Evidence Synthesis
Number 95

Screening for HIV: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
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Contract No. HHSA-290-2007-10057-I, Task Order No. 8

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AHRQ Publication No. 12-05173-EF-1
November 2012

This report is based on research conducted by the Oregon Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0024). The investigators involved have declared no conflicts of interest with objectively conducting this research. The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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Acknowledgements: The authors acknowledge Laurie Hoyt Huffman, MS, for contributions to the report. The authors also thank the AHRQ Medical Officer, Jennifer Croswell, MD, MPH, as well as the U.S. Preventive Services Task Force leads, Susan Curry, PhD, Virginia Moyer, MD, MPH, Wanda Nicholson, MD, MPH, MBA, Timothy Wilt, MD, MPH, and Douglas Owens, MD, MS.

Suggested Citation: Chou R, Selph S, Dana T, Bougatsos C, Zakher B, Blazina I, Korthuis PT. Screening for HIV: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation. Evidence Synthesis No. 95. AHRQ Publication No. 12-05173-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; November 2012.

Structured Abstract

Background: A 2005 U.S. Preventive Services Task Force (USPSTF) review found good evidence that HIV screening tests are accurate and that identification of undiagnosed HIV infection and treatment of immunologically advanced disease is associated with substantial clinical benefits. However, it found insufficient evidence to estimate effects of diagnosis and subsequent interventions on transmission risks, or to estimate clinical benefits of antiretroviral treatment in patients with less immunologically advanced disease.

Purpose: To systematically update the 2005 USPSTF review on benefits and harms of screening for HIV infection in adolescents and adults, focusing on research gaps identified in the prior review.

Data Sources: We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the second quarter of 2012) and Ovid MEDLINE (2004 through June 2012) and manually reviewed reference lists.

Study Selection: We selected randomized trials and observational studies that compared different HIV screening strategies and reported clinical outcomes; the uptake, yield, or harms of screening; CD4 counts at diagnosis; or rates of linkage to care. We also selected randomized trials and observational studies that reported the effects of starting antiretroviral therapy (ART) at different CD4 count thresholds and long-term harms associated with ART, and randomized trials and observational studies that reported the effects of screening and subsequent interventions on risky behaviors and transmission risk.

Data Extraction: One investigator abstracted data and a second investigator checked data abstraction for accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF.

Data Synthesis (Results): No study directly evaluated effects of screening for HIV infection versus no screening on clinical outcomes, or compared effects of repeat screening versus one-time screening. Evidence from studies comparing effects of different HIV screening strategies on the uptake or yield of screening, CD4 count at diagnosis, linkage to care, or harms associated with screening is too limited to draw reliable conclusions. New evidence provides strong evidence for effectiveness of earlier initiation of ART, including a subgroup analysis from a randomized trial that found initiation of ART at CD4 counts $<0.250 \times 10^9$ cells/L associated with markedly increased risk of death or acquired immunodeficiency syndrome (AIDS) events compared with initiation at CD4 counts $>0.350 \times 10^9$ cells/L after a mean of 18 months (hazard ratio, 5.3 [95% CI, 1.3 to 9.6]). Large, fair-quality cohort studies also consistently found initiation of ART at CD4 counts of 0.350 to 0.500×10^9 cells/L associated with decreased risk of mortality and clinical events compared with delayed initiation. New evidence from good-quality cohort studies confirm a small increase in risk of long-term cardiovascular events associated with certain antiretroviral drugs. Although direct clinical evidence showing that changes in risky behaviors as a result of screening or subsequent interventions reduces transmission risk remains unavailable, there is now strong evidence from a randomized trial as well as consistent evidence from multiple observational studies that ART use is associated with an approximately 10- to 20-

fold reduction in risk of sexual transmission of HIV infection.

Limitations: Only English-language articles were included. Observational studies were included. Studies conducted in resource-poor or high-prevalence settings were included, but might be of limited applicability to general screening in the United States.

Conclusions: Prior studies have shown that HIV screening is accurate, targeted screening misses a substantial proportion of cases, and treatments are effective at improving clinical outcomes in patients with advanced immunodeficiency. New evidence indicates that ART reduces risk of AIDS-defining events and mortality in persons with less advanced immunodeficiency and reduces sexual transmission. More research is needed to understand effects of different screening strategies on the uptake and yield of screening, harms, CD4 count at diagnosis, and linkage to care.

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CHAPTER 1. INTRODUCTION

Purpose of Review and Prior USPSTF Recommendations

The purpose of this report is to update a previous systematic review[1-3] commissioned by the U.S. Preventive Services Task Force (USPSTF) on screening for asymptomatic HIV infection in nonpregnant adults and adolescents. It will be used by the USPSTF to update its 2005 recommendation on screening for HIV in nonpregnant adolescents and adults.[4] A separate report updates the evidence on prenatal HIV screening.[5]

In 2005, based on the earlier evidence review,[1-3] the USPSTF recommended screening all adolescents and adults at increased risk (defined as persons reporting HIV risk factors or evaluated in settings with an HIV infection prevalence of >1%) for HIV infection (grade A recommendation).[4] The USPSTF based its recommendation on the high yield of screening in these patients, good evidence that standard and rapid HIV screening tests accurately detect HIV infection (sensitivity and specificity each >99%), and good evidence that identification and treatment of unsuspected HIV infection at immunologically advanced stages of disease (defined as CD4 counts $<0.200 \times 10^9$ cells/L) with antiretroviral therapy (ART) and other interventions (such as prophylaxis for opportunistic infections) results in marked reduction in risk of progression to acquired immunodeficiency syndrome (AIDS) and AIDS-related clinical events and mortality. Although the USPSTF found ART associated with short-term adverse events and increased risk of long-term cardiovascular events, it determined that estimated benefits greatly outweighed harms.

The USPSTF made no recommendation for or against routinely screening for HIV in adolescents and adults not at increased risk for HIV infection (grade C recommendation*).[4] Because of the lower prevalence of HIV infection in persons not at increased risk, the USPSTF determined that benefits from screening would be smaller than screening in higher-risk populations, resulting in a close balance between potential benefits and harms, including false-positive results, labeling, anxiety, and adverse events associated with ART and other interventions. Importantly, the USPSTF found insufficient evidence to estimate benefits from screening in persons at less immunologically advanced stages of disease (CD4 counts $>0.200 \times 10^9$ cells/L) or effects of screening and subsequent interventions on risk of HIV transmission.

In 2006, the Centers for Disease Control and Prevention (CDC) issued its revised guideline recommending routine voluntary HIV screening of all persons ages 13 to 64 years, unless the prevalence of undiagnosed HIV infection has been documented to be <0.1 percent.[6] The CDC also recommended that testing be performed on an opt-out basis (screening after notifying the patient that an HIV test will be performed unless the patient declines) without a requirement for pretest prevention counseling, in order to reduce barriers to screening. A key reason for the differences

* The USPSTF definition of a "C" recommendation has changed since this guideline was published. In 2005, a "C" recommendation indicated that the USPSTF "makes no recommendation for or against" routinely screening this population. Now, a "C" recommendation indicates that "clinicians may provide this service to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms there is likely to be only a small benefit from this service."

between the CDC and USPSTF recommendations is evidence showing that 20 to 26 percent of patients with HIV infection report no risk factors,[7] suggesting that any screening strategy based on risk factor identification will miss an important proportion of infected persons. Other reasons for the differences between the CDC and USPSTF recommendations include greater weight placed by the CDC on studies showing reductions in self-reported risky behaviors following diagnosis of HIV infection, acceptance of modeling studies to estimate effects of HIV diagnosis and reductions in risky behaviors on transmission risk, and greater weight placed on studies showing acceptable incremental cost-effectiveness ratios for screening versus no screening in very low-prevalence populations. The USPSTF subsequently commissioned a focused update of its 2005 report with the studies included in the CDC guideline,[1] but found insufficient evidence to change its C recommendation on screening in persons not at higher risk.[4] The USPSTF found methodological shortcomings in the studies showing reduced risky behaviors following HIV diagnosis, which made estimations of reductions in transmission risk unreliable. In addition, some evidence suggested that cost-effectiveness of HIV screening in low-prevalence populations is sensitive to transmission benefits, and the cost-effectiveness analyses did not compare universal with targeted screening in low-prevalence settings.[8, 9]

This report updates the prior USPSTF review on the benefits and harms of HIV screening in nonpregnant adolescents and adults, focusing on key research gaps identified in the earlier review, including the yield and outcomes of routine versus targeted screening; periodicity of screening; effects of screening, counseling, and ART use on risky behaviors and HIV transmission risk; effectiveness of treatments in HIV-infected persons with CD4 counts >0.200 x 10^9 cells/L, and long-term harms of ART. This report also addresses areas not addressed in the prior USPSTF review, including effects of different screening methods (e.g., rapid vs. standard testing, different methods of pretest counseling, opt-out vs. opt-in testing) on uptake, CD4 count at diagnosis, linkage to followup care, and harms, in order to help inform optimal screening strategies. This report does not re-examine evidence considered to be well-established, such as the diagnostic accuracy of HIV screening tests, the effectiveness of ART in persons with CD4 counts <0.200 x 10^9 cells/L, or the effectiveness of prophylaxis for opportunistic infections.[2, 3] The review primarily focuses on evidence from studies of low- or average-risk populations, as there is strong evidence supporting screening in high-risk populations, with consensus across guidelines.[4, 6]

Condition Definition

HIV is a ribonucleic acid (RNA) retrovirus that infects the immune cells of its human hosts, in particular, CD4 helper T cells, and leads to AIDS in most patients if left untreated. HIV is a communicable disease with two types: HIV-1 and HIV-2. HIV-2 infection is very uncommon in the United States, primarily affects persons from West Africa, and is less likely to progress to AIDS.[10] AIDS is a life-threatening disease defined by severe immune dysfunction (CD4 T cell count ≤0.200 x 10^9 cells/L) or one or more neoplastic conditions or opportunistic infections.[11]

Prevalence and Burden of Disease

Since the first cases of AIDS were reported in 1981, an estimated 1,108,611 people in the United

States have been diagnosed with AIDS and nearly 594,500 have died.[12] The CDC estimates that 1.2 million people in the United States were living with HIV infection in 2008, with approximately one in five infected persons unaware of their positive status.[12-14] The incidence of HIV in the United States is approximately 50,000 cases per year.[12, 15] Although incidence prior to 2006 was estimated at about 40,000 cases per year,[16] these data are not directly comparable with current estimates because methods for estimating incidence have changed.[15] Estimates of HIV incidence were relatively stable from 2006 through 2009.[12, 15]

The groups most affected by HIV infection in the United States are gay and bisexual men, African Americans, and Hispanics/Latinos. Between 2006 and 2009, there was a 21 percent increase in HIV incidence for people ages 13 to 29 years, driven largely by a 34 percent increase in young men who have sex with men (MSM), who were the only risk group to experience a significant increase in incidence during this period ($p<0.001$).[15] Approximately 75 percent of people living with HIV are men.[17] CDC data from 40 States in 2009 estimated prevalence at 0.02 percent (19.5 cases per 100,000 persons) for 13- to 14-year-olds and 0.04 percent (39 cases per 100,000 persons) for 15- to 19-year-olds. For 20- to 24-year-olds, the prevalence was 0.13 percent. Prevalence increases through ages 40 to 49 years (0.7%), where it then decreases to 0.2 percent in ages 60 to 64 years and to 0.07 percent at age 65 years and older.[18]

Etiology and Natural History

HIV is acquired through percutaneous exposure with infected bodily fluids such as blood, semen, and genital tract secretions. Factors facilitating sexual transmission include the presence of sexually transmitted diseases (STDs), high-risk sexual practices such as unprotected penile-anal intercourse, and high viral load in the infected partner.[19, 20] In injection drug users, factors associated with HIV infection include increased frequency or duration of injection, sharing needles, and backloading (injecting drugs from one syringe into the back of another opened syringe).[21]

The primary HIV infection syndrome usually develops 2 to 4 weeks following initial exposure to HIV.[22] A clinical syndrome resembling infectious mononucleosis is often associated with acute infection.[23, 24] Very early after acute infection, there is rapid virus production that declines to a set point (which varies between individuals) as the host immune system responds, although continuous rapid virus production and clearance occurs at all stages of infection.[25-30]

Although a small proportion of untreated HIV-infected persons remain asymptomatic and show little evidence of progressive immune suppression after 10 or more years of infection, over 90 percent of untreated patients eventually develop AIDS.[11] Before the highly active antiretroviral therapy (HAART) era, the median time from seroconversion to the development of AIDS was 7.7 to 11.0 years, and median survival ranged from 7.5 to 12 years.[31, 32]

The primary mechanism through which chronic HIV infection causes immune deficiency is through a decrease in the level and functioning of CD4+ T lymphocytes. On average, the CD4 count declines 0.050 to 0.075 x 10^9 cells/L per year.[33] Most patients with CD4 counts >0.200 x 10^9 cells/L are either asymptomatic or have mild disease,[34] though research indicates an increased risk of AIDS or death even in patients with CD4 counts >0.500 x 10^9 cells/L.[35] Patients with CD4 counts <0.200

x 10^9 cells/L have advanced immunodeficiency and are at markedly increased risk for AIDS-related opportunistic infections and other AIDS-related complications.[36-38]

A higher HIV viral load is a strong independent predictor of more rapid progression to AIDS.[36-41] Other predictors of more rapid progression include older age at the time of infection,[31, 32, 36, 37, 40, 42, 43] more severe symptoms at the time of primary HIV infection,[44] and other clinical and genetic factors. A host factor consistently associated with slow progression is the homozygous presence of the CCR5 delta32 genotype.[45-49]

Risk Factors/Indicators

Persons considered to be at increased risk for HIV infection include MSM; men and women having unprotected vaginal or anal intercourse with more than one partner; men and women who exchange sex for drugs or money; people with a history of or current injection drug use; people seeking treatment for other sexually transmitted infections (STIs); people with a history of blood transfusion between 1978 and 1985; people whose past or present sex partners are HIV-infected, bisexual, or injection drug users; and people who do not report one of these risk factors but who request HIV testing. Settings in which the prevalence of HIV infection is often >1 percent include STD clinics, correctional facilities, homeless shelters, tuberculosis clinics, clinics caring predominately for MSM, and adolescent clinics with a high prevalence of STIs.[3]

Rationale for Screening/Screening Strategies

Identification and treatment of asymptomatic HIV-positive individuals may lead to interventions that reduce the risk of progression to AIDS, AIDS-defining clinical events, and mortality. The 2005 USPSTF review found treatment (including ART and prophylaxis for opportunistic infections) of HIV-infected persons with immunologically advanced disease (CD4 counts $\leq$0.200 x 10^9 cells/L) associated with substantially improved health outcomes.[3] More evidence is now available on the effectiveness of treatments for patients with less immunologically advanced disease (see key question 4c). In addition, screening may help identify patients at higher CD4 counts before they develop severe immune deficiency or present with an AIDS-defining event. Earlier detection of asymptomatic HIV-positive patients may also help reduce the risk of transmission to others, through effects of knowledge of positive HIV serostatus or counseling interventions on behaviors, or through other interventions (such as use of ART) that may reduce the risk of transmission. It is estimated that approximately 20,000 infections per year are due to transmission of HIV by persons who are unaware that they are infected.[50, 51]

Interventions/Treatment

There remains no effective vaccine to prevent HIV infection and no cure for chronic infection. Interventions for HIV-infected patients include ART, prophylaxis for opportunistic infections, immunizations, Papanicolaou testing, counseling to reduce high-risk behaviors, and routine monitoring and followup. HAART, defined as three or more antiretroviral agents used in

combination (usually from at least two drug classes), is the standard of care for ART (because all currently recommended antiretroviral regimens meet criteria for HAART, this report will primarily simply refer to "antiretroviral therapy," in accordance with current treatment guidelines).[52] Of the interventions used to treat chronic HIV infection, ART has the greatest impact on clinical outcomes, including survival.[53] Clinical practice has generally evolved toward earlier initiation of ART in asymptomatic individuals, though decisions are more individualized at higher CD4 counts (>0.350 x 10^9 cells/L).[52] Detailed and regularly updated guidelines for the U.S. population regarding specifically recommended antiretroviral regimens[52] and chemoprophylaxis for opportunistic infections[54] are available.

Current Clinical Practice

The use of repeatedly reactive enzyme immunoassay on an office-based venipuncture specimen followed by confirmatory Western blot or immunofluorescent assay for positive tests is associated with a sensitivity and specificity >99 percent.[55, 56] Rapid, point-of-care HIV antibody tests on blood or oral fluid specimens provide results in 5 to 40 minutes compared with 1 to 2 weeks for standard testing, with diagnostic accuracy comparable with standard testing.[57, 58] However, initial positive results on a rapid test can represent false-positives and require confirmation. A revised CDC HIV testing algorithm is expected in 2012. The algorithm, which will utilize combination immunoassays that screen simultaneously for both the p24 antigen and HIV antibody and test for HIV RNA without requiring Western blot confirmation, is intended to detect acute HIV infection earlier and to differentiate HIV-2 from HIV-1 infection.[59]

About 45 percent of U.S. adults ages 18 to 64 years report ever being tested for HIV infection.[60] Screening rates for HIV vary by State, age, sex, race/ethnicity, and other factors. For example, African Americans and Latinos are more likely to report testing than whites.

