disproportionately targeting vulnerable and disenfranchised populations, particularly MSM and blacks within specific geographic regions.²⁸ For example, in Washington, DC, the city with the highest HIV seroprevalence in the United States, HIV prevalence is highest among black males (6.5%); among MSM in that city, blacks account for 58% of all HIV/AIDS cases.²⁹ In New York City, the US city with the largest number of people living with HIV, 1 in 10 MSM are estimated to be infected with HIV.³⁰ Additionally, recently published data found that black men comprise the city's largest demographic group of new HIV diagnoses (33%) and persons living with HIV/AIDS (29%) and have the city's highest HIV prevalence (3.7%).³¹ Special efforts are needed to effectively reach these populations in a culturally appropriate manner that avoids further stigmatization.

Although the Centers for Disease Control and Prevention recommended almost 4 years ago that all Americans aged 13 through 64 be tested for HIV at least once, only 10% indicate that they were HIV tested during the past year.^{32,33} Many factors impede expansion of HIV screening, including health care providers' continued reliance on risk-based testing rather than on routine screening. It is more common for health care providers to offer testing when HIV is suspected clinically or based on their perception of an individual's risk.³⁴ This approach is fraught with limitations since HIV risk in the United States is often related more

to an individual's sexual network than to his or her risk behaviors—information that many persons do not share with their health care providers.^{34,35}

Despite the challenges, successful initiatives have expanded HIV testing in some geographic regions. A recent scale-up effort led by the New York City Department of Health, called “The Bronx Knows,” has coincided with a statistically significant increase in the percent of Bronx residents between the ages of 18 through 64 reporting that they have ever been tested for HIV.³⁶

Diagnosis at Late Stage of Disease

Evidence indicates that many individuals in the United States are being tested late in the course of their HIV infection: Approximately 40% of individuals receiving their first HIV-positive test result are diagnosed with AIDS within a year.³⁷ In New York City in 2008, 25% of those tested had a concurrent HIV/AIDS diagnosis.³⁸ In a study that examined surveillance data from New York City, concurrent diagnosis of AIDS and HIV infection was substantially more common among blacks and Latinos than among whites.³⁹ The frequency of late diagnosis is of concern both to the individual and the community. Those testing late in the course of HIV infection miss out on the clinical benefits of HIV care and treatment and may also unknowingly contribute to the spread of HIV to others within their communities, since their higher plasma HIV RNA levels are also correlated with increased infectiousness. Alone, expanded HIV testing could have a substantial impact on HIV transmission in the United States, as it has the potential to lead to earlier diagnosis of HIV and earlier adoption of safer behaviors⁴⁰ and allows for earlier access to care and treatment, with its demonstrated benefits in terms of immunological response and better outcomes and survival.^{41,42}

Delay in Linkage to HIV Care after HIV Diagnosis

The promise of treatment as a prevention strategy also depends on individuals promptly linking to care, initiating treatment when recommended, and achieving sustained viral suppression as well as decreasing risk-taking behavior. In terms of linkage to care, findings from New York City indicate that of 1,928 newly diagnosed individuals, only 63.7% were linked to HIV care within 3 months, and 17.2% never initiated care.⁴³ Studies demonstrate that not only is HIV care initiated late or not at all in some cases but there are also racial, ethnic, gender, and other disparities related to when and whether care is started. Multiple studies demonstrate that nonwhite race, foreign birth, and female sex predict delayed initiation of care.^{43–45} Studies have also shown that injection drug users delay care and are particularly likely to be homeless and incarcerated and to have untreated psychiatric illness that may hinder or complicate ART delivery and adherence. Injection drug users also experience more rapid HIV disease progression.^{46,47} The personal and societal benefits of timely HIV diagnosis can be realized only when it is combined with timely initiation of clinical care. Earlier linkage to care results in greater opportunities for virological and immunologic monitoring and initiation of ART, once eligibility is established, as well as greater access to interventions for prevention for positives.⁴⁸