Recommendations of Other Groups

As described above, in 2006 the CDC recommended routine voluntary HIV screening of all adults ages 13 to 64 years regardless of other recognized risk factors, unless the prevalence of HIV has been documented to be <0.1 percent.[6] The CDC also recommended "opt-out" HIV testing, meaning that all patients should be informed about testing and tested unless they specifically decline, without a requirement for prevention counseling prior to screening in order to reduce barriers to testing. In 2009, the American College of Physicians endorsed the CDC approach.[61] The Infectious Diseases Society of America recommends routine HIV screening for all sexually active adults,[62] the American Congress of Obstetricians and Gynecologists recommends routine opt-out screening in all women ages 19 to 64 years and targeted screening in women with risk factors outside of that age range,[63] and the American Academy of Pediatrics recommends routine HIV testing be offered to all adolescents at least once by ages 16 to 18 years when prevalence of HIV is >0.1 percent in the community and testing of all sexually active adolescents and those with risk factors in low-prevalence settings.[64] In 2007, the American Academy of Family Physicians recommended screening for HIV in high-risk groups and in areas where the HIV prevalence is at least 1 percent.[65]

CHAPTER 2. METHODS

Key Questions and Analytic Framework

Using the methods developed by the USPSTF,[66] the USPSTF and the Agency for Healthcare Research and Quality (AHRQ) determined the scope and key questions for this review. Investigators created an analytic framework with the key questions and the patient populations, interventions, and outcomes reviewed (**Figure**). The target population for HIV screening was nonpregnant adolescents and adults without signs or symptoms of HIV infection. We defined "universal" testing to mean routine testing of all persons ages 13 to 64 years, unless the prevalence of HIV infection has been documented to be <0.1 percent,[6] and "targeted" screening to mean routine screening of persons with risk factors or in high-prevalence (>1%) settings.[4] We defined "opt-out" testing as screening after notifying the patient that an HIV test will be performed unless the patient declines and "opt-in" testing to mean that screening is offered but only performed if the patient actively agrees to it.[6]

A contextual question was also requested by the USPSTF to help inform the report. (Contextual questions are not reviewed using systematic review methodology.)

Key Questions

Key Question 1. What are the benefits of universal or targeted HIV screening versus no screening or each other in asymptomatic, nonpregnant adolescents and adults on disease transmission, morbidity, mortality, and quality of life?

Key Question 2a. What is the yield (number of new diagnoses) of HIV screening at different intervals in nonpregnant adolescents and adults?

Key Question 2b. What are the effects of universal versus targeted HIV screening on testing acceptability and uptake in nonpregnant adolescents and adults?

Key Question 2c. What is the effect of opt-out versus opt-in testing or different pre- or post-test HIV counseling methods on screening uptake or rates of followup and linkage to care in nonpregnant adolescents and adults?

Key Question 2d. What are the adverse effects (including false-positive results and anxiety) of rapid versus standard HIV testing in nonpregnant adolescents and adults not known to be at higher risk?

Key Question 2e. What are the effects of universal versus targeted HIV screening on CD4 counts at the time of diagnosis?

Key Question 2f. What are the effects of universal versus targeted HIV screening on rates of followup and linkage to care in nonpregnant adolescents and adults who screen positive?

Key Question 3a. To what extent does knowledge of HIV-positive status affect behaviors associated with increased risk of HIV transmission in nonpregnant adolescents and adults?

Key Question 3b. To what extent does use of ART affect behaviors associated with increased risk of HIV transmission in nonpregnant adolescents and adults?

Key Question 4a. How effective is ART in reducing transmission of HIV in nonpregnant adolescents and adults with chronic HIV infection?

Key Question 4b. How effective is behavioral counseling in reducing transmission of HIV in nonpregnant adolescents and adults with chronic HIV infection?

Key Question 4c. In asymptomatic, nonpregnant adolescents and adults with chronic HIV infection, what are the effects of initiating ART at different CD4 counts or viral load thresholds on morbidity, mortality, and quality of life?

Key Question 5. What are the longer-term harms associated with ART in nonpregnant adolescents and adults with chronic HIV infection?

Key Question 6a. To what extent are improvements in viremia associated with reductions in HIV transmission rates in nonpregnant adolescents and adults?

Key Question 6b. To what extent are improvements in risky behaviors associated with reductions in HIV transmission rates in nonpregnant adolescents and adults?

Contextual Question. What is the cost-effectiveness of universal versus targeted HIV screening in low- or average-prevalence populations?

Key question 1 focuses on direct evidence on effects of screening for HIV infection versus no screening or different screening strategies on important health outcomes. Such direct evidence on the effectiveness of screening interventions may be sparse or unavailable. Therefore, the remainder of the analytic framework (key questions 2 through 6) evaluates the chain of indirect evidence needed to link screening for HIV infection with improvement in important health outcomes. Links in the chain of indirect evidence include the performance, yield, and acceptability of the screening test and different screening strategies for identifying HIV infection, the effectiveness of interventions for improving intermediate outcomes (such as reduced risky behaviors) or clinical outcomes (such as mortality, AIDS-related events, and HIV transmission), and any harms associated with screening and subsequent interventions. Implicit in the indirect chain of evidence is that to understand benefits and harms of screening, it is not sufficient to show that patients with HIV infection can be identified; it is also necessary to show that identification leads to effective treatments, and to understand how many screen-detected patients (e.g., based on CD4 count at diagnosis) are likely to benefit from treatments.

Because this review is a targeted update that focuses on research gaps identified in the 2005 USPSTF review and subsequent update,[1-3] it does not cover all aspects relevant to HIV screening.

The general diagnostic accuracy of HIV testing was not re-reviewed, since it is well established as a very accurate test, and direct harms of screening compared with no screening (e.g., labeling and anxiety) were not re-reviewed, given that direct harms associated with screening were estimated as minimal to small and are likely unchanged. Similarly, the general effectiveness of ART, prophylaxis for opportunistic infections, and immunizations was not re-reviewed. Instead, this report focuses on new evidence on the effectiveness of ART in patients with less immunologically advanced disease and harms of long-term ART; the yield of repeat screening and the effects of different screening strategies on uptake of screening, linkage to care, and CD4 counts at diagnosis; the effects of knowledge of positive HIV status and subsequent interventions on risky behaviors and transmission risk; and the association between changes in risky behaviors and transmission risk. This report also addresses areas not covered in the prior report on effects of different screening methods (e.g., rapid vs. standard testing, different methods of pretest counseling, opt-out vs. opt-in testing) on uptake, CD4 count at diagnosis, linkage to followup care, and harms, in order to help inform optimal screening strategies.

Search Strategies

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the second quarter of 2012) and Ovid MEDLINE (2004 through June 2012) for relevant studies and systematic reviews. Search strategies are available in **Appendix A1**. We also reviewed reference lists of relevant articles.

Study Selection

At least two reviewers independently evaluated each study to determine inclusion eligibility. We selected studies on the basis of inclusion and exclusion criteria developed for each key question (**Appendix A2**). Articles were selected for full review if they were about HIV infection in nonpregnant adolescents and adults, were relevant to a key question, and met the predefined inclusion criteria. We restricted inclusion to English-language articles and excluded studies only published as abstracts. Studies of nonhuman subjects were also excluded, and studies had to include original data.

For key questions related to screening, we included studies of nonpregnant adolescents and adults. Prenatal screening for HIV infection is covered in a separate review.[5] For key questions related to interventions and behavior changes after diagnosis, we included studies of HIV-positive persons, focusing when possible on studies not specifically performed in high-risk populations (such as MSM or injection drug users) or high-prevalence populations. We excluded studies from countries with high HIV prevalence and in which management practices differ substantially from the United States, unless evidence from settings more applicable to the United States was not available. The screening interventions were standard or rapid HIV antibody testing and screening strategies included universal or targeted screening and opt-in or opt-out testing. For treatment interventions, we focused on ART and counseling and other interventions to reduce risky behaviors. Outcomes were mortality, progression to AIDS, other morbidity and quality of life, HIV transmission risk, and harms from screening (including false-positive results and anxiety) and long-term (defined as 2 or

more years following initiation of treatment) cardiovascular harms associated with ART. We included randomized, controlled trials and cohort studies for all key questions. If such studies were not available, we also included uncontrolled screening series in low-risk populations. We also included recent (published since 2010) systematic reviews that met all predefined quality criteria.[67] **Appendix A3** shows the results of our literature search and selection process and **Appendix A4** lists excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

We abstracted details about the study design, patient population, setting, screening method, interventions, analysis, followup, and results. Two investigators independently applied criteria developed by the USPSTF[66] to rate the quality of each study as good, fair, or poor (**Appendixes A5** and **A6**). Discrepancies were resolved through a consensus process.

Data Synthesis

We assessed the aggregate internal validity (quality) of the body of evidence for each key question (good, fair, or poor) using methods developed by the USPSTF, based on the number, quality, and size of studies, consistency of results between studies, and directness of evidence.[66] Meta-analysis was not attempted due to the inability to pool data from studies.

External Review

The draft report was be reviewed by content experts, USPSTF members, AHRQ Project Officers, and collaborative partners and revised prior to finalization (**Appendix A7**).

CHAPTER 3. RESULTS

Key Question 1. What Are the Benefits of Universal or Targeted HIV Screening Versus No Screening or Each Other in Asymptomatic, Nonpregnant Adolescents and Adults on Disease Transmission, Morbidity, Mortality, and Quality of Life?

No randomized trial or observational study compared clinical outcomes between adults and adolescents screened and not screened for HIV infection.

Key Question 2a. What Is the Yield (Number of New Diagnoses) of HIV Screening at Different Intervals in Nonpregnant Adolescents and Adults?

No randomized trial or observational study evaluated the yield of repeat HIV screening compared with one-time screening, or compared the yield of different strategies for repeat screening (e.g., risk-based repeat screening vs. a routine repeat test). The yield of repeated screening would depend in part on the frequency of new HIV infections. Some modeling studies have estimated the cost-effectiveness of strategies involving repeat screening (see the contextual question below).

Key Question 2b. What Are the Effects of Universal Versus Targeted HIV Screening on Testing Acceptability and Uptake in Nonpregnant Adolescents and Adults?

Summary

No study directly evaluated the acceptability of universal versus targeted HIV screening. One fair-quality, nonrandomized study of emergency department (ED) patients found universal, opt-out rapid screening associated with higher likelihood of testing compared with physician-directed, targeted rapid screening (25% vs. 0.8%; relative risk [RR], 30 [95% CI, 26 to 34]), but testing uptake (the proportion of patients offered testing who accepted) was not reported. In two uncontrolled implementation studies of universal HIV screening conducted in primary care settings, 35 percent (standard test) and 60 percent (rapid test) of those offered screening underwent it.

Evidence

The prior USPSTF review found no studies that directly compared acceptance of universal versus targeted HIV screening.[1-3] It found that general acceptance of voluntary HIV testing in the United States varied from 11 to 91 percent, with greater uptake in higher prevalence settings, in patients

with perceived or acknowledged HIV risk factors, when confidentiality protections were present, and when providers believed testing was beneficial.[1-3] Other factors that appeared to increase HIV testing uptake were use of opt-out testing, anonymous testing, and for adolescents, removal of parental consent.

One nonrandomized study published since the prior USPSTF review compared testing rates during periods of universal opt-out rapid HIV screening versus physician-directed, targeted rapid screening in sequential 4-month intervals over 2 years in an ED.[68] Universal screening was associated with a much higher likelihood of testing (25% [6,933/28,043] vs. 0.8% [243/29,925]; RR, 30 [95% CI, 26 to 34]), but testing uptake (the proportion of patients offered testing who accepted) was not reported. One uncontrolled implementation study of universal testing in a primary care setting reported 60 percent (574/954) of patients were offered and accepted rapid HIV testing,[69] and another reported that 35 percent (105/300) of patients accepted standard HIV testing[70] (**Appendixes B1** and **B2**).

Key Question 2c. What Is the Effect of Opt-Out Versus Opt-In Testing or Different Pre- or Post-Test HIV Counseling Methods on Screening Uptake or Rates of Followup and Linkage to Care in Nonpregnant Adolescents and Adults?

Summary

One observational study of computerized, kiosk-based screening found an opt-out approach associated with higher likelihood of testing compared with an opt-in approach (13% vs. 7%; RR, 2.1 [95% CI, 1.9 to 2.4]), but patients who underwent opt-out testing were more likely to report that they had not been informed of HIV testing. Only two patients had newly diagnosed HIV infection, precluding conclusions regarding rates of followup or linkage to care. One other study found opt-out testing associated with lower testing uptake compared with opt-in testing, but results may have been confounded by differences in who offered the testing.

No study compared effects of different pre- or post-test HIV counseling methods on screening uptake or rates of followup and linkage to care.

Evidence

The prior USPSTF review included an uncontrolled implementation study that found that 35 percent (26/74) of HIV-infected persons identified through a routine voluntary screening program in an urgent care center had entered care within 4 months.[71] No study was found on effects of opt-out versus opt-in testing on screening uptake in nonpregnant persons, or on effects of different pre- or post-test HIV counseling methods on screening uptake or rates of followup and linkage to care.

One fair-quality, prospective observational study (n=12,827) published since the prior USPSTF review of computerized, kiosk-based screening in the ED found opt-out screening associated with a higher likelihood of testing compared with opt-in testing (13% vs. 7%; RR, 2.1 [95% CI, 1.9 to

2.4])[72] (**Appendixes B3** and **B4**). However, patients who underwent opt-out testing were also more likely to report that they had not been informed of HIV testing compared with those who underwent opt-in testing (54% vs. 2.5%; RR, 21 [95% CI, 5.4 to 85]). Only two patients in the study were diagnosed with HIV infection (both during the opt-in period); both were successfully linked to ongoing HIV care.

One other observational study (n=8,732) in an ED setting reported lower testing uptake with opt-out screening offered by ED front desk registration staff compared with opt-in screening offered by ED triage nurses and providers (31% vs. 63%; $p<0.01$), but results may have been confounded by differences in who offered the testing.[73]

No study compared effects of different pre- or post-test HIV counseling methods on screening uptake or rates of followup and linkage to care. One randomized trial compared streamlined versus traditional pretest counseling but was excluded because of other differences between arms other than the counseling intervention, including referral for possible testing versus on-site counseling and testing, physician- versus nurse-directed testing, and use of rapid versus standard HIV testing.[74]

Key Question 2d. What Are the Adverse Effects (Including False-Positive Results and Anxiety) of Rapid Versus Standard HIV Testing in Nonpregnant Adolescents and Adults Not Known to Be at Higher Risk?

Summary

The prior USPSTF review found standard and rapid HIV testing with confirmatory Western blot associated with high sensitivities and specificities, though the positive predictive value associated with rapid testing prior to confirmatory testing decreased as the prevalence of HIV infection decreased. One randomized trial published since the prior USPSTF review directly compared rapid versus standard HIV testing but only identified one confirmed HIV infection. In large studies of rapid testing (without a comparison to standard testing), the positive predictive value was 95 percent in one study of a higher-prevalence (1.1%) setting, and varied widely (16% to 83%) in four studies of lower-prevalence (0.2% to 0.4%) settings. No study compared psychological or other harms associated with rapid versus standard HIV testing.

Evidence

No study in the prior USPSTF review directly compared harms associated with rapid versus standard HIV testing. The prior USPSTF review found standard HIV testing followed by confirmatory Western blot associated with sensitivity $\geq$99.7 percent and specificity $\geq$98.5 percent, with a false-alarm rate (1 – positive predictive value) in low-prevalence settings of about 1 in 250,000 (95% CI, 1 in 173,000 to 1 in 379,000).[1-3] It found rapid testing prior to confirmatory testing associated with a sensitivity $\geq$94 percent and specificity $\geq$99 percent, with positive predictive values of 25 to 50 percent (in settings with a prevalence of 0.3%), and 85 to 95 percent (in settings with a prevalence of 5%). The prior USPSTF review also identified anecdotal reports of other

harms of screening, including stigmatization (including verbal and physical abuse) and anxiety, but found insufficient evidence to estimate their magnitude.[1-3]

One trial published since the prior USPSTF review randomized patients in a Department of Veterans Affairs primary care setting to universal HIV screening based on one of three strategies: nurse-initiated rapid testing (n=84), nurse-initiated standard testing (n=84), or physician-initiated standard testing (n=83), but only identified one patient with a preliminary positive result.[74] No other study directly compared rapid versus standard testing and reported positive predictive values.