Initiation of ART at Low CD4+ Cell Counts

Studies have shown that many HIV-infected individuals in the United States initiate ART at low CD4+ cell counts, substantially below the thresholds currently recommended by US guidelines for use of ART.⁴⁹ In one study, among 35,009 patients followed from 1996 to 2007, although the median CD4+ cell count at first presentation slightly increased from 234 to 327 cells/mm³, 53% of patients still had CD4+ cell counts at presentation below the prevailing guideline threshold for ART initiation.⁵⁰ In another study, treatment-eligible

injection drug users from Baltimore who were observed from 1996 to 2007 initiated therapy, after lengthy delays, with advanced immunosuppression. Nearly one third of individuals who became eligible for treatment had not initiated ART when guidelines would suggest optimal benefit.⁵¹

In addition to late diagnoses of HIV, a number of other factors contribute to delays in ART initiation, including limited treatment literacy; patient refusal to begin ART for fear of side effects; and reluctance by some providers to prescribe ART due to real or perceived barriers to adherence.⁵² Resource constraints among state AIDS drug assistance programs (ADAPs), which provide support for ART to approximately one quarter of all patients enrolled in HIV/AIDS care in the United States,⁵³ also account for some delays in ART initiation. Some ADAPs already have waiting lists for patients in need of ART, a situation that may be exacerbated in view of the revised ART guidelines released in 2009, which recommend initiation of ART at higher CD4+ cell count thresholds, combined with limited public health resources in the setting of a severe economic recession.⁵⁴

Difficulty in Achieving and Maintaining High Rates of Adherence with ART

Achievement of viral suppression on ART is dependent on correct and consistent use of effective antiretroviral regimens. Results from a meta-analysis of 31 adherence studies showed that only 55% of HIV-infected patients achieved adequate ART adherence in North America.⁵⁵ However, research suggests that high levels of adherence, between 80% and 95% depending on regimen type, may be necessary to maintain viral suppression.⁵⁶ Various complex factors have been shown to contribute to suboptimal adherence, including active substance use (including the use of alcohol), young age, and depression—all issues that highlight the importance of providing HIV-infected patients with access to supportive services.⁵⁷⁻⁵⁸ Indeed, retaining patients in care is a prerequisite for achievement of the high rates of ART utilization and adherence required for garnering the potential benefits of the ART for prevention strategy. A recently published modeling study in which the effectiveness of a comprehensive approach to test and treat that included enhanced linkage to care after diagnosis and high retention in care was compared to solely universal test and treat demonstrated that the former package of interventions was associated with substantially increased benefits.⁵⁹ It is also important to note that even with optimal adherence, suppression of viral replication is not always achievable and the possibility of discordance between HIV viral load in the plasma and genital secretions remains, issues that underscore the need for other interventions for prevention for positives.⁶⁰ Several positive prevention interventions have been shown to be associated with a decrease in high-risk behaviors (eg, unprotected anal sex), a decrease in substance use, and an increase in condom use.⁶⁰ Ultimately, the use of such interventions will be critical to complement the effects of ART for prevention.

The Way Forward

Continued HIV transmission in the United States has generated interest in the potential use of ART for prevention. A recent report of the results of a mathematical model utilizing data from Washington, DC, demonstrated only a modest effect on HIV transmission with expanded HIV screening and ART.¹⁶ Nonetheless, momentum has been generated to test this concept by embarking on feasibility studies of such an approach. From a conceptual perspective, taking into account the unique characteristics of the HIV epidemic in the United States is critical to the design of such studies and to the design of the types of interventions to include as part of the test and treat strategy. One study to address these issues is in development by the HIV Prevention Trials Network (HPTN 065), the Test, Link to Care, Plus Treat (TLC-Plus) study, a collaboration between the National Institutes of Health, the

Centers for Disease Control and Prevention, local health departments, and a broad array of stakeholders.⁶¹ The study will focus on specific interventions to optimize testing, linkage to care, and suppression of viral replication in the Bronx and Washington, DC, and may inform other large-scale domestic initiatives in the future. Based on the issues delineated above, embarking on such an effort will require addressing the factors that influence a cascade of events: individuals' access to and acceptance of HIV testing and the impediments to engagement in HIV care, adherence to ART and positive prevention behaviors. Barriers such as stigma, mistrust of health systems, misperceptions of HIV risk, access to services, support for comorbid conditions, and psychosocial impediments need to be addressed if the test and treat approach is to succeed. In a parallel manner, interventions will be needed to address provider skills and attitudes regarding HIV testing, perceptions of eligibility for ART initiation, skills in support of adherence, and attitudes regarding the balance of patient versus societal benefits of ART. Indeed, beyond a focus on test and treat as the two elements of a successful ART-for-prevention strategy, the United States epidemic compels a much more comprehensive perspective that entails a seek, test, link, treat, and support approach, necessitating an unprecedented partnership involving communities, providers, support organizations, and persons living with HIV themselves.