Five large (sample sizes, 2,002 to 23,900) uncontrolled observational studies published since the 2005 USPSTF review reported positive predictive values associated with rapid testing[68, 73, 75-77] (**Table 1**). In lower-prevalence (0.2% to 0.4%) settings, positive predictive values varied dramatically, from 16 to 83 percent.[68, 73, 76, 77] One study appeared to be an outlier,[77] reporting a positive predictive value of 16 percent compared with 77 to 83 percent in the other studies. Stratification of the low-prevalence studies according to whether they evaluated a rapid test using an oral fluid (16% and 78%)[77] versus finger-stick (77%)[76] or whole-blood specimen (83%)[68] did not explain the variability in positive predictive values.

One large study (n=23,900) in a higher-prevalence (1.1%) setting reported a positive predictive value following a positive rapid HIV test (oral fluid or finger-stick specimen) of 94 percent.[75]

No study evaluated psychological or other adverse effects associated with rapid versus standard HIV testing.

Key Question 2e. What Are the Effects of Universal Versus Targeted HIV Screening on CD4 Counts at the Time of Diagnosis?

Summary

One fair-quality study found universal testing associated with a higher median CD4 count and lower likelihood of CD4 count $<0.200 \times 10^9$ cells/L at the time of diagnosis compared with targeted HIV screening, but these differences were not statistically significant. No other studies directly compared effects of universal versus targeted HIV screening, though epidemiologic data indicate temporal trends suggesting earlier diagnosis since the 2006 CDC recommendation on routine HIV screening was issued.

Evidence

A high proportion of HIV-infected patients are diagnosed at late stages of disease. In 2008, about one third of patients received an AIDS diagnosis within 1 year of testing HIV-positive.[13] The prior USPSTF review[1-3] identified no studies on the effects of universal screening on the proportion of patients with HIV infection identified shortly before being diagnosed with AIDS or concurrently with their AIDS diagnosis.

One fair-quality cohort study published since the prior USPSTF review of patients in a large urban ED compared universal opt-out rapid HIV testing (n=6,702) with targeted HIV testing (n=243) (**Appendixes B5** and **B6**).[68] The median CD4 count at the time of HIV diagnosis was 0.069 x 10^9 cells/L (interquartile range, 0.017 to 0.430 x 10^9 cells/L) for 16 confirmed infections identified during opt-out testing (prevalence, 0.24%) versus 0.013 x 10^9 cells/L (interquartile range, 0.011 to 0.015 x 10^9 cells/L) for five confirmed infections (prevalence, 2.1%) identified during diagnostic testing phases (p=0.02 for difference). Nine of 15 patients with HIV infections identified during universal opt-out testing had an initial CD4 count <0.200 x 10^9 cells/L compared with all four confirmed HIV infections identified during targeted testing (60% vs. 100%; RR, 0.66 [95% CI, 0.40 to 1.1]).

One other observational study (n=8,732) reported a mean CD4 count of 0.415 x 10^9 cells/L (standard deviation [SD], 0.237 x 10^9 cells/L) in eight new, confirmed HIV infections (prevalence, 0.2%) identified during universal opt-in screening offered by ED triage nurses and providers versus 0.307 x 10^9 cells/L (SD, 0.274 x 10^9 cells/L) in 21 infections (prevalence, 0.4%) identified during universal opt-out screening offered by ED front desk registration staff (p=0.84).[73] Twenty-five percent of patients diagnosed during opt-in screening had a CD4 count <0.200 x 10^9 cells/L versus 48 percent diagnosed during opt-out screening (RR, 0.52 [95% CI, 0.15 to 1.9]). Results may have been confounded by differential HIV testing acceptance rates in the two groups (31% for opt-out testing and 63% for opt-in testing), perhaps due in part to differences in who offered the testing.

No other study directly evaluated effects of universal versus targeted screening on CD4 counts at the time of diagnosis, though epidemiologic data may provide some indirect evidence. The CDC reported that the proportion of newly diagnosed patients in the United States with a late diagnosis (defined as CD4 cell count <0.200 x 10^9 cells/L or AIDS-defining illness within 12 months of HIV diagnosis) decreased from 37 percent between 2001 and 2004 to 32 percent in 2007.[60] Similarly, a large cohort study (n=44,491) reported a decrease over time in the proportion of HIV-positive patients initially presenting to care with a CD4 cell count <0.350 x 10^9 cells/L from 1997 to 2007 (from 62% to 54%), with an increase in median CD4 count at presentation of 0.061 x 10^9 cells/L.[78] One study (n=4,478) in Washington, D.C., found that the median CD4 count at the time of HIV diagnosis increased from 0.266 x 10^9 cells/L in 2005 to 0.361 x 10^9 cells/L in 2009, though the statistical significance of the difference was not reported.[79] Another, smaller study (n=1,203) also reported a temporal trend for lower likelihood of late diagnosis (39% in 2000–2001 and 35% in 2008–2009), though the difference was not statistically significant.[80] Although these trends appear to temporally coincide with the CDC recommendations for universal opt-out HIV screening released in 2006,[6] it is not possible to determine causality between increased testing and earlier diagnosis based on these data.

Key Question 2f. What Are the Effects of Universal Versus Targeted HIV Screening on Rates of Followup and Linkage to Care in Nonpregnant Adolescents and Adults Who Screen Positive?

Summary

Three observational studies published since the prior USPSTF review reported rates of followup or linkage to care following a new HIV diagnosis found during universal testing, ranging from 75 to 100 percent. The only study that directly compared universal with targeted testing reported very high rates of followup (defined as attending at least one HIV clinic visit) with either strategy (97% to 100%). All studies were limited by small numbers of patients with newly diagnosed HIV infection.

Evidence

In order to realize the potential clinical benefits from HIV screening, patients must be successfully linked to HIV care following diagnosis. The prior USPSTF review identified little evidence on the effect of universal versus targeted HIV screening on linkage to care following HIV diagnosis.[1-3] It included one uncontrolled study that found that 35 percent (26/74) of HIV-infected persons identified through a universal voluntary screening program in an urgent care center had entered care within 4 months.[71] Another uncontrolled study, also performed in an urgent care center, found that at least 70 percent (42/60) of newly diagnosed HIV-infected persons had one or more documented followup visits following identification through routine screening.[81]

Three studies[68, 73, 76] published since the prior USPSTF review reported linkage to care following universal HIV testing (**Appendixes B7** and **B8**). One study compared universal with targeted screening and two reported rates of linkage to care after universal testing (one study[73] evaluated two strategies of universal testing). All studies were limited by small numbers of newly diagnosed HIV infections (17 to 36 cases).

The study that directly compared universal with targeted screening (36 new HIV cases) was a fair-quality, nonrandomized study conducted in a large urban ED that found a very high likelihood of attending at least one HIV clinic appointment in patients diagnosed with either universal or targeted testing (97% vs. 100%; RR, 1.0 [95% CI, 0.81 to 1.3]).[68] An uncontrolled study of universal rapid HIV testing in Federally Qualified Health Centers found 14 of 17 (82%) patients with confirmed HIV infections were linked to HIV care following diagnosis.[76] A pre-post evaluation of universal opt-in or opt-out rapid oral HIV screening implementation (29 new HIV cases identified) in an ED reported similar rates of linkage to care within 90 days following HIV diagnosis with either strategy (75% [6/8] vs. 77% [16/21]; RR, 0.98 [95% CI, 0.62 to 1.6]).[73]

Key Question 3a. To What Extent Does Knowledge of HIV-Positive Status Affect Behaviors Associated With Increased Risk of HIV Transmission in Nonpregnant Adolescents and Adults?

Summary

Four before-after studies not included in the prior USPSTF review addressed effects of knowledge of HIV-positive status on risk behaviors. As in the prior USPSTF review, the studies found knowledge of HIV-positive status associated with reduced self-reported risky behaviors in all populations studied.

Evidence

The prior USPSTF evidence review[1-3] included two systematic reviews on the association between HIV-positive status and high-risk behaviors.[82, 83] Both reviews found greater self-reported reductions in unprotected intercourse in persons testing HIV positive and in serodiscordant couples compared with those testing negative or those who were untested or unaware of their status. Interpretation of these findings was difficult because the primary studies in the reviews evaluated diverse populations and frequently had methodological shortcomings, such as retrospective design, low participation rates, or high loss to followup. Although these studies relied on self-reported behavior, with its attendant shortcomings, there is no practical alternative for assessing these outcomes. Reasons for HIV testing were typically not reported in the primary studies, so the applicability of results to asymptomatic patients undergoing screening was unclear.

Four before-after studies not considered in the prior USPSTF review evaluated the association between knowledge of HIV-positive status and behaviors associated with increased risk of HIV transmission[84-87] (**Table 2**, **Appendix B9**). Sample sizes ranged from 73 to 560 and behaviors were evaluated from 1 month to 2 or more years following diagnosis. One study was rated good-quality[87] and three studies fair-quality[84-86] (**Appendix B10**). All studies relied on self-reported risky behaviors and one[86] relied on retrospective recall of pre-HIV diagnosis behaviors. Two studies focused on high-risk groups (MSM or injection drug users), potentially limiting applicability to individuals without these risk factors.[85, 87]

One retrospective before-after study of a mixed population (n=487) of HIV-positive persons (injection drug users, noninjection drug-using heterosexual individuals, and MSM) found a significantly lower likelihood of self-reported injection drug use 2 or more years following HIV diagnosis compared with prior to diagnosis (32% vs. 54%).[86] The study also found increased condom use after compared with before HIV diagnosis during vaginal (40% vs. 5.5%), anal (32% vs. 4.1%), or oral-genital sex (9.0% vs. 0.9%) with stable partners ($p<0.0005$ for all differences). Although patients were also less likely to have stable partners following an HIV diagnosis compared with before diagnosis (77% vs. 89%; $p<0.0005$), likelihood of condom use during intercourse with occasional partners also increased after HIV diagnosis. Patients were also less likely to report engaging in sex for money or drugs following HIV diagnosis (6.8% vs. 13%;

p<0.0005) or engaging in sex with sex workers (7.2% vs. 16%; p<0.0005). One other small (n=16) before-after study of heterosexual individuals also found reduced risky sexual behaviors 3 months following a diagnosis of HIV infection compared with before diagnosis.[84]

Two studies of high-risk populations also found decreases in high-risk behaviors following HIV diagnosis. A prospective before-after study of MSM with primary HIV infection (n=98) found greater self-reported condom use (proportion always using during insertive anal intercourse, 61% vs. 31%; p<0.01) and fewer sexual partners (66% reported fewer sex partners, 27% no change, and 7.1% more partners; p<0.001) 3 months following diagnosis compared with at the time of testing.[87] Seventy-six percent reported no high-risk behaviors at all following HIV diagnosis (high-risk behaviors defined as unprotected anal intercourse with a regular partner of unknown or HIV-negative status, unprotected anal intercourse with a casual male partner, or incident STI). Another prospective before-after study found that 26 percent (11/42) of HIV-positive injection drug users reported cessation of injection drug use 1 to 6 months following diagnosis, 73 percent (19/26) stopped lending needles, 62 percent (23/37) stopped borrowing needles, and 38 percent (27/72) increased use of needle exchange programs.[85] Among males, 50 percent (9/18) had ceased sexual relations over the past 3 months, and all five men previously engaged in sex work had stopped this activity.

Key Question 3b. To What Extent Does Use of Antiretroviral Therapy Affect Behaviors Associated With Increased Risk of HIV Transmission in Nonpregnant Adolescents and Adults?

Summary

Seven observational studies not included in the prior USPSTF review addressed the effect of ART use on HIV risk behaviors. The studies primarily used a cross-sectional design and had methodological shortcomings, including failure to report baseline differences or to adjust for potential confounders. They found no clear association between ART use and increase in self-reported risky behaviors, with some studies showing decreased risky behaviors.

Evidence

The prior USPSTF review identified one good-quality meta-analysis that found no association between ART use in HIV-infected persons and increased likelihood of unprotected sex.[89] However, some individual studies included in the prior USPSTF review reported associations between ART use and increased risk of high-risk sexual behaviors and in MSM,[90] as well as associations between ART use and increased likelihood of developing an STD[91] and higher risk for pregnancy.[92]

Five cross-sectional studies,[93-97] one prospective cohort study,[98] and one before-after study[99] not included in the prior USPSTF review evaluated the association between ART use and high-risk behaviors (**Table 3**, **Appendix B11**). Sample sizes ranged from 67 to 4,016. In the prospective cohort study, duration of followup averaged 8 years.[98] All studies were rated fair-quality[93-99] (**Appendix B12**). Methodological shortcomings included group differences between those taking

and not taking ART[93] or insufficient information to compare groups by ART use at baseline.[94-97] Three studies did not adjust for or did not clearly describe statistical adjustments for potential confounders,[93, 96, 98] and one study did not adjust for sex.[95] Risky behaviors were self-reported in all studies.[93-99] Three studies included only high-risk groups (MSM or injection drug users).[96, 98, 99]

Three observational studies of women or mixed (male or female) populations of heterosexual patients found no association between ART use and increased risky sexual behaviors, with two studies showing decreased risk.[93, 95, 97] A cross-sectional Spanish study of 625 HIV-serodiscordant heterosexual couples found lower likelihood of self-reported unprotected sexual intercourse in the preceding 6 months in couples in which the index partner was taking ART compared with couples in which the index partner was not taking ART (46% vs. 57%; p=0.02).[93] A cross-sectional U.S. study also found trends toward reduced likelihood of engaging in risky behaviors in women (n=1,104) or heterosexual men (n=803) taking ART compared with those not taking ART, though differences were not statistically significant.[97] A cross-sectional United Kingdom study found no association between ART use and unprotected intercourse in women (n=480) or heterosexual men (n=224).[95]

Six observational studies of high-risk populations (MSM or injection drug users) also found no clear increases in risky behaviors (high-risk sexual behaviors or injection drug use) after initiation of ART compared with before initiation of therapy, or in HIV-infected patients taking ART compared with those not on therapy.[94-99] Two of these studies found ART use associated with reduced likelihood of high-risk behaviors.[94, 97] One (n=4,016) found ART use associated with decreased risk of engaging in risky sexual behaviors over the past 6 months in MSM (adjusted odds ratio [OR], 0.73 [95% CI, 0.54 to 1.0]).[97] The other (n=874) found ART use associated with decreased risk of unprotected anal or vaginal intercourse (adjusted OR, 0.70 [95% CI, 0.50 to 1.0]) in a population primarily consisting of gay men and injection drug users.[94]

Key Question 4a. How Effective Is Antiretroviral Therapy in Reducing Transmission of HIV in Nonpregnant Adolescents and Adults With Chronic HIV Infection?

Summary

A good-quality systematic review found consistent evidence from one randomized, controlled trial and seven observational studies that ART use is associated with decreased risk of HIV transmission from HIV-positive persons to uninfected sexual partners. In the randomized trial, the risk of HIV seroconversion in uninfected sexual partners of patients with baseline CD4 counts of 0.350 to 0.550 x 10^9 cells/L was much lower in those randomized to immediate versus delayed ART after 1.7 years of followup (HR, 0.04 [95% CI, 0.01 to 0.27] for genomically linked seroconversion), consistent with the pooled risk estimate from observational studies (HR, 0.16 [95% CI, 0.07 to 0.35]).

Evidence

The prior USPSTF review[1-3] identified no studies that directly evaluated the association between

ART use and risk of transmission. However, ART could decrease risk of HIV transmission from infected persons by decreasing viral load.[19, 104-106] One pre-HAART era cohort study found zidovudine associated with lower risk of heterosexual transmission compared with no treatment in monogamous men (RR, 0.5 [95% CI, 0.1 to 0.9]).[107]

A recent, good-quality systematic review evaluated the association between ART use and risk of HIV transmission from HIV-positive persons to uninfected sexual partners[108] (**Appendixes B13** and **B14**). It included one randomized, controlled trial[109] and seven observational studies.[93, 107, 110-114]

The good-quality randomized, controlled trial (HIV Prevention Trials Network [HPTN] 052) compared early ART (started at enrollment) versus delayed therapy (after a decline in CD4 count to $<0.250 \times 10^9$ cells/L or onset of symptoms) in HIV-infected patients with baseline CD4 counts of 0.350 to 0.550×10^9 cells/L and an HIV-negative partner[109] (**Appendixes B15** and **B16**). Fifty-four percent of the 1,763 couples were from Africa, with the remainder from Brazil, India, Thailand, and the United States. Ninety-seven percent of couples were heterosexual and 94 percent were married. All couples received condoms and counseling along with quarterly HIV testing of uninfected partners. The trial was designed to follow patients for 5 years, but was terminated early after meeting prespecified criteria for efficacy in interim analyses. At a median followup of 1.7 years, there were 39 seroconversions among all participants in the trial (1.2 per 100 person-years). Risk of seroconversion in HIV-negative partners was much lower in the early compared with the delayed therapy group (0.3 vs. 2.2 per 100 person-years; HR, 0.11 [95% CI, 0.04 to 0.32]). When restricted to the 28 cases that were genomically linked to the HIV-infected patient enrolled in the trial (one transmission in the early-therapy group and 27 transmissions in the delayed-therapy group), the HR was 0.04 (95% CI, 0.01 to 0.27). All cases of linked transmission in the delayed-therapy group occurred prior to initiation of ART in the HIV-infected partner.

Results of seven observational studies[93, 107, 110-114] (**Appendixes B15** and **B17**) included in the systematic review[108] were consistent with the randomized trial.[109] Sample sizes ranged from 93 to 3,408 couples, with typical followup between 1 and 3 years (range, 3 months to 9 years). All seven observational studies were cohort studies of HIV-serodiscordant, heterosexual couples from Africa, Italy, Spain, Brazil, or China. Six cohort studies were rated fair-quality[93, 107, 110-112, 114] and the seventh[113] was reported as a conference abstract only and could not be quality rated. Three studies adjusted for possible confounding variables such as age, sex, condom use, or frequency of sexual intercourse.[107, 110, 114] Four studies reported low loss to followup.[107, 110, 111, 114]

Six of the seven observational studies reported decreased risk of HIV transmission from persons taking ART compared with those who were untreated.[93, 107, 110-113] Of the 436 total HIV transmissions in the seven observational studies, 71 were in couples in which the HIV-infected individual was receiving ART and 365 transmissions were in couples in which the HIV-infected individual was not receiving ART (pooled HR, 0.34 [95% CI, 0.13 to 0.92]).[108] However, there was substantial statistical heterogeneity (I^2=73%). Excluding one study with inadequate person-time data[114] and one older study that included persons treated with monotherapy only[107] resulted in a pooled HR of 0.16 (95% CI, 0.07 to 0.35) and eliminated the statistical heterogeneity (I^2=0%). The treatment effect was also more pronounced when the analysis was restricted to couples in which the HIV-infected individual had a CD4 count $<0.200 \times 10^9$ cells/L (pooled HR, 0.06 [95% CI, 0.01 to 0.54]),[93, 110-112] couples in which the index case was male (pooled HR, 0.02 [95% CI, 0.00 to

0.89]),[93, 113] or couples residing in low/middle income countries (pooled HR, 0.24 [95% CI, 0.06 to 1.03]).[110-114]

Key Question 4b. How Effective Is Behavioral Counseling in Reducing Transmission of HIV in Nonpregnant Adolescents and Adults With Chronic HIV Infection?

Summary

Two studies of counseling interventions identified too few cases of new HIV infection to reliably estimate effects of counseling on risk of transmission.

Evidence

The prior USPSTF review[1-3] found no randomized trials or controlled observational studies on the effects of counseling HIV-positive persons regarding risky behaviors on HIV transmission risk. One uncontrolled prospective U.S. study of 144 serodiscordant heterosexual couples reported reduced risky behaviors and no HIV transmission following counseling after 193 couple-years of followup.[115]

There remains little direct evidence on effects of testing and counseling regarding risky behaviors on HIV transmission (**Appendixes B18**, **B19**, and **B20**). Trials of counseling have generally not been designed to assess the effect of counseling on HIV transmission rates and have been underpowered. A cluster-randomized, controlled trial of African American, HIV-serodiscordant, heterosexual couples (n=536 couples) from four U.S. cities who had recently engaged in unprotected sexual intercourse found an Afrocentric HIV-STD risk-reduction counseling intervention[116] associated with increased likelihood of condom use compared with an attention-matched, individual-focused health promotion comparison group (63% vs. 48%; RR, 1.4 [95% CI, 1.2 to 1.7]), but after 12 months, there were only two HIV transmissions out of 260 couples in the counseling group and only three HIV transmissions out of 275 couples in the comparison group.[117] Similarly, a before-after study of 564 serodiscordant couples who participated in couples counseling and testing in Madrid from 1989 to 2007 found an increased likelihood of 100 percent condom use following counseling compared with before counseling (69% vs. 49%; $p<0.001$), but there were only five seroconversions during 1,279 couple-years of followup.[118]

No study estimated the effects of testing and counseling HIV-positive persons on injection drug use behaviors and transmission rates.

Key Question 4c. In Asymptomatic, Nonpregnant Adolescents and Adults With Chronic HIV Infection, What Are the Effects of Initiating Antiretroviral Therapy at Different CD4 Counts or Viral Load Thresholds on Morbidity, Mortality, and Quality of Life?

Summary

The prior USPSTF review found good-quality evidence that ART is associated with decreased risk of AIDS events and mortality compared with placebo or less-intensive regimens in patients with CD4 counts <0.200 x 10^9 cells/L. Two randomized, controlled trials (including one subgroup analysis) published after the prior USPSTF review found initiation of ART at CD4 counts <0.250 x 10^9 cells/L associated with substantially increased risk of death or AIDS events compared with initiation at CD4 counts >0.350 x 10^9 cells/L. Recent large, observational studies incorporating data from 12 to 23 cohorts also consistently found initiation of ART at CD4 counts between 0.350 and 0.500 x 10^9 cells/L associated with decreased risk of mortality, or a trend toward decreased risk, compared with deferred or no ART. Four studies evaluating initiation of ART at CD4 counts >0.500 x 10^9 cells/L were inconsistent, with one study showing beneficial effects on clinical outcomes and three studies finding no clear benefit.

Two studies reported inconsistent results for the association between viral load at the time of initiation of ART and subsequent mortality.

Evidence

CD4 count. The prior USPSTF review included good-quality randomized, controlled trials[119-121] and observational studies[36, 122-128] that consistently found ART associated with decreased risk of AIDS events and mortality compared with placebo or less-intensive regimens in patients with CD4 counts <0.200 x 10^9 cells/L. Evidence showing benefits of starting ART at higher CD4 counts was limited. Although a Swiss cohort study found starting ART at CD4 counts >0.350 x 10^9 cells/L associated with reduced risk of mortality and progression to AIDS compared with starting at counts <0.350 x 10^9 cells/L,[129] three U.S. cohort studies found no difference in risk between starting ART at CD4 counts between 0.350 and 0.500 x 10^9 cells/L versus delaying until CD4 counts were between 0.200 and 0.350 x 10^9 cells/L.[126-128]

Two good-quality randomized trials[109, 130] published since the prior USPSTF and one subgroup analysis[131] from another good-quality randomized trial evaluated effects of initiating ART at different CD4 count thresholds (**Appendixes B21** and **B22**). Five observational studies (reported in six publications) that each combined data from 12 to 23 U.S., European, and Australian cohorts (~9,000 to >60,000 participants; duration of followup, 1 to 5 years, with substantial overlap in the cohorts included in the studies) also evaluated effects of starting ART at different CD4 count thresholds[132-137] (**Appendix B23**). All studies were rated fair-quality (**Appendix B24**). None reported blinding of outcome assessors or those analyzing data, and attrition rates were often not reported or unclear. Although all studies adjusted for important confounders in their analyses, most

provided insufficient information to determine baseline comparability of patients started and not started on ART in different CD4 count strata.

Three randomized, controlled trials found delayed initiation of ART associated with increased risk of the combined outcome of death or AIDS-related events (**Table 4**). A retrospective subgroup analysis of patients (n=477) in the Strategies for Management of Antiretroviral Therapy (SMART) randomized trial who were treatment-naive or had been off therapy for at least 6 months found initiation of ART at CD4 counts <0.250 x 10^9 cells/L associated with increased risk of death or AIDS events compared with initiation at CD4 counts >0.350 x 10^9 cells/L after a mean of 18 months (HR, 5.3 [95% CI, 1.3 to 9.6]).[131] The SMART trial was conducted in 33 primarily nonresource-poor countries. HPTN 052, conducted in 1,763 serodiscordant partners from primarily resource-poor countries, found initiation of ART at CD4 counts <0.250 x 10^9 cells/L associated with increased risk for the combined endpoint of death or AIDS events compared with initiation at CD4 counts between 0.350 and 0.550 x 10^9 cells/L (adjusted HR, 1.7 [95% CI, 1.1 to 2.5]), though these results were strongly influenced by the incidence of extrapulmonary tuberculosis (RR, 5.6 [95% CI, 1.7 to 20]).[109] Results for mortality or pulmonary tuberculosis were not significant when these outcomes were considered individually. The third randomized trial (n=816) found initiation of ART at CD4 counts <0.200 x 10^9 cells/L associated with increased risk of mortality compared with initiation at CD4 counts of 0.201 to 0.350 x 10^9 cells/L (HR, 4.0 [95% CI, 1.6 to 9.8]; p=0.001), but is less directly applicable to the U.S. population, as it was conducted in Haiti and CD4 count thresholds for treatment in both groups were lower than those typically used in the United States.[130]

Four observational studies consistently found initiation of ART at CD4 counts between 0.350 and 0.500 x 10^9 cells/L associated with decreased risk of mortality compared with deferred or no ART (**Table 4**).[132, 134-136] One other study found a reduction in risk that was not statistically significant.[137] The largest study, the HIV Cohorts Analyzed Using Structural Approaches to Longitudinal Data (HIV-CAUSAL) (n=62,760 from 12 cohorts), found initiation of ART at CD4 counts of 0.350 to 0.500 x 10^9 cells/L associated with decreased risk of mortality compared with noninitiation within this CD4 count range after an average of 3.3 years of followup (adjusted HR, 0.55 [95% CI, 0.41 to 0.74]).[134] Similarly, the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) (n=17,517 from 22 cohorts) found initiation of ART at CD4 counts of 0.350 to 0.500 x 10^9 cells/L associated with decreased risk of death compared with deferred treatment within these thresholds after an average of 3 years of followup (adjusted RR, 0.61 [95% CI, 0.46 to 0.83]).[135] Initiation of ART at CD4 counts >0.350 x 10^9 cells/L was also associated with decreased risk of the combined outcome of AIDS-defining events or death compared with deferred or no initiation of ART in two studies (**Table 4**).[132, 136] One other study found a reduction in risk that was not statistically significant.[137]

Studies on initiation of ART at CD4 counts >0.500 x 10^9 cells/L were less consistent. NA-ACCORD found initiation of ART at CD4 counts >0.500 x 10^9 cells/L associated with decreased mortality compared with deferred therapy (adjusted RR, 0.54 [95% CI, 0.35 to 0.83]),[135] and HIV-CAUSAL found decreased mortality risk that was not statistically significant after 3 years (adjusted HR, 0.77 [95% CI, 0.58 to 1.0]).[134] Another analysis from HIV-CAUSAL that directly compared initiation of ART at CD4 counts >0.500 x 10^9 cells/L versus initiation at counts >0.350 x 10^9 cells/L found no difference in mortality (HR, 0.99 [95% CI, 0.73 to 1.4]).[133] Two other large cohort studies found initiation of ART at CD4 counts >0.500 x 10^9 cells/L associated with no difference in risk of

mortality when compared with noninitiation after 5 years (adjusted HR, 1.0 [95% CI, 0.49 to 2.1])[132] or when compared with slightly delayed initiation after 3 years (adjusted HR, 0.93 [95% CI, 0.60 to 1.4] for starting at CD4 counts of 0.451 to 0.550 versus 0.351 to 0.450 x 10^9 cells/L).[137] In all four studies, absolute mortality rates were low in patients with CD4 counts >0.500 x 10^9 cells/L (range, 2% to 5%).

Results were also mixed for the combined outcome of mortality plus AIDS-defining events, which was not reported in NA-ACCORD.[135] HIV-CAUSAL found initiation above a threshold of 0.500 x 10^9 cells/L associated with decreased risk of AIDS-defining events or death compared with initiation above 0.350 x 10^9 cells/L (HR, 0.72 [95% CI, 0.59 to 0.88]).[133] Two other studies found no clear association between starting versus not starting ART at CD4 counts >0.500 x 10^9 cells/L and risk of AIDS-defining events or death (**Table 4**).[132, 137]

Viral load. Two studies reported inconsistent results for the association between viral load at time of initiation of ART and subsequent mortality (**Appendix B23**).[134, 136] HIV-CAUSAL (n=62,760 from 12 cohorts) found initiation of ART at higher viral loads associated with greater reduction in mortality risk (adjusted HR, 0.82 [95% CI, 0.64 to 1.0] for initiation at viral load <10,000 copies/mL vs. noninitiation; adjusted HR, 0.46 [95% CI, 0.36 to 0.60] for viral load of 10,000 to 100,000 copies/mL; and adjusted HR, 0.36 [95% CI, 0.28 to 0.45] for viral load >100,000 copies/mL).[134] Another study, the Antiretroviral Therapy Cohort Collaboration (n=20,379 from 12 cohorts), found initiation of ART at viral loads of 10,000 to <100,000 copies/mL and 1,000 to <10,000 copies/mL each associated with decreased risk of mortality or progression to AIDS compared with initiation at a viral load ≥100,000 copies/mL (adjusted HRs, 0.80 [95% CI, 0.73 to 0.88] and 0.80 [95% CI, 0.68 to 0.95], respectively).[136]

Key Question 5. What Are the Longer-Term Harms Associated With Antiretroviral Therapy in Nonpregnant Adolescents and Adults With Chronic HIV Infection?

Summary

The 2005 USPSTF review included results from the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study, which found longer duration of exposure to ART associated with increased risk of myocardial infarction (adjusted RR per year of exposure, 1.3 [95% CI, 1.1 to 1.4]). More recent analyses from DAD with up to 6 years of followup were consistent with earlier results in finding slightly increased risk of myocardial infarction with use of some protease inhibitors. Two studies (DAD and one other cohort study) found abacavir associated with increased risk of cardiovascular events, but two other studies found no such association. There was no clear association between use of other nucleoside reverse transcriptase inhibitors or nonnucleoside reverse transcriptase inhibitors and increased risk of adverse cardiovascular events.

Evidence

The prior USPSTF review included results from the large (n=23,468), ongoing DAD study, which

found increased risk of myocardial infarction associated with longer exposure to ART (adjusted RR per year of exposure, 1.3 [95% CI, 1.1 to 1.4]), though absolute event rates were low (3.5/1,000 person-years).[141]

Subsequent analyses from DAD[142-144] and three other cohort studies reported cardiovascular harms associated with ART through up to 4 to 6 years of followup (**Appendix B25**).[145-147] Sample sizes ranged from 2,952 to >30,000. All of the studies were rated good-quality except for one,[145] which was rated fair-quality due to lack of detail about baseline patient characteristics and blinding of study personnel (**Appendix B26**).

Like the earlier DAD results, the most recent DAD analysis found longer exposure to indinavir alone (adjusted RR per year of exposure, 1.1 [95% CI, 1.1 to 1.2]), ritonavir-boosted indinavir (adjusted RR per year of exposure, 1.2 [95% CI, 1.1 to 1.3]), and ritonavir-boosted lopinavir (adjusted RR per year of exposure, 1.1 [95% CI, 1.0 to 1.2]) each associated with slightly increased risk of myocardial infarction compared with nonuse, after adjustment for age, sex, HIV infection risk group, ethnicity, calendar year, family history of cardiovascular disease, prior cardiovascular disease, smoking status, body mass index, and other factors (**Table 5**).[144] No other protease inhibitor was associated with increased myocardial risk.

Evidence on the association between the nucleoside reverse transcriptase inhibitor abacavir and risk of myocardial infarction is mixed. Although two studies found abacavir use associated with increased risk (adjusted RRs, 1.7 and 2.0),[144, 146] two others found no association (adjusted HRs, 0.6 and 1.2)[145, 147] after 4 to 6 years of followup (**Table 5**).

The DAD study also found recent didanosine use associated with increased myocardial infarction risk (adjusted RR, 1.4 [95% CI, 1.1 to 1.8]), but no association when analyses were based on cumulative didanosine exposure.[144] There was no association between use of other nucleoside reverse transcriptase inhibitors or the nonnucleoside reverse transcriptase inhibitors nevirapine or efavirenz and increased risk of cardiovascular events.[144]

Key Question 6a. To What Extent Are Improvements in Viremia Associated With Reductions in HIV Transmission Rates in Nonpregnant Adolescents and Adults?

Summary

The prior USPSTF review included seven observational studies that consistently found a strong association between lower individual viral load and decreased risk of heterosexual transmission of HIV infection. Three observational studies not included in the prior USPSTF review reported results consistent with these findings. Three other observational studies (two with overlapping populations) found lower community viral load (defined as the average viral load in a defined population) associated with decreased risk of HIV transmission.