Acknowledgments

The authors wish to acknowledge contributions by Blayne Cutler, Lucia Torian, Shannon Hader, Tiffany West, and Nnemdi Kamanu Elias. We acknowledge support by the HIV Prevention Trials Network (HPTN). Financial support provided by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Mental Health (NIMH) under award number U01 AI069466.

REFERENCES

1. Garnett GP, Baggaley RF. Treating our way out of the HIV pandemic: could we, would we, should we? *Lancet*. 2009; 373:9–11. doi:10.1016/S0140-6736(08)61698-0. [PubMed: 19038439]
2. 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. doi:10.1016/S0140-6736(08)61697-9. [PubMed: 19038438]
3. Cohen MS, Mastro TD, Cates W Jr. Universal voluntary HIV testing and immediate antiretroviral therapy [correspondence; authors' reply, 1080–1081]. *Lancet*. 2009; 373:1077–1081. doi:10.1016/S0140-6736(09)60640-1, doi:10.1016/S0140-6736(09)60648-6. [PubMed: 19328992]
4. Dieffenbach CW, Fauci AS. Universal voluntary testing and treatment for prevention of HIV transmission. *JAMA*. 2009; 301:2380–2382. doi:10.1001/jama.2009.828. [PubMed: 19509386]
5. Assefa Y, Lera M. Universal voluntary HIV testing and immediate antiretroviral therapy. *Lancet*. 2009; 373:1080–1081. doi:10.1016/S0140-6736(09)60647-4. [PubMed: 19328998]
6. Cu-Uvin S, Snyder B, Harwell JI, et al. Association between paired plasma and cervicovaginal lavage fluid HIV-1 RNA levels during 36 months. *J Acquir Immune Defic Syndr*. 2006; 42:584–587. doi:10.1097/01.qai.0000229997.52246.95. [PubMed: 16837866]
7. Cohen MS, Hoffman IF, Royce RA, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. AIDSCAP Malawi Research Group. *Lancet*. 1997; 349:1868–1873. doi:10.1016/S0140-6736(97)02190-9. [PubMed: 9217758] Cohen MS, Hoffman IF, Royce RA, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. AIDSCAP Malawi Research Group. *Lancet*. 1997; 349:1868–1873. doi:10.1016/S0140-6736(97)02190-9. [PubMed: 9217758]
8. 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]
9. Fiore JR, Suligoi B, Saracino A, et al. Correlates of HIV-1 shedding in cervicovaginal secretions and effects of antiretroviral therapies. *AIDS*. 2003; 17:2169–2176. doi:10.1097/01.aids.0000088178.01779.b4. [PubMed: 14523273]