Evidence

The prior USPSTF report[3] included seven observational studies[19, 106, 150-154] that consistently found an association between lower individual viral load and lower risk of heterosexual transmission of HIV infection (**Table 6**). The strongest evidence was from a good-quality prospective cohort study of 415 serodiscordant couples in rural Uganda (a setting in which ART was not available), which found viral load to be the strongest predictor for heterosexual HIV transmission (male to female or female to male).[19] The rate of transmission in patients with HIV-1 viral load <1,500 copies/mL was zero out of 51, and increased in a dose-response fashion to 23 per 100 person-years at a viral load ≥50,000 copies/mL. The adjusted RR for transmission was 12 (95% CI, 5.0 to 35) for a viral load >50,000 copies/mL compared with <3,500 copies/mL. Another analysis of the same Ugandan cohort reported an adjusted RR of transmission per coital act of 16 (95% CI, 3.1 to 296) for a viral load of 1,700 to 12,499 copies/mL versus <1,700 copies/mL, 18 (95% CI, 3.4 to 329) for viral loads of 12,500 to 38,499 copies/mL, and 28 (95% CI, 5.4 to 507) for viral loads ≥38,500 copies/mL.[20]

Three observational studies not included in the prior USPSTF review evaluated the association between viral load in individual patients and risk of HIV transmission[110, 155, 156] (**Table 6**, **Appendixes B27** and **B28**). Two evaluated heterosexual couples in Africa.[110, 155] One cohort study evaluated 3,408 HIV-discordant couples in seven African countries in which the index case was infected with both HIV and herpes simplex virus-2 and had CD4 counts >0.250 x 10^9 cells/L.[110] The group at greatest risk for HIV transmission were individuals with CD4 counts of 0.200 to 0.349 x 10^9 cells/L and a viral load of ≥50,000 copies/mL (incidence per 100 person-years, 4.7 [95% CI, 3.2 to 6.6]). A case-control study of heterosexual couples in Zambia (109 cases of HIV transmission to the uninfected partner and 208 control couples with no transmission) found a dose-dependent association between higher viral load and risk of transmission from females to males (RR per log viral load, 2.5 [95% CI, 1.5 to 4.0]) as well as from males to females (RR per log viral load, 1.8 [95% CI, 1.2 to 2.8]).[155] HIV RNA viral load was also a predictor of transmission risk in a cohort study (1,144 men, 41 cases) of MSM in the United Kingdom (RR per log viral load, 1.6 [95% CI, 1.2 to 2.3]).[156]

Studies that evaluated community viral load (the average viral load in a defined population) also found an association between higher viral load and increased risk of transmission[157-159] (**Appendixes B27** and **B28**). One study found that for every 10-fold decrease in the median viral load of all HIV-infected individuals in a specific year in British Columbia, the number of new HIV cases decreased by a factor of 0.86 (95% CI, 0.75 to 0.98) after adjusting for year and number of individuals taking ART, despite increased rates of other STDs in this population.[158] An analysis of a subgroup of the above population, consisting of injection drug users in inner-city Vancouver, also found community viral load independently associated with time to HIV seroconversion (HR per $\log_{10}$ increase, 3.3 [95% CI, 1.8 to 6.1]) after adjusting for other markers of risk.[159] Similarly, a study based on San Francisco's HIV/AIDS surveillance system found both higher mean community viral load and sum total viral load associated with increased risk of HIV incidence (unadjusted, p=0.003 and p=0.002, respectively).[157]

Key Question 6b. To What Extent Are Improvements in Risky Behaviors Associated With Reductions in HIV Transmission Rates in Nonpregnant Adolescents and Adults?

Summary

The prior USPSTF review included two systematic reviews that found consistent condom use associated with substantially reduced risk of sexual transmission of HIV infection. Two observational studies not included in the prior USPSTF review were consistent with these findings.

No study evaluated effects of safer injection drug use behaviors by HIV-positive patients on risk of HIV transmission.

Evidence

The prior USPSTF review included a systematic review[1-3] (11 prospective studies, two retrospective studies, and one case report) of primarily HIV-discordant heterosexual couples from the United States, Europe, Africa, and Haiti that found consistent use of condoms (defined as use of a condom for all acts of penetrative vaginal intercourse) associated with an 80 percent reduction in heterosexual transmission of HIV.[160] Another pooled analysis found consistent condom users were 10 to 20 times less likely to become infected when exposed to the virus than inconsistent or nonusers.[161]

The 2007 USPSTF update[1] also included a study that used a mathematical formula to estimate that transmission risk was 3.5 times higher in HIV-positive patients unaware of their status (6.9%) compared with those aware (2.0%) of their HIV infection, resulting in a projected 31 percent decline in new sexual infections per year (from 32,000 to 22,150) if all HIV-positive patients unaware of their status became aware.[51] However, these results were based on estimates for reduced risky behaviors from studies with methodological shortcomings, and may not have adequately accounted for other important factors that might affect transmission risk (such as type of risky behaviors, number of risky behavior episodes, number of sexual partners, viral load, use of ART, presence of other STDs, CD4 count, and time since diagnosis).[162]

Two observational studies published since the prior USPSTF review reported results consistent with previous findings[93, 114] (**Appendixes B29** and **B30**). One prospective cohort study of 476 heterosexual Spanish individuals (1,355 couple-years of followup) found self-reported condom use associated with decreased risk of HIV transmission per act of intercourse compared with intercourse without a condom (unadjusted RR, 0.07 [95% CI, 0.01 to 0.58]).[93] A Chinese study of 1,927 serodiscordant couples found not always using condoms associated with increased risk of seroconversion (RR, 8.4 [95% CI, 4.8 to 15]) in multivariate analysis when compared with always using a condom, after adjusting for frequency of sexual intercourse, switching of ART regimen, and physical and psychological quality-of-life scores.[114]

No study evaluated effects of safer injection drug use behaviors by HIV-positive patients on risk of

HIV transmission.

Contextual Question. What Is the Cost-Effectiveness of Universal Versus Targeted HIV Screening in Low- or Average-Prevalence Populations?

The 2005 USPSTF review included two good-quality studies[8, 9] that estimated cost-effectiveness of HIV screening in low- or average-prevalence populations. One study by Sanders et al estimated <$50,000 (2004 U.S. dollars) per quality-adjusted life-year (QALY) for one-time screening versus no screening at an HIV prevalence of 0.5 percent, excluding potential transmission benefits.[9] After incorporating potential transmission benefits, cost-effectiveness remained <$50,000 per QALY at an HIV prevalence of 0.05 percent, or substantially lower than seen in the general population. Another study by Paltiel et al, which did not directly incorporate secondary transmission benefits, estimated incremental cost-effectiveness of one-time screening in the general population (prevalence of undiagnosed HIV infection, 0.1%; corresponding to an overall HIV prevalence of about 0.4%) of $113,000 (2001 U.S. dollars) per QALY compared with no screening.[8] Neither study evaluated the incremental cost-effectiveness of a strategy of universal versus targeted screening in low-prevalence populations,[163] though one of the studies included assumptions about background testing rates in the no screening arm.[8] Long-term cardiovascular harms were not accounted for in either model. In the study that included secondary transmission benefits, cost-effectiveness in low-prevalence settings was sensitive to estimates of beneficial effects of screening on transmission.[9] The other cost-effectiveness analysis did not directly incorporate secondary transmission benefits when estimating cost-effectiveness,[8] though a subsequent analysis found that increasing rates of test notification and entry into care had a greater impact on cost-effectiveness than similar increases in rates of testing.[164]

The cost-effectiveness analyses included in the prior USPSTF review also evaluated screening strategies involving repeat testing.[8, 9] They found screening every 5 years in a population with 1 percent prevalence associated with a cost-effectiveness ratio <$50,000 per QALY when secondary transmission benefits were included and annual incidence was at least 0.09 percent. In low-prevalence (0.1% undiagnosed HIV infection) settings, one of these studies found that repeat screening at any interval cost >$100,000 per QALY at all plausible incidences.[8] This study also found that in a high-risk setting (incidence, 1.2%; prevalence, 3.0%), screening every 5 years cost $50,000 per QALY compared with one-time screening, screening every 3 years cost $63,000 per QALY compared with screening every 5 years, and screening annually cost $100,000 per QALY compared with screening every 3 years.

Subsequent cost-effectiveness analyses based on the models used in the above studies have been published.[165-167] Paltiel et al estimated cost-effectiveness ratios of <$50,000 (2004 U.S. dollars) per QALY for one-time rapid screening compared with no screening in settings with HIV prevalence as low as 0.20 percent, when assuming moderately favorable effects of ART on transmission (decrease in the basic reproductive number [R_0], 1.44 to 1.27).[167] Cost-effectiveness ratios remained <$50,000 per QALY for screening every 5 years compared with no screening at prevalences as low as 0.45 percent and annual incidences as low as 0.0075 percent. Sanders et al estimated cost-effectiveness ratios of <$60,000 (2007 U.S. dollars) per QALY for one-time screening with streamlined

counseling compared with no screening in persons ages 55 to 75 years with a sexual partner at risk at an HIV prevalence as low as 0.1 percent, assuming favorable effects on transmission.[165] Cost-effectiveness ratios were also <$60,000 per QALY for one-time screening with streamlined counseling compared with no screening in persons ages 55 to 65 years without a sexual partner at risk at an HIV prevalence of 0.5 percent. With traditional counseling, cost-effectiveness ratios of screening compared with no screening were >$100,000 per QALY for screening persons ages 75 years or older with a sexual partner at risk or persons ages 65 years or older without a sexual partner at risk. In a separate study, Sanders et al estimated a cost-effectiveness ratio of $10,660 per QALY for nurse-initiated routine screening with rapid HIV testing and streamlined counseling compared with traditional HIV counseling and testing.[166]

One other study published since the 2005 USPSTF review estimated a cost-effectiveness ratio of $22,382 (2009 U.S. dollars) per QALY for one-time screening of low-risk persons (HIV prevalence, 0.10% in men and 0.22% in women) plus annual screening of high-risk persons compared with current practice (annual rate of screening, 23% in high-risk persons and 10% in low-risk persons), assuming a 20 percent reduction in sexual activity after screening, with an associated reduction in risk of HIV transmission.[168] Assuming the same screening strategy plus an increase in ART utilization in 75 percent of infected persons resulted in a similar cost-effectiveness ratio, though more infections would be prevented. Screening low-risk persons every 3 years or more frequently was associated with cost-effectiveness ratios of >$100,000 per QALY compared with one-time screening of low-risk persons, with annual screening of high-risk persons included as part of both strategies.

No study directly compared cost-effectiveness of universal versus targeted screening in low-prevalence populations, or explicitly included potential long-term cardiovascular harms of combination ART in models.

CHAPTER 4. DISCUSSION

Summary of Review Findings

As in the 2005 USPSTF review,[1-3] we found no direct evidence on effects of screening for HIV infection versus no screening on clinical outcomes. Other evidence reviewed in this update is summarized in **Table 7**.

The 2005 USPSTF review found good evidence that HIV screening tests are accurate and that identification of undiagnosed HIV infection and treatment of immunologically advanced disease (CD4 count <0.200 x 10^9 cells/L) are associated with substantial clinical benefits, but insufficient evidence to estimate effects of diagnosis and subsequent interventions on transmission risks or to estimate clinical benefits of ART in patients with less immunologically advanced disease. New studies included in this update provide strong evidence for effectiveness of initiation of ART at CD4 counts of 0.350 to 0.500 x 10^9 cells/L,[131, 132, 134-137] though evidence is less consistent for CD4 counts >0.500 x 10^9 cells/L.[132, 134, 135, 137] Recent studies indicate that about 54 percent of patients presented for initial HIV care with CD4 counts <0.350 x 10^9 cells/L,[78] and about 75 percent were diagnosed with CD4 counts <0.500 x 10^9 cells/L,[80] suggesting that a large proportion of patients identified by screening could directly benefit from immediate initiation of ART. Additional research confirms previous findings of a small but statistically significant increase in risk of long-term cardiovascular harms primarily associated with use of protease inhibitors.[142-144, 146] Such long-term cardiovascular harms are an important consideration when initiating ART or selecting specific regimens, since patients will typically continue ART indefinitely. In the DAD study, the overall rate of myocardial infarction (fatal or nonfatal) after 5.8 years was 3.2 per 1,000 person-years (5.8 years median followup), with an increase in risk associated with protease inhibitors of about 10 percent per year of exposure, for an absolute increase of about 0.3 myocardial infarctions per 1,000 person-years.[144] In the largest cohort study, HIV-CAUSAL, all-cause mortality after a mean of 3.3 years ranged from 28.8 per 1,000 person-years at a CD4 count of <100 x 10^9 cells/L to 7.0 per 1,000 person-years at a CD4 count of 0.350 to <0.500 x 10^9 cells/L, with a decrease in risk with initiation versus noninitiation of ART of 71 and 45 percent, respectively, for an absolute decrease in mortality of about 3.2 to 20 per 1,000 person-years.[134] Whether current first-line protease inhibitors and other antiretrovirals are also associated with increased cardiovascular risk is not yet established. Long-term ART is also associated with other harms, including osteoporotic fractures[169] and lipodystrophy,[170] that were not addressed in this review.

Although direct clinical evidence showing that changes in risky behaviors as a result of knowledge of positive HIV status or that counseling interventions in HIV-positive persons reduces transmission risk is still not available, there is now strong evidence from a randomized trial as well as consistent evidence from multiple observational studies that ART use is associated with a 10- to 20-fold reduction in risk of sexual transmission.[108, 109] These findings are consistent with other evidence confirming a strong association between reduced viral load (individual or community) and transmission risk.[110, 155-159] The implications of these findings for reducing spread of HIV infection are substantial. Recent evidence showing that counseling interventions were relatively ineffective in reducing risky behaviors in HIV-infected persons suggest that beneficial effects of screening on transmission are likely to be driven by use of ART.[171]

Evidence on effects of different HIV screening strategies (such as universal vs. targeted screening, rapid vs. standard testing, opt-out vs. opt-in testing, or streamlined vs. traditional pretest counseling) on the uptake or yield of screening, CD4 count at diagnosis, linkage to care, or harms associated with screening are limited. Few studies directly compared these strategies, and in those that reported these outcomes, small numbers of HIV infection were identified, precluding reliable conclusions. Nonetheless, limited evidence suggests high rates of linkage of care following universal testing.[68, 73, 76] There is insufficient evidence to estimate effects of different HIV screening strategies on rates of uptake, which may also be affected by the clinical setting, the perceived risk in the individual being offered testing, and other factors. There is also insufficient evidence to determine effects of different HIV screening strategies on CD4 count at diagnosis, though epidemiologic data indicate some recent trends toward earlier diagnosis, temporally coinciding with when the CDC recommendation for routine HIV screening was issued.[60, 78, 80] Studies indicate that rapid testing is associated with higher false-alarm rates in lower-prevalence settings, though estimates varied widely.[68, 73, 76, 77] The consequences of initially false-positive rapid test results have not been evaluated, but will depend on whether patients are notified prior to confirmatory testing, and are likely to be affected by other factors, such as how patients are counseled about results. Patients are unlikely to receive ART based on a false-positive result, given routine confirmation of positive test results and because use of ART depends in part on CD4 count and presence of viremia.

Modeling studies suggest that screening is likely to be cost-effective at prevalences similar to or lower than observed in the general population.[9, 167] In addition, the modeling studies may underestimate cost-effectiveness, given relatively modest assumed reductions in risk of transmission (20%) relative to the results observed in the randomized trial described above.[109]

No clinical study has evaluated the yield of repeat HIV screening. Modeling studies suggest that repeat screening of low-risk individuals is unlikely to be associated with cost-effectiveness ratios <$100,000 per QALY compared with one-time screening, though repeat screening in high-risk individuals may be cost-effective, depending on the frequency of testing and incidence of new infections.[8, 167, 168]

Limitations

We excluded nonEnglish-language articles, which could result in language bias, though we identified no nonEnglish-language studies that would have met inclusion criteria. We did not search for studies published only as abstracts and could not formally assess for publication bias with graphical or statistical methods because of small numbers of studies for each key question, and differences in study design, populations, and outcomes assessed. We included observational studies, which are more susceptible to bias and confounding than well-conducted randomized trials, though we focused on results from studies that performed statistical adjustment for potential confounding. When evidence from settings more applicable to U.S. practice and screening in low- and average-risk populations was sparse or unavailable, we included studies conducted in resource-poor and high-prevalence settings, which could limit applicability to U.S. practice.

Emerging Issues

ART regimens and indications for initiating long-term ART continue to evolve. Since the 2005 USPSTF review, four new antiretroviral agents have been approved by the Food and Drug Administration for use in HIV-positive patients. Two represent new drug classes: the CCR5 antagonist maraviroc and the integrase inhibitor raltegravir. The other two drugs are the nonnucleoside reverse transcriptase inhibitor etravirine and the protease inhibitor darunavir. Although these medications have primarily been approved for use in patients with resistance to first-line medications, raltegravir has been approved for treatment-naive individuals. Regularly updated guidelines on selection of ART are available.[52] A new CDC HIV testing algorithm is expected in 2012. Although it is believed to be at least as accurate as the prior testing algorithm, and is designed to diagnose patients sooner in the "window" period before seroconversion, studies should be performed to confirm its accuracy in clinical practice.