10. Nagot N, Ouedraogo A, Weiss HA, et al. Longitudinal effect following initiation of highly active antiretroviral therapy on plasma and cervico-vaginal HIV-1 RNA among women in Burkina Faso. *Sex Transm Infect.* 2008; 84:167–170. doi:10.1136/sti.2007.027987. [PubMed: 18055582]
11. Xu, C.; Politch, JA.; Tucker, L., et al. Factors associated with increased levels of human immunodeficiency virus type 1 DNA in semen; *J Infect Dis.* 1997 [Accessed August 15, 2010]. p. 941-947. Available at: <http://www.journals.uchicago.edu/doi/pdf/10.1086/516539>
12. Al-Harthi, L.; Kovacs, A.; Coombs, RW., et al. A menstrual cycle pattern for cytokine levels exists in HIV-positive women: implication for HIV vaginal and plasma shedding; *AIDS.* 2001 [Accessed August 15, 2010]. p. 1535-1543. Available at: http://journals.lww.com/aidsonline/Fulltext/2001/08170/A_menstrual_cycle_pattern_for_cytokine_levels.11.aspx
13. Velasco-Hernandez JX, Gershengorn HB, Blower SM. Could widespread use of combination antiretroviral therapy eradicate HIV epidemics? *Lancet Infect Dis.* 2002; 2:487–493. doi:10.1016/S1473-3099(02)00346-8. [PubMed: 12150848]
14. Wagner BG, Kahn JS, Blower S. Should we try to eliminate HIV epidemics by using a 'Test and Treat' strategy? *AIDS.* 2010; 24:775–776. doi:10.1097/QAD.0b013e3283366782. [PubMed: 20177359]
15. Dodd PJ, Garnett GP, Hallett TB. Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings. *AIDS.* 2010; 24:729–735. doi:10.1097/QAD.0b013e32833433fe. [PubMed: 20154580]
16. Walensky RP, Paltiel AD, Losina E, et al. Test and treat DC: forecasting the impact of a comprehensive HIV strategy in Washington DC. *Clin Infect Dis.* 2010; 51:392–400. doi: 10.1086/655130. [PubMed: 20617921]
17. Bunnell, R.; Ekwaru, JP.; Solberg, P., et al. Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda; *AIDS.* 2006 [Accessed August 15, 2010]. p. 85-92. Available at: http://journals.lww.com/aidsonline/Fulltext/2006/01020/Changes_in_sexual_behavior_and_risk_of_HIV.12.aspx
18. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet.* 2010; 375:2092–2098. doi:10.1016/S0140-6736(10)60705-2. [PubMed: 20537376]
19. Wang L, Ge Z, Luo J, et al. HIV transmission risk among serodiscordant couples: a retrospective study of former plasma donors in Henan, China [published online ahead of print, post author corrections, July 26, 2010]. *J Acquir Immune Defic Syndr.* doi:10.1097/QAI.0b013e3181e9b6b7.
20. 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(6):e11068. doi:10.1371/journal.pone.0011068. [PubMed: 20548786]
21. 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 Jul 16. doi:10.1016/S0140-6736(10)60936-1.
22. Fang CT, Hsu HM, Twu SJ, et al. Decreased HIV transmission after a policy of providing free access to highly active antiretroviral therapy in Taiwan. *J Infect Dis.* 2004; 190:879–885. doi: 10.1086/422601. [PubMed: 15295691]
23. Cohen MS, Gay CL. Treatment to prevent transmission of HIV-1. *Clin Infect Dis.* 2010; 50 suppl 3:S85–S95. doi:10.1086/651478. [PubMed: 20397961]
24. Hall HI, Song R, Rhodes P, et al. Estimation of HIV incidence in the United States. *JAMA.* 2008; 300:520–529. PMID:PMC2919237. [PubMed: 18677024]
25. Campsmith ML, Rhodes PH, Hall HI, et al. Undiagnosed HIV prevalence among adults and adolescents in the United States at the end of 2006 [erratum in: *J Acquir Immune Defic Syndr.* 2010;54:112]. *J Acquir Immune Defic Syndr.* 2010; 53:619–624. doi:10.1097/QAI.0b013e3181bf1c45. [PubMed: 19838124]
26. Marks G, Crepaz N, Janssen RS. Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. *AIDS.* 2006; 20:1447–1450. doi: 10.1097/01.aids.0000233579.79714.8d. [PubMed: 16791020]