Future Research

More research is needed on the effects of different HIV screening strategies on testing uptake, CD4 count at diagnosis, linkage to care, and harms. Studies should be designed with adequate statistical power to evaluate outcomes such as CD4 count at diagnosis, linkage to care, and harms, which may require collaborative efforts like those used to assess effects of initiation of ART at different CD4 count strata. Continued followup of patients taking ART is needed to further understand effects of long-term exposure to ART, as many patients are exposed for far longer than the 6 years evaluated in the longest studies to date. The Strategic Timing of Antiretroviral Treatment randomized trial, which compares initiation of ART at CD4 counts $>0.500 \times 10^9$ cells/L compared with deferred treatment until CD4 counts decline to $<0.350 \times 10^9$ cells/L, is currently in its recruitment phase and should help further clarify effects of very early initiation of ART.[172]

Conclusions

Prior studies have shown that HIV screening is accurate, targeted screening misses a substantial proportion of cases, and treatments are effective in patients with advanced immunodeficiency. New evidence indicates that ART reduces risk of AIDS-defining events and mortality in persons with less advanced immunodeficiency and reduces sexual transmission. More research is needed to understand effects of different screening strategies on the uptake and yield of screening, harms, CD4 count at diagnosis, and linkage to care.

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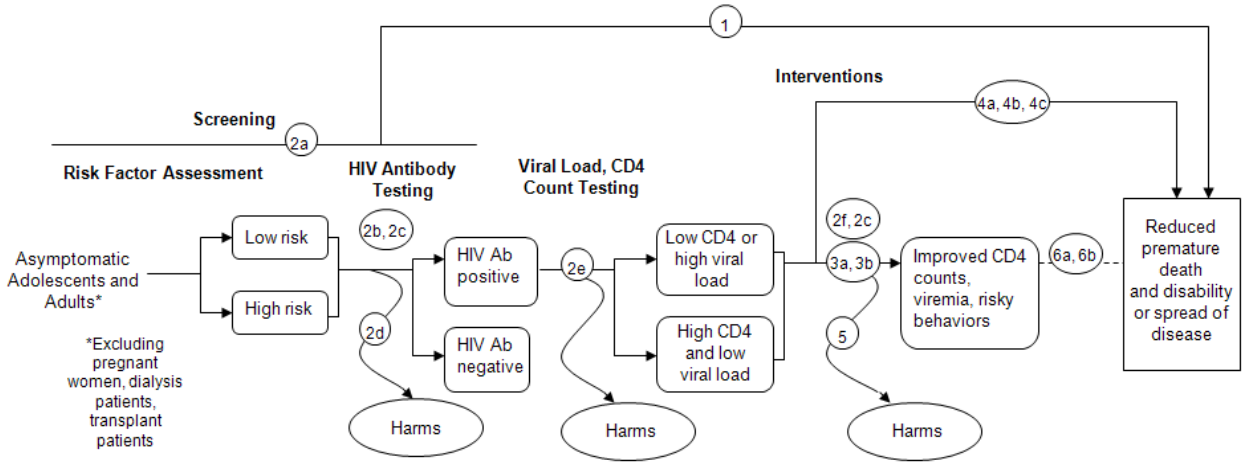
Figure. Analytic Framework for Screening for HIV in Nonpregnant Adolescents and Adults



Key Questions

1. What are the benefits of universal or targeted HIV screening versus no screening or each other in asymptomatic, nonpregnant adolescents and adults on disease transmission, morbidity, mortality, and quality of life?
2. a. What is the yield (number of new diagnoses) of HIV screening at different intervals in nonpregnant adolescents and adults?
   b. What are the effects of universal versus targeted HIV screening on testing acceptability and uptake in nonpregnant adolescents and adults?
   c. What is the effect of opt-out versus opt-in testing or different pre- or post-test HIV counseling methods on screening uptake or rates of followup and linkage to care in nonpregnant adolescents and adults?
   d. What are the adverse effects (including false-positive results and anxiety) of rapid versus standard HIV testing in nonpregnant adolescents and adults not known to be at higher risk?
   e. What are the effects of universal versus targeted HIV screening on CD4 counts at the time of diagnosis?
   f. What are the effects of universal versus targeted HIV screening on rates of followup and linkage to care in nonpregnant adolescents and adults who screen positive?
3. a. To what extent does knowledge of HIV-positive status affect behaviors associated with increased risk for HIV transmission in nonpregnant adolescents and adults?
   b. To what extent does use of ART affect behaviors associated with increased risk for HIV transmission in nonpregnant adolescents and adults?
4. a. How effective is ART in reducing transmission of HIV in nonpregnant adolescents and adults with chronic HIV infection?
   b. How effective is behavioral counseling in reducing transmission of HIV in nonpregnant adolescents and adults with chronic HIV infection?
   c. In asymptomatic, nonpregnant adolescents and adults with chronic HIV infection, what are the effects of initiating ART at different CD4 counts or viral load thresholds on morbidity, mortality, and quality of life?
5. What are the longer-term harms associated with ART in nonpregnant adolescents and adults with chronic HIV infection?
6. a. To what extent are improvements in viremia associated with reductions in HIV transmission rates in nonpregnant adolescents and adults?
   b. To what extent are improvements in risky behaviors associated with reductions in HIV transmission rates in nonpregnant adolescents and adults?

Contextual Question. What is the cost-effectiveness of universal versus targeted HIV screening in low- or average-prevalence populations?

Table 1. Positive Predictive Values and False-Positive Results Associated With HIV Rapid Testing

Study, Year	Prevalence of HIV infection	Total N tested for HIV	Initial positive	Confirmed (true) positive	False positive	Positive predictive value*	Comments
Bowles et al, 2008[75]	1.1%	23,900	331	267	17	94%	40 declined confirmatory testing, 2 had indeterminate results, 5 had missing information
Haukoos et al, 2010[68]	0.4%	7,176	36	30	6	83%	Combined groups; both opt-out and targeted used rapid screening
Myers et al, 2009[76]	0.2%	10,769	39	17	5	77%	
Walensky et al, 2011[77]	0.4%	2,002	54	7	36	16%	11 declined confirmatory testing
White et al, 2011[73]	0.4%	8,732	49	38	11	77%	

*Positive predictive value = true positive/(true positive + false positive).

Table 2. Effect of Knowledge of HIV-Positive Status on Risky Behaviors

Author, year	Setting	Sample	Type of study	Risk behavior outcomes	Quality rating
Amaro et al, 2005[84]	United States HIV counseling and testing sites	560 heterosexual participants (16 HIV-positive)	Before-after observational	All HIV-positive participants adopted safer behavior with main and nonmain partners at post test (3 months after HIV testing) (statistics for this group not reported)	Fair
Brogly et al, 2002[85]; Bruneau et al, 2001[88]	Canada Self-referral, hospital detoxification unit, IDU centers	73 HIV-positive IDUs	Before-after observational	Behavior change in IDUs who received positive test result (at least 1 month after diagnosis) 26% (11/42) stopped injecting, 73% (19/26) stopped lending needles, 62% (23/37) stopped borrowing needles, 38% (27/72) increased use of needle exchange program, 50% (9/18) of men stopped sexual relations, 100% (5/5) of men stopped sex work	Fair
Camoni et al, 2009[86]	Italy Infectious diseases and sexually transmitted infections clinics	487 HIV-positive individuals diagnosed for at least 2 years (253 contributed drug use behavior data)	Retrospective before-after observational	Comparing drug use, before vs. after HIV diagnosis Injecting drug use: Yes; 54% (n=138) vs. 32% (n=82); p<0.0005 Comparing sexual behavior, before vs. after HIV diagnosis Sex for money or drugs: Yes; 13% (n=64) vs. 6.8% (n=33); p<0.0005 Sex with sex workers: Yes; 16% (n=78) vs. 7.2% (n=35); p<0.0005 Comparing sexual behavior with stable partner and occasional partner, before vs. after HIV diagnosis Stable partner: Yes; 89% (n=434) vs. 77% (n=377); p<0.0005 Condom use, vaginal sex: Always; 5.5% (n=24) vs. 40% (n=150); p<0.0005 Condom use, anal sex: Always; 4.1% (n=18) vs. 32% (n=120); p<0.0005 Condom use, oral-genital sex: Always; 0.9% (n=4) vs. 9.0% (n=34); p<0.0005 Occasional partners: Yes; 82% (n=400) vs. 58% (n=283); p<0.0005 Condom use, vaginal sex: Always; 10% (n=41) vs. 38% (n=107); p<0.0005 Condom use, anal sex: Always; 10% (n=42) vs. 41% (n=115); p<0.0005 Condom use, oral-genital sex: Always; 2.7% (n=11) vs. 17% (n=49); p<0.0005	Fair
Fox et al, 2009[87]	United Kingdom HIV clinic	98 men who have sex with men with primary HIV infection	Before-after observational	12 weeks following HIV diagnosis 76% (n=74) of men posed no risk for onward transmission during that period (defined as unprotected anal intercourse with a regular partner of unknown or negative HIV status, unprotected anal intercourse with casual male partners or incident sexually transmitted infection); 66% (n=65) decreased number of partners, 27% (n=26) had no change, and 7.1% (n=7) increased number of partners, p<0.001. Proportion always using condoms during receptive anal intercourse with casual partners increased from 17% (13/76) to 64% (29/45), p<0.001; and for insertive anal intercourse from 31% (22/72) to 61% (28/46), p<0.01	Good

ART = antiretroviral therapy; IDU = injection drug user.

Table 3. Effect of Use of Antiretroviral Therapy on Risky Behaviors

Author, year	Setting	Sample	Type of study	Risk behavior outcomes	Quality rating
Del Romero et al, 2010[93]	Spain HIV clinic	625 serodiscordant heterosexual couples engaging in sexual relationship over preceding 6 months	Cross sectional	Proportion engaging in unprotected sexual intercourse in preceding 6 months (at baseline), ART vs. no ART: 46% (69/149) vs. 57% (273/476); p=0.02	Fair
Diamond et al, 2005[94]	United States HIV clinic	874 HIV-infected individuals who were sexually active in preceding 3 months	Cross sectional	Proportion engaging in unprotected sexual intercourse, ART vs. no ART: 215/689 (31%) vs. 86/185 (46%); adjusted OR, 0.70 [95% CI, 0.50–1.0]; p<0.04	Fair
Elford et al, 2007[95]; Elford et al, 2006[100]	United Kingdom HIV clinic	1,687 HIV infected participants (including 758 gay men, 224 black African heterosexual men, 480 black African heterosexual women)	Cross sectional	No significant association between ART use and engaging in unprotected intercourse amongst gay men or black African heterosexual men and women; p>0.05	Fair
Miguez-Burbano et al, 2002[96]	United States Community clinic	85 HIV-infected drug abusers	Cross sectional	Men receiving ART tended to have unprotected anal sex when compared with those not receiving ART; OR, 2 [95% CI, 0.47–12]; p=0.07 Contaminated needles used by 18 participants, 85% of this group was receiving ART	Fair
Morin et al, 2007[97]	United States HIV clinic	4,016 HIV-infected individuals (2,109 men who have sex with men, 1,104 women, 803 men who have sex with women)	Cross sectional	ART use was negatively associated with transmission risk sex amongst men who have sex with men, women, and men who have sex with women. Association was only significant for men who have sex with men: ART use vs. no ART use, HIV transmission risk act 19% vs. 28%; adjusted OR, 0.73 [95% CI, 0.54–1.0]; p=0.05	Fair
Smit et al, 2006[98]; van Haastrecht et al, 1991[101]	The Netherlands Methadone and sexually transmitted diseases clinics, word of mouth	67 HIV-infected drug users using ART matched to 130 HIV-infected drug users not using ART	Prospective cohort	Proportion of injection drug users that reported injecting drugs was significantly lower among ART users than nonART users at all visits (p<0.05), except the last two. Modeled piecewise, ART users and nonART users showed nonsignificant declines in injecting drugs over time, which did not change after ART initiation. Significant differences between ART users and nonusers were seen at every visit (p<0.05). ART users reported significantly more unprotected sex than nonART users at 3/7 visits (p<0.05). Modeled piecewise, sexual risk behavior nonsignificantly increased before ART initiation (OR, 1.67 per year [95% CI, 0.98–2.83]; p=0.06), and nonsignificantly changed after initiation (OR, 0.33 per year [95% CI, 0.10–1.08]; p=0.07). Sexual risk behavior did not change over time for nonART users	Fair
Tun et al, 2004[99]; Vlahov et al, 1991[102]; Vlahov et al, 2001[103]	United States Community outreach	190 HIV-infected injection drug users	Before-after	Proportion of participants who engaged in any sexual intercourse (66% to 72%), unprotected sex (23% to 26%), any drug injection (53% to 49%), and/or needle sharing (20% to 26%) remained stable or increased slightly from before to after ART initiation, not significant. At individual level, approximately 6% to 11% discontinued any one of the behaviors, approximately 7% to 14% initiated any one of the behaviors after starting ART, and approximately 80% continued same behaviors before and after ART	Fair

ART = antiretroviral therapy; OR = odds ratio.

Table 4. Effect of Initiating Antiretroviral Therapy at Different CD4 Counts or Viral Load Thresholds on Progression to AIDS or Mortality

Author, year or study name	Number of patients	Duration of followup	Comparison groups (CD4 count)	Mortality	Progression to AIDS or AIDS events	Mortality or progression to AIDS or AIDS events
Randomized Controlled Trials						
Cohen et al, 2011[109]	n=1,763 serodiscordant couples	42 months	Delayed treatment: Initiation after 2 consecutive measures of CD4 count ≤0.250 x 10^9 cells/mL or at onset of AIDS-related illness (n=877) Early treatment: Immediate initiation of ART at CD4 count of 0.350-0.550 x 10^9 cells/mL (n=886)	Delayed treatment, 13/877 (2%) vs. early treatment, 10/886 (1%); HR, 1.3 (95% CI, 0.57 to 3.0)	Extrapulmonary tuberculosis Delayed treatment, 17/877 (2%) vs. early treatment, 3/886 (0.3%); RR, 5.7 (CI, 1.7 to 20) Pulmonary tuberculosis Delayed treatment, 15/877 (2%) vs. early treatment, 13/886 (2%); RR, 1.2 (CI, 0.56 to 2.4)	Delayed treatment, 65/877 (7%) vs. early treatment, 40/886 (5%); adjusted HR, 1.7 (CI, 1.1 to 2.5)
Severe et al, 2010[130]	n=816	21 months	Standard treatment (n=408): Same intervention as early treatment group, started when CD4 count ≤0.200 x 10^9 cells/L Early treatment (n=408): Started at CD4 count of 0.201–0.350 x 10^9 cells/L; lamivudine 150 mg + zidovudine 300 mg bid, efavirenz 600 mg qd	Standard treatment, 23/408 (6%) vs. early treatment, 6/408 (2%); unadjusted HR, 4 (95% CI, 1.6 to 9.8)	Tuberculosis Standard treatment, 36/408 (9%) vs. early treatment, 18/408 (4%); unadjusted HR, 2 (95% CI, 1.2 to 3.6)	Not reported
SMART Study Group, 2008[131] Other publication: SMART Study Group, 2006[138]	n=477 (249 ART-naive)	18 months	Intermittent ART/drug conservation group: CD4 count <0.250 x 10^9 cells/L or CD4 percentage <15% or symptomatic (n=131 ART-naive) Continuous ART/viral suppression group: CD4 count >0.350 x 10^9 cells/L (n=118 ART-naive)	Not reported	Drug conservation vs. continuous ART (fatal and nonfatal AIDS events): 3/131 (2/100 person-years) vs. 1/118 (0.5/100 person-years); HR, 4.1; p=0.22	Drug conservation vs. continuous ART: 4/131 (2.7/100 person-years) vs. 1/118 (0.5/100 person-years); HR, 5.3; p=0.13

Table 4. Effect of Initiating Antiretroviral Therapy at Different CD4 Counts or Viral Load Thresholds on Progression to AIDS or Mortality