27. MacKellar DA, Valleroy LA, Secura GM, et al. Unrecognized HIV infection, risk behaviors, and perceptions of risk among young men who have sex with men: opportunities for advancing HIV prevention in the third decade of HIV/AIDS. *J Acquir Immune Defic Syndr*. 2005; 38:603–614. [PubMed: 15793373]
28. El-Sadr WM, Mayer KH, Hodder SL. AIDS in America--forgotten but not gone. *N Engl J Med*. 2010; 362:967–970. doi:10.1056/NEJMp1000069. [PubMed: 20147707]
29. Department of Health, HIV/AIDS Administration. District of Columbia HIV/AIDS Epidemiology Update 2008. Washington, DC: Government of the District of Columbia; 2009 February [Accessed August 15, 2010]. Available at: http://dchealth.dc.gov/doh/lib/doh/pdf/dc_hiv-aids_2008_updatereport.pdf
30. Nguyen TQ, Gwynn RC, Kellerman SE, et al. Population prevalence of reported and unreported HIV and related behaviors among the household adult population in New York City, 2004. *AIDS*. 2008; 22:281–287. doi:10.1097/QAD.0b013e3282f2ef58. [PubMed: 18097231]
31. Wiewel EW, Hanna DB, Begier EM, et al. High HIV prevalence and diagnosis rates in New York City black men [published online ahead of print June 24, 2010]. *J Community Health*. doi: 10.1007/s10900-010-9291-0.
32. Branson, BM.; Handsfield, HH.; Lampe, MA., et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings; *MMWR Recomm Rep*. 2006 [Accessed August 15, 2010]. p. 1-17. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm>
33. Centers for Disease Control and Prevention. Persons tested for HIV-United States, 2006; *MMWR Morb Mortal Wkly Rep*. 2008 [Accessed August 15, 2010]. p. 845-849. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5731a1.htm>
34. Beckwith CG, Flanagan TP, del Rio C, et al. It is time to implement routine, not risk-based, HIV testing. *Clin Infect Dis*. 2005; 40:1037–1040. doi:10.1086/428620. [PubMed: 15824997]
35. Millett GA, Peterson JL. The known hidden epidemic HIV/AIDS among black men who have sex with men in the United States. *Am J Prev Med*. 2007 Apr.32 suppl 1:S31–S33. doi:10.1016/j.amepre.2006.12.028. [PubMed: 17386333]
36. New York, NY: New York City Department of Health and Mental Hygiene; [Accessed August 15, 2010]. EpiQuery: NYC Interactive Health Data System, Community Health Survey 2009 [database online]. Available at: <http://nyc.gov/health/epiquery>
37. Valdiserri RO, Holtgrave DR, West GR. Promoting early HIV diagnosis and entry into care. *AIDS*. 1999; 13:2317–2330. [PubMed: 10597773]
38. New York City Department of Hygiene and Mental Health. HIV Epidemiology & Field Services Semiannual Report. 2009 April [Accessed August 15, 2010]. Available at: <http://www.nyc.gov/html/doh/downloads/pdf/dires/dires-2009-report-semi1.pdf>
39. Hanna DB, Pfeiffer MR, Torian LV, et al. Concurrent HIV/AIDS diagnosis increases the risk of short-term HIV-related death among persons newly diagnosed with AIDS, 2002–2005. *AIDS Patient Care STDS*. 2008; 22:17–28. doi:10.1089/apc.2007.0042. [PubMed: 18095838]
40. Marks G, Crepaz N, Senterfitt JW, et al. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. *J Acquir Immune Defic Syndr*. 2005 39:446–453. Available at: [PubMed: 16010168]
41. Robbins GK, Spritzler JG, Chan ES, et al. Incomplete reconstitution of T cell subsets on combination antiretroviral therapy in the AIDS Clinical Trials Group Protocol 384. *Clin Infect Dis*. 2009; 48:350–361. doi:10.1086/595888. [PubMed: 19123865]
42. Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet*. 2009; 373:1352–1363. doi:10.1016/S0140-6736(09)60612-7. [PubMed: 19361855]
43. Torian, LV.; Wiewel, EW.; Liu, KL., et al. Risk factors for delayed initiation of medical care after diagnosis of human immunodeficiency virus; *Arch Intern Med*. 2008 Jun 9 [Accessed August 15, 2010]. p. 1181-1187. Available at: <http://archinte.ama-assn.org/cgi/content/full/168/11/1181>
44. Gebo, KA.; Fleishman, JA.; Conviser, R., et al. Racial and gender disparities in receipt of highly active antiretroviral therapy persist in a multistate sample of HIV patients in 2001; *J Acquir*