Author, year or study name	Number of patients	Duration of followup	Comparison groups (CD4 count)	Mortality	Progression to AIDS or AIDS events	Mortality or progression to AIDS or AIDS events
Cohort Studies						
HIV-CAUSAL Collaboration, 2011[133] Other publication: HIV-CAUSAL Collaboration, 2010[134]	12 cohorts n=20,971 (restricted to patients with CD4 counts >0.500 x 10^9 cells/L at baseline)	Mean 1 year	0.200 x 10^9 (n=8,066*) 0.250 x 10^9 (n=8,078) 0.300 x 10^9 (n=8,101) 0.350 x 10^9 (n=8,144) 0.400 x 10^9 (n=8,201) 0.450 x 10^9 (n=8,281) 0.500 x 10^9 (n=8,392) *Patient-level data may cross CD4 thresholds	<u>Initiation of ART at CD4 count of 0.500 x 10^9 cells/L (n=65/8392) vs.:</u> 0.200 x 10^9 (n=99/8066): HR, 0.83 (CI, 0.68 to 1.03) 0.250 x 10^9 (n=95/8078): HR, 0.92 (CI, 0.78 to 1.09) 0.300 x 10^9 (n=97/8101): HR, 0.99 (CI, 0.84 to 1.18) 0.350 x 10^9 (n=94/8144): HR, 0.99 (CI, 0.82 to 1.19) 0.400 x 10^9 (n=89/8201): HR, 0.95 (CI, 0.79 to 1.16) 0.450 x 10^9 (n=81/8281): HR, 0.97 (CI, 0.88 to 1.09) <u>Initiation of ART at CD4 count of 0.350 x 10^9 cells/L (n=94/8144) vs.:</u> 0.200 x 10^9 (n=99/8066): HR, 0.85 (CI, 0.68 to 1.05) 0.250 x 10^9 (n=95/8078): HR, 0.93 (CI, 0.75 to 1.16) 0.300 x 10^9 (n=97/8101): HR, 1.01 (CI, 0.79 to 1.28) 0.400 x 10^9 (n=89/8201): HR, 0.97 (CI, 0.85 to 1.10) 0.450 x 10^9 (n=81/8281): HR, 0.99 (CI, 0.79 to 1.22) 0.500 x 10^9 (n=65/8392): HR, 1.01 (CI, 0.74 to 1.41)	Not reported	<u>Initiation of ART at CD4 count of 0.500 x 10^9 cells/L (n=158/8392) vs.:</u> 0.200 x 10^9 (n=330/8066): HR, 0.53 (CI, 0.47 to 0.60) 0.250 x 10^9 (n=329/8078): HR, 0.60 (CI, 0.54 to 0.67) 0.300 x 10^9 (n=317/8101): HR, 0.68 (CI, 0.61 to 0.75) 0.350 x 10^9 (n=296/8144): HR, 0.72 (CI, 0.64 to 0.81) 0.400 x 10^9 (n=256/8201): HR, 0.78 (CI, 0.68 to 0.87) 0.450 x 10^9 (n=209/8281): HR, 0.88 (CI, 0.82 to 0.93) <u>Initiation of ART at CD4 count of 0.350 x 10^9 cells/L (n=296/8144) vs.:</u> 0.200 x 10^9 (n=330/8066): HR, 0.73 (CI, 0.64 to 0.83) 0.250 x 10^9 (n=329/8078): HR, 0.83 (CI, 0.72 to 0.95) 0.300 x 10^9 (n=317/8101): HR, 0.93 (CI, 0.81 to 1.09) 0.400 x 10^9 (n=256/8201): HR, 1.06 (CI, 0.99 to 1.16) 0.450 x 10^9 (n=209/8281): HR, 1.20 (CI, 1.05 to 1.39) 0.500 x 10^9 (n=158/8392): HR, 1.39 (CI, 1.14 to 1.69)
HIV-CAUSAL Collaboration, 2010[134] Other publication: HIV-CAUSAL Collaboration, 2011[133]	12 cohorts n=62,760	Mean 3 years	<0.100 x 10^9 (n=5,319) 0.100 to <0.200 x 10^9 (n=6,521) 0.200 to <0.350 x 10^9 (n=14,886) 0.350 to <0.500 x 10^9 (n=15,360) ≥0.500 x 10^9 (n=20,674)	<u>Initiation vs. no initiation of ART, by CD4 count:</u> <0.100 x 10^9: HR, 0.29 (CI, 0.22 to 0.37) 0.100 to <0.200 x 10^9: HR, 0.33 (CI, 0.25 to 0.44) 0.200 to <0.350 x 10^9: HR, 0.38 (CI, 0.28 to 0.52) 0.350 to <0.500 x 10^9: HR, 0.55 (CI, 0.41 to 0.74) ≥0.500 x 10^9: HR, 0.77 (CI, 0.58 to 1.01)	Not reported	Not reported
Kitahata et al, 2009[135]	22 cohorts n=17,517	Mean 3 years	<u>0.351 to 0.500 x 10^9</u> Early therapy (n=2,084) Deferred therapy (n=6,278) <u>>0.500 x 10^9</u> Early therapy (n=2,220) Deferred therapy (n=6,936)	Initiation of ART at CD4 count 0.351 to 0.500 x 10^9 vs. ≤0.350 x 10^9: adjusted RR, 0.61 (CI, 0.46 to 0.83) Initiation of ART at CD4 count >0.500 x 10^9 vs. ≤0.500 x 10^9: adjusted RR, 0.54 (CI, 0.35 to 0.83)	Not reported	Not reported
May et al, 2007[136] Other publications: Lanoy et al, 2009[139] Moore et al, 2009[140]	12 cohorts n=20,379	Mean 3 years	<0.025 x 10^9 (n=2,034) 0.025 to 0.049 x 10^9 (n=1,295) 0.050 to 0.099 x 10^9 (n=2,059) 0.100 to 0.199 x 10^9 (n=3,782) 0.200 to 0.349 x 10^9 (n=5,550) ≥0.350 x 10^9 (n=5,659)	<u>Initiation of ART at varying CD4 counts vs. <0.025 x 10^9 cells/L:</u> 0.025 to 0.049 x 10^9: 111/1295 vs. 222/2034; HR, 0.82 (CI, 0.66 to 1.04) 0.050 to 0.099 x 10^9: 162/2059 vs. 222/2034; HR, 0.77 (CI, 0.63 to 0.95) 0.100 to 0.199 x 10^9: 202/3782 vs. 222/2034; HR, 0.67 (CI, 0.55 to 0.82) 0.200 to 0.349 x 10^9: 178/5550 vs. 222/2034; HR, 0.48 (CI, 0.39 to 0.60) ≥0.350 x 10^9: 130/5659 vs. 222/2034; HR, 0.34 (CI, 0.27 to 0.44)	Not reported	<u>Initiation of ART at varying CD4 counts vs. <0.025 x 10^9 cells/L:</u> 0.025 to 0.049 x 10^9: 277/1295 vs. 519/2034; HR, 0.85 (CI, 0.73 to 0.98) 0.050 to 0.099 x 10^9: 408/2059 vs. 519/2034; HR, 0.76 (CI, 0.66 to 0.87) 0.100 to 0.199 x 10^9: 445/3782 vs. 519/2034; HR, 0.49 (CI, 0.43 to 0.56) 0.200 to 0.349 x 10^9: 361/5550 vs. 519/2034; HR, 0.29 (CI, 0.25 to 0.33) ≥0.350 x 10^9: 298/5659 vs. 519/2034; HR, 0.23 (CI, 0.19 to 0.27)

Table 4. Effect of Initiating Antiretroviral Therapy at Different CD4 Counts or Viral Load Thresholds on Progression to AIDS or Mortality

Author, year or study name	Number of patients	Duration of followup	Comparison groups (CD4 count)	Mortality	Progression to AIDS or AIDS events	Mortality or progression to AIDS or AIDS events
When to Start Consortium, 2009[137]	18 cohorts n=45,691 (24,444 received ART)	Mean 3 years	CD4 count: <0.051 x 10^9 (n=2,594) 0.051 to 0.150 x 10^9 (n=4,638) 0.151 to 0.250 x 10^9 (n=6,406) 0.251 to 0.350 x 10^9 (n=5,753) 0.351 to 0.400 x 10^9 (n=3,260) 0.451 to 0.500 x 10^9 (n=1,793)	Initiation of ART at varying CD4 counts vs. 0.351 to 0.400 x 10^9 cells/L: 0.451 to 550 x 10^9: HR, 0.93 (CI, 0.6 to 1.4) 0.251 to 0.350 x 10^9: HR, 0.83 (CI, 0.59 to 1.25) 0.151 to 0.250 x 10^9: HR, 0.67 (CI, 0.51 to 0.99)	Not reported	Initiation of ART at varying CD4 counts vs. 0.351 to 0.450 x 10^9 cells/L: 0.451 to 550 x 10^9: HR, 0.90 (CI, 0.76 to 1.29) 0.251 to 0.350 x 10^9: HR, 0.74 (CI, 0.59 to 0.95) 0.151 to 0.250 x 10^9: HR, 0.45 (CI, 0.37 to 0.53)
Writing Committee for the CASCADE Collaboration, 2011[132]	23 cohorts n=9,455	Median 5 years	Unique individuals (numbers overlap): 0 to 0.049 x 10^9 (n=183) 0.050 to 0.199 x 10^9 (n=1,521) 0.200 to 0.349 x 10^9 (n=4,459) 0.350 to 0.499 x 10^9 (n=5,527) 0.500 to 0.799 x 10^9 (n=5,162)	ART vs. no ART initiation during the index month, by CD4 count: 0 to 0.049 x 10^9: HR, 0.37 (CI, 0.14 to 0.95); RD, -18.2 (CI, -32 to -4.4) 0.050 to 0.199 x 10^9: HR, 0.55 (CI, 0.28 to 1.07); RD, -7.2 (CI, -10.1 to -4.4) 0.200 to 0.349 x 10^9 L: HR, 0.71 (CI, 0.44 to 1.15); RD, -1.4 (CI, -3.0 to 0.3) 0.350 to 0.499 x 10^9: HR, 0.51 (CI, 0.33 to 0.80); RD, -1.4 (CI, -2.2 to -0.6) 0.500 to 0.799 x 10^9: HR, 1.02 (CI, 0.49 to 2.12); RD, -0.4 (CI, -2 to 1.2)	Not reported	ART vs. no ART initiation during index month, by CD4 count: 0 to 0.049 x 10^9: HR, 0.32 (CI, 0.17 to 0.59); RD, -30 (CI, -45.1 to -15) 0.050 to 0.199 x 10^9: HR, 0.48 (CI, 0.31 to 0.74); RD, -15 (CI, -19.7 to -10.3) 0.200 to 0.349 x 10^9: HR, 0.59 (CI, 0.43 to 0.81); RD, -4.8 (CI, -7 to -2.6) 0.350 to 0.499 x 10^9: HR, 0.75 (CI, 0.49 to 1.14); RD, -2.9 (CI, -5 to -0.9) 0.500 to 0.799 x 10^9: HR, 1.10 (CI, 0.67 to 1.79); RD, 0.3 (CI, -3.7 to 4.2)

ART = antiretroviral therapy; HR = hazard ratio; RD = risk difference; RR = relative risk.

Table 5. Cardiovascular Events and Antiretroviral Therapy Use

Author, Year Title	Duration of followup	Population characteristics	Interventions	Adjusted variables for statistical analysis	Myocardial infarction	Other cardiovascular events/composite outcomes
Bedimo et al, 2011[145]	Median 4 years	n=19,424 Median age, 46 years 98% male 29% smokers 13% diabetes 38% hypertension 26% hypercholesterolemia 8% chronic kidney disease 32% HCV infection	Any ART (n=14,063)	Age, diabetes, hypertension, hypercholesterolemia, smoking	MI, cumulative exposure (adjusted HR [95% CI]) Abacavir: 1.18 (0.92 to 1.5; p=0.19) Other NRTIs: 0.99 (0.87 to 1.11; p=0.87) Mono- or dual-therapy ART: 1.29 (1.10 to 1.52; p=0.002)	Not reported
DAD Study Group, 2010[144]	Median 6 years	n=33,308 Median age, 44 years 26% female Race not reported Framingham risk, total population: 53% low risk 15% moderate risk 4% high risk Framingham risk, patients with MI: 26% low risk 30% moderate risk 18% high risk Framingham risk, patients without MI: 54% low risk 15% moderate risk 4% high risk	Protease inhibitors: Nelfinavir (n=10,370) Indinavir (n=11,985) Lopinavir-ritonavir (n=9,995) Saquinavir (n=8,070) NRTIs: Zidovudine (n=25,754) Didanosine (n=13,851) Zalcitabine (n=4,951) Stavudine (n=16,840) Lamivudine (n=28,835) Abacavir (n=12,511) Tenofovir (n=13,100) NNRTIs: Nevirapine (n=12,194) Efavirenz (n=13,522)	Age, sex, HIV transmission group, race, calendar year, cohort, smoking, family history of CVD, previous CV event, BMI, exposure to other ART	Cumulative PI use (adjusted relative rate [95% CI]) Nelfinavir: 1.04 (0.98 to 1.11) Indinavir: 1.12 (1.07 to 1.18) Lopinavir-ritonavir: 1.13 (1.05 to 1.21) Saquinavir: 1.04 (0.98 to 1.11) Per year of PI exposure (adjusted relative rate [95% CI]) Indinavir: 1.11 (1.05 to 1.18) Indinavir + ritonavir: 1.18 (1.07 to 1.30) Saquinavir: 1.07 (0.97 to 1.20) Saquinavir + ritonavir: 1.06 (0.97 to 1.14) Cumulative NRTI use (adjusted relative rate [95% CI]) Zidovudine: not significant (data not reported) Didanosine: 1.41 (1.09 to 1.82) Zalcitabine: not significant (data not reported) Stavudine: not significant (data not reported) Lamivudine: not significant (data not reported) Abacavir: 1.07 (1.00 to 1.14) Tenofovir: 1.04 (0.91 to 1.18) Recent NRTI use (adjusted relative rate [95% CI]) Abacavir: 1.7 (1.17 to 2.47) Tenofovir: 1.14 (0.85 to 1.53) Cumulative NNRTI use (adjusted relative rate [95% CI]) Nevirapine: 0.97 (0.92 to 1.03) Efavirenz: 1.02 (0.96 to 1.08)	Not reported
DAD Study Group, 2008[143]	Median 5 years	n=33,347 Mean age, 43 years 26% female Framingham risk, patients with MI: 22% (113/517) low risk 26% (134/517) moderate risk 23% (120/517) high risk 29% (150/517) unknown risk	NRTIs (n not reported): Zidovudine Didanosine Stavudine Lamivudine Abacavir	Age, sex, risk group, race, cohort, BMI, family history of CVD, smoking, previous CV event, year, cumulative exposure to other ART	Cumulative exposure (adjusted relative rate [95% CI]) Zidovudine: 1.04 (0.99 to 1.09; p=0.15) Didanosine: 1.00 (0.93 to 1.07; p=0.91) Stavudine: 1.02 (0.95 to 1.09; p=0.6) Lamivudine: 0.99 (0.93 to 1.06; p=0.8) Abacavir: 1.00 (0.92 to 1.08; p=0.91) Recent exposure Zidovudine: 1.22 (0.82 to 1.81) Didanosine: 1.53 (1.10 to 2.13) Stavudine: 1.22 (0.84 to 1.77) Lamivudine: 1.69 (1.02 to 2.8) Abacavir: 1.94 (1.48 to 2.55) Past exposure Zidovudine: 1.29 (0.89 to 1.85) Didanosine: 1.08 (0.84 to 1.39) Stavudine: 1.24 (0.93 to 1.66) Lamivudine: 1.45 (0.88 to 2.4) Abacavir: 1.29 (0.94 to 1.77)	MI, CV death, or invasive CV procedure, cumulative exposure Zidovudine: 1.04 (1.00 to 1.08) Didanosine: 0.99 (0.94 to 1.05) Stavudine: 1.04 (0.99 to 1.10) Lamivudine: 1.01 (0.96 to 1.06) Abacavir: 1.03 (0.96 to 1.10) MI, CV death, or invasive CV procedure, any recent exposure Zidovudine: 0.98 (0.79 to 1.21) Didanosine: 1.40 (1.11 to 1.77) Stavudine: 0.99 (0.78 to 1.25) Lamivudine: 1.15 (0.91 to 1.44) Abacavir: 1.63 (1.3 to 2.04)