- Immune Defic Syndr. 2005 [Accessed August 15, 2010]. p. 96-103. Available at: http://journals.lww.com/jaids/Fulltext/2005/01010/Racial_and_Gender_Disparities_in_Receipt_of_Highly.17.aspx
45. Reif S, Whetten K, Thielman N. Association of race and gender with use of antiretroviral therapy among HIV-infected individuals in the southeastern United States. *South Med J*. 2007; 100:775–781. doi:10.1097/SMJ.0b013e3180f626b4. [PubMed: 17713302]
 46. Lucas GM, Griswold M, Gebo KA, et al. Illicit drug use and HIV-1 disease progression: a longitudinal study in the era of highly active antiretroviral therapy. *Am J Epidemiol*. 2006; 163:412–420. doi:10.1093/aje/kwj059. [PubMed: 16394200]
 47. Strathdee SA, Stockman JK. Epidemiology of HIV among injecting and non-injecting drug users: current trends and implications for interventions. *Curr HIV/AIDS Rep*. 2010; 7:99–106. doi: 10.1007/s11904-010-0043-7. [PubMed: 20425564]
 48. Stall R. Efforts to prevent HIV infection that target people living with HIV/AIDS: what works? *Clin Infect Dis*. 2007; 45 suppl 4:S308–S312. doi:10.1086/522555. [PubMed: 18190304]
 49. Althoff KN, Gange SJ, Klein MB, et al. Late presentation for human immunodeficiency virus care in the United States and Canada. *Clin Infect Dis*. 2010; 50:1512–1520. doi:10.1086/652650. [PubMed: 20415573]
 50. Althoff, K.; Gange, S.; Klein, M., et al. Late presentation for HIV care in the US and Canada [paper #982]. 17th Conference of Retroviruses and Opportunistic Infections (CROI); February 16–19, 2010; San Francisco, California. [Accessed August 15, 2010]. Poster presentation available at: <http://www.retroconference.org/2010/PDFs/982.pdf>
 51. Mehta SH, Kirk GD, Astemborski J, et al. Temporal trends in highly active antiretroviral therapy initiation among injection drug users in Baltimore, Maryland, 1996–2008. *Clin Infect Dis*. 2010; 50:1664–1671. doi:10.1086/652867. [PubMed: 20450418]
 52. Bogart, LM.; Kelly, JA.; Catz, SL., et al. Impact of medical and nonmedical factors on physician decision making for HIV/AIDS antiretroviral treatment; *J Acquir Immune Defic Syndr*. 2000 [Accessed August 15, 2010]. p. 396-404. Available at: http://journals.lww.com/jaids/Fulltext/2000/04150/Impact_of_Medical_and_Nonmedical_Factors_on.6.aspx
 53. Crustinger-Perry, B.; Penner, MC.; Pund, B. for the National Alliance of State and Territorial AIDS Directors (NASTAD). National ADAP Monitoring Project Annual Report. May 2010. Washington, DC: NASTAD; 2010 [Accessed August 15, 2010]. Available at: http://www.nastad.org/Docs/highlight/201053_2010%20National%20ADAP%20Monitoring%20Report.pdf
 54. Sack, K. Economy hurts government aid for H.I.V. drugs. *The New York Times*. 2010 June 30 [Accessed August 15, 2010]. Available at: http://www.nytimes.com/2010/07/01/us/01aidsdrugs.html?_r=1&scp=1&sq=Economy%20Hurts%20Government%20Aid%20for%20HIV%20Drugs&st=cse
 55. Mills, EJ.; Nachega, JB.; Buchan, I., et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis; *JAMA*. 2006 [Accessed August 15, 2010]. p. 679-690. Available at: <http://jama.ama-assn.org/cgi/content/full/296/6/679>
 56. Bangsberg DR. Preventing HIV antiretroviral resistance through better monitoring of treatment adherence. *J Infect Dis*. 2008; 197 suppl 3:S272–S278. doi:10.1086/533415. [PubMed: 18447613]
 57. Lazo M, Gange SJ, Wilson TE, et al. Patterns and predictors of changes in adherence to highly active antiretroviral therapy: longitudinal study of men and women. *Clin Infect Dis*. 2007; 45:1377–1385. doi:10.1086/533415. [PubMed: 17968839]
 58. Levine AJ, Hinkin CH, Castellon SA, et al. Variations in patterns of highly active antiretroviral therapy (HAART) adherence. *AIDS Behav*. 2005; 9:355–362. doi:10.1007/s10461-005-9009-y. [PubMed: 16088365]
 59. Bendavid E, Brandeau ML, Wood R, et al. Comparative effectiveness of HIV testing and treatment in highly endemic regions. *Arch Intern Med*. 2010; 170:1347–1354. doi:10.1001/archinternmed.2010.249. [PubMed: 20696960]
 60. Fisher JD, Smith LR, Smith EM. Secondary prevention of HIV in the United States: past, current, and future perspectives. *J Acquir Immune Defic Syndr*. In press.

61. Vermund SH, Hodder SL, Justman JE, et al. Addressing research priorities for prevention of HIV infection in the United States. *Clin Infect Dis*. 2010; 50 suppl 3:S149–S155. doi:10.1086/651485. [PubMed: 20397942]

Figure 1.
Common characteristics of the United States HIV epidemic and challenges to achieving potential for ART as prevention. * denotes AIDS drug assistance programs, †antiretroviral therapy.