Table 5. Cardiovascular Events and Antiretroviral Therapy Use

Author, Year Title	Duration of followup	Population characteristics	Interventions	Adjusted variables for statistical analysis	Myocardial infarction	Other cardiovascular events/composite outcomes
DAD Study Group, 2007[142] Other publication: Friis-Møller et al, 2003[141]	Median 5 years	n=23,437 Median age, 39 years 24% female 61% current/former smokers 14% hypertension 42% dyslipidemia	Any ART use (n=21,921) Protease inhibitors (n=18,919) NNRTI (n=15,142)	Model 1: Age, sex, cohort, HIV transmission group, race, age, BMI, family history of CVD, smoking, previous CV event, calendar year Model 2: All from Model 1 plus total cholesterol, HDL, hypertension, diabetes	ART use (adjusted relative rate [95% CI]) Incidence: 97 events/16805 person-years; 5.77/1000 person-years Model 1: 1.16 (1.09 to 1.23) PI use (adjusted relative rate [95% CI]) Model 1: 1.16 (CI 1.10 to 1.23) Model 2: 1.10 (CI 1.04 to 1.18) Excluding patients exposed to NRTIs: 1.15 (CI 1.06 to 1.25) NRTI use (adjusted relative rate, 95% CI) Model 1: 1.05 (0.98 to 1.13) Model 2: 1.00 (0.93 to 1.09) Excluding patients exposed to PIs: 0.94 (0.74 to 1.19)	Not reported
Danish HIV Cohort Study, Obel et al, 2010[146] Other publication: Obel et al, 2008[148] Lohse et al, 2006[149]	Mean 6 years	n=2,952 Median age, 39 years 76% male CV risk factors not reported	Triple NRTI regimen including abacavir NNRTI or PI regimen including abacavir Specific drugs: Abacavir (n=1,761) Zidovudine (n=2,711) Lamivudine (n=2,867) Stavudine (n=1,031) Didanosine (n=813)	Age, gender, year of diagnosis, year of HAART initiation, CD4 count, viral load, race, injecting drug use, use of other antiretrovirals, comorbidities	Abacavir use vs. nonuse Any abacavir exposure: Incidence, 2.4/1000 (95% CI,1.7 to 3.4) vs. 5.7/1000 (CI, 4.1 to 7.9); adjusted RR, 2.0 (CI, 1.1 to 3.6) Actual abacavir use: RR, 1.95 (CI, 1.05 to 3.6) Early abacavir use: RR, 2.37 (CI, 0.88 to 6.36) Abacavir as part of triple NRTI: RR, 1.91 (CI, 0.88 to 4.17) Abacavir with NNTRI or PI: RR, 2.06 (CI, 1.06 to 4.01) Abacavir initiated within 2 years of ART: RR, 1.77 (CI, 0.82 to 3.82) Abacavir initiated >2 years after starting ART: RR, 2.66 (CI, 1.31 to 5.39)	Not reported
Ribaudo et al, 2011[147]	Median 3 years	n=5,056 (1,122 with 6-year data) Median age, 37 years 18% female 40% white 36% black 21% Hispanic 10% prior IV drug user 15% 2 or more CVD risk factors 5% CVD 10-year risk score ≥10	Abacavir (n=1,704) No abacavir (n=3,352)	Age, sex, race, CVD risk factors, smoking, family history of CVD	Abacavir use vs. nonuse (adjusted HR [95% CI]) 1 year: 0.7 (0.2 to 2.6) 6 years: 0.6 (0.3 to 1.4)	Serious CVD events, abacavir use vs. nonuse (adjusted HR [95% CI]) 1 year: 1.1 (0.5 to 2.1) 6 years: 0.9 (0.5 to 1.3)

ART = antiretroviral therapy; BMI = body mass index; CV = cardiovascular; CVD = cardiovascular disease; DAD = Data Collection on Adverse Events of Anti-HIV Drugs; HCV = hepatitis C virus; HDL = high-density lipoprotein; HR = hazard ratio; IV = intravenous; MI = myocardial infarction; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RR = relative risk.

Table 6. HIV Transmission by Viral Load*

Study, Year, Country	Study design	Sample size	Transmission frequency/rate		Viral load	p-Value	Population
Donnell et al, 2010[110] 7 African countries	Cohort	3408 HIV-discordant couples	11/1676 P-Y 17/1300 P-Y 66/1491 P-Y	656 1.308 4.427	<10,000 10,000–49,999 ≥50.000	NR NR NR	HIV and HSV-2 with heterosexual transmission
Fideli et al, 2001[155] Zambia	Case-control	109 transmitters, 208 nontransmitting controls	8/56 38/122 58/133	0.143 0.311 0.436	<10,000 10,000–99,999 ≥100,000	NR NR NR	Heterosexual
			Median viral load for transmitters:123,507 Median viral load nontransmitters: 51,310			<0.001	
Fiore et al, 1997[150] Italy	Uncertain	14 couples in which male is HIV+	1/2 0/3 1/4 5/5	0.500 0.000 0.250 0.100	Not detectable <10,000 10,001–100,000 >100,000	0.0039	IDU with heterosexual transmission
Fisher et al, 2010[156] United Kingdom	Longitudinal study	1,144 HIV+ individuals	2/3176 P-Y 2/482 P-Y 5/427 P-Y 15/941 P-Y 14/611 P-Y	0.063 0.415 1.171 1.594 2.291	<50 50–1,000 1001–10,000 10,001–100,000 >100,000	0.0005 0.22 NR 0.55 0.20	MSM
			Rate ratio in univariate analysis: 2.32 (95% CI, 1.79–3.01) Rate ratio in multivariate analysis: 1.61 (95% CI, 1.15–2.25)			0.0001 0.005	
Gray et al, 2001[20] Uganda Other publication: Quinn et al, 2000[19]	Cohort	174 monogamous, HIV-discordant couples	1/43 11/45 11/42 15/44	0.023 0.244 0.262 0.341	<1,700 1,700–12,499 12,500–38,499 ≥38,500	NR NR NR NR	Heterosexual
			Transmission probabilities increased from 0.0001 per sex act at viral loads <1700 to 0.0023 per sex act at 38,500 copies			0.02	
Operskalski et al, 1997[106] United States	Cohort	18 HIV+ persons with 19 long-term sexual partners	0/6 5/12	0.000 0.417	<5,623 ≥5,623	NR NR	Transfusion recipients with heterosexual transmission
			Mean viral load for transmitters: 4.3 $\log_{10}$ Mean viral load for nontransmitters: 3.6 $\log_{10}$			0.05	
Pedraza et al, 1999[152] Spain	Cohort	38 highly exposed couples with at least one member HIV+	10/38	0.26	Median viral load in transmitters: 21,139 Median viral load in nontransmitters: 5,484	0.03	Heterosexual transmission with frequent unprotected sex
Ragni et al, 1998[153] United States	Cross-sectional	39 couples, all males HIV+	0/1 1/15 1/17 3/6	0.000 0.067 0.059 0.500	<1000 1,000–9,999 10,000–99,999 >100,000	NS NS NS 0.027	Hemophiliacs-heterosexual transmission
Tovanabutra et al, 2002[154] Thailand	Cross-sectional	493 married couples, all males HIV+	0/3 1/14 15/39 32/95 70/141 67/138 30/58 3/5	0.000 0.071 0.385 0.337 0.496 0.486 0.517 0.600	<500 500–1,580 1,581–4,999 5,000–15,810 15,811–49,999 50,000–158,110 158,114–499,999 500,000+	0.047	Heterosexual
			In multivariate analysis, each $\log_{10}$ increment of HIV RNA in the man was associated with an 81% increased rate of HIV transmission to his wife (OR, 1.81 [95% CI, 1.33–2.48])			<0.05	

*Studies from prior and current USPSTF reports.

HSV-2 = herpes simplex virus 2; IDU = intravenous drug users; MSM = men who have sex with men; NR = not reported; NS = not significant; OR = odds ratio; P-Y = person-years.

Table 7. Summary of Evidence

Main findings from 2005 USPSTF review	Number and type of studies identified for update *Overall quality**	Limitations	Consistency	Applicability	Summary of findings
KQ 1. What are the benefits of universal or targeted HIV screening vs. no screening or each other in asymptomatic, nonpregnant adolescents and adults on disease transmission, morbidity, mortality, and quality of life?					
No evidence	No studies	No studies	No studies	No studies	No study directly compared clinical outcomes between adults and adolescents screened and not screened for HIV infection.
KQ 2a. What is the yield (number of new diagnoses) of HIV screening at different intervals in nonpregnant adolescents and adults?					
No evidence	No studies	No studies	No studies	No studies	No study evaluated the yield of repeat HIV screening compared with one-time screening.†
KQ 2b. What are the effects of universal vs. targeted HIV screening on testing acceptability and uptake in nonpregnant adolescents and adults?					
No evidence	1 cohort study and 2 uncontrolled screening series ***Overall quality: Poor***	No study of universal vs. targeted screening reported testing acceptability and uptake	Some inconsistency	No major issues	No study directly compared the acceptability of universal vs. targeted HIV screening strategies. One fair-quality, nonrandomized study of emergency department patients found universal, opt-out rapid screening associated with higher likelihood of testing compared with physician-directed, targeted rapid screening (25% vs. 0.8%; RR, 30 [95% CI, 26 to 34]), but testing uptake (the proportion of patients offered testing who accepted) was not reported. In 2 uncontrolled implementation studies of universal HIV screening conducted in primary care settings, 35% (standard test) and 60% (rapid test) of those offered screening underwent screening.
KQ 2c. What is the effect of opt-out vs. opt-in testing or different pre- or post-test HIV counseling methods on screening uptake or rates of followup and linkage to care in nonpregnant adolescents and adults?					
1 uncontrolled implementation study found 35% of patients with HIV infection identified through routine screening in an urgent care setting entered care within 4 months	2 cohort studies ***Overall quality: Poor***	No RCTs; no data on rates of followup and linkage to care; no evidence on different counseling methods	Some inconsistency	Studies conducted in emergency department setting	One cohort study found an opt-out approach associated with higher likelihood of testing compared with an opt-in approach (13% vs. 7%; RR, 2.1 [95% CI, 1.9 to 2.4]), but patients who underwent opt-out testing were more likely to report that they had not been informed of HIV testing. One other study found opt-in testing associated with lower testing uptake compared with opt-out testing, but results may have been confounded by differences in who offered the testing. No study compared effects of different pre- or post-test HIV counseling methods on screening uptake or rates of followup and linkage to care.
KQ 2d. What are the adverse effects (including false-positive results and anxiety) of rapid vs. standard HIV testing in nonpregnant adolescents and adults not known to be at higher risk?					
Good evidence that standard and rapid HIV testing with confirmatory Western blot are associated with high sensitivities and specificities	5 uncontrolled screening series‡ ***Overall quality: Poor***	No comparative studies	Moderate inconsistency	Prevalence of HIV infection varied	In 5 large studies of rapid testing (without a comparison with standard testing), positive predictive value was 94% in 1 study of a higher-prevalence (1.1%) setting, and varied widely (16% to 83%) in 4 studies of lower-prevalence (0.2% to 0.4%) settings. No study evaluated psychological or other harms associated with rapid vs. standard HIV testing.
KQ 2e. What are the effects of universal vs. targeted HIV screening on CD4 counts at the time of diagnosis?					
No evidence	2 cohort studies ***Overall quality: Poor***	No RCTs; potential confounding based on who was offering testing	Consistent	Studies conducted in emergency department settings	One fair-quality study found universal testing associated with a higher median CD4 count and lower likelihood of CD4 count $<0.200 \times 10^9$ cells/L at the time of diagnosis compared with targeted HIV screening, but these differences were not statistically significant. No other studies directly compared effects of universal vs. targeted HIV screening, though epidemiologic data indicate temporal trends suggesting earlier diagnosis since the 2006 CDC recommendation on routine HIV screening was issued.

Table 7. Summary of Evidence

Main findings from 2005 USPSTF review	Number and type of studies identified for update *Overall quality**	Limitations	Consistency	Applicability	Summary of findings
KQ 2f. What are the effects of universal vs. targeted HIV screening on rates of followup and linkage to care in nonpregnant adolescents and adults who screen positive?					
2 uncontrolled studies found 35% to 70% of HIV-positive patients identified through universal screening in urgent care centers were linked to care.	1 cohort study and 2 uncontrolled screening series ***Overall quality: Poor***	Small numbers of patients diagnosed with HIV infection, only 1 controlled study	Moderate	Cohort study was conducted in an emergency department setting	The only study that directly compared universal with targeted testing reported very high rates of followup (defined as attending at least 1 HIV clinic visit) with either strategy (97% to 100%). Two other observational studies reported rates of followup or linkage to care of 75% to 82% following a new HIV diagnosis found during universal testing.
KQ 3a. To what extent does knowledge of HIV-positive status affect behaviors associated with increased risk for HIV transmission in nonpregnant adolescent and adults?					
Systematic reviews found knowledge of HIV status associated with reductions in self-reported sexual risk behaviors, but the studies included in the systematic reviews had methodological shortcomings.	4 before-after or cross-sectional studies ***Overall quality: Fair***	Reliance on self-reported behaviors, sometimes based on retrospective recall	Consistent	2 studies focused on high-risk populations	Four before-after studies found knowledge of HIV-positive status associated with reduced risky behaviors.
KQ 3b. To what extent does use of antiretroviral therapy affect behaviors associated with increased risk for HIV transmission in nonpregnant adolescent and adults?					
1 meta-analysis found no association between use of HAART and increased likelihood of high-risk sexual behaviors, though some individual studies reported associations between HAART use and increased high-risk behaviors in some populations.	7 observational studies ***Overall quality: Fair***	Some studies did not adjust for confounders or had important baseline differences between groups	Some inconsistency	3 studies focused on high-risk populations	Seven observational studies found no clear association between antiretroviral use and increase in risky behaviors, with some studies showing decreased risky behaviors.
KQ 4a. How effective is antiretroviral therapy in reducing transmission of HIV in nonpregnant adolescents and adults with chronic HIV infection?					
No studies	1 systematic review (1 RCT and 7 observational studies) ***Overall quality: Good***	Only 1 RCT	Consistent	Some studies conducted in resource-poor settings	An RCT found immediate antiretroviral therapy in persons with a baseline CD4 count of 0.350 to 0.550 x 10^9 cells/L associated with substantially reduced risk for transmission compared with delayed therapy (HR, 0.04 [95% CI, 0.01 to 0.27]). Observational studies were consistent with the RCT (pooled HR, 0.16 [95% CI, 0.07 to 0.35]).
KQ 4b. How effective is behavioral counseling in reducing transmission of HIV in nonpregnant adolescents and adults with chronic HIV infection?					
No RCTs or controlled observational studies	1 RCT and 1 before-after study ***Overall quality: Poor***	Underpowered to evaluate effects on transmission	Unable to determine	No major issues	Studies identified too few cases of new HIV infection to adequately evaluate effects of counseling interventions on transmission risk.
KQ 4c. In asymptomatic, nonpregnant adolescents and adults with chronic HIV infection, what are the effects of initiating antiretroviral therapy at different CD4 counts or viral load thresholds on morbidity, mortality, and quality of life?					
1 cohort study found initiation of HAART at CD4 counts >0.350 x 10^9 cells/L associated with decreased risk for AIDS events and mortality compared with delayed initiation, but 3 others found no difference in risk	3 RCTs and 5 large collaborative cohort studies ***Overall quality: Good***	1 RCT reported a subgroup analysis, some overlap in patients evaluated in the cohort studies	Some inconsistency for CD4 counts >0.500 x 10^9 cells/L	1 RCT evaluated CD4 count thresholds not applicable to U.S. practice in a resource-poor setting	One RCT and one subgroup analysis from an RCT found initiation of antiretroviral therapy at CD4 counts <0.250 x 10^9 cells/L associated with substantially increased risk for death or AIDS events compared with initiation at CD4 counts >0.350 x 10^9 cells/L. Five large observational studies also found initiation of antiretroviral therapy at CD4 counts of 0.350 to 0.500 x 10^9 cells/L associated with decreased risk for mortality compared with deferred or no antiretroviral therapy. Four studies on initiation of antiretroviral therapy at CD4 counts >0.500 x 10^9 cells/L did not consistently demonstrate clinical benefits.

Table 7. Summary of Evidence

Main findings from 2005 USPSTF review	Number and type of studies identified for update *Overall quality**	Limitations	Consistency	Applicability	Summary of findings
KQ 5. What are the longer-term harms associated with antiretroviral therapy in nonpregnant adolescents and adults with chronic HIV infection?					
1 large cohort study found longer duration of exposure to HAART associated with increased risk of myocardial infarction (RR, 1.3 per year of exposure [95% CI, 1.1 to 1.4])	4 cohort studies (reported in 6 publications) ***Overall quality: Good***	No major limitations	Consistent	Duration of followup about 6 years	Additional followup from a large cohort study included in the prior USPSTF review found some protease inhibitors associated with increased risk for myocardial infarction (RR, 1.1 to 1.2 per year of exposure). Evidence on abacavir was mixed from four cohort studies, and there was no clear association between other antiretrovirals and increased risk for cardiovascular events.
KQ 6a. To what extent are improvements in viremia associated with reductions in HIV transmission rates in nonpregnant adolescents and adults?					
7 observational studies consistently found an association between lower individual viral load and lower risk for heterosexual transmission of HIV infection	6 observational studies ***Overall quality: Good***	No major limitations	Consistent	Some studies conducted in resource-poor settings	Observational studies consistently found a dose-dependent association between higher viral load and risk for transmission in various settings and populations.
KQ 6b. To what extent are improvements in risky behaviors associated with reductions in HIV transmission rates in nonpregnant adolescents and adults?					
2 systematic reviews of primarily heterosexual couples found consistent use of condoms associated with substantially lower (80% to 95%) risk of HIV transmission.	2 cohort studies ***Overall quality: Good***	No major limitations	Consistent	No study evaluated drug use behaviors; studies focused on condom use	Observational studies consistently found self-reported condom use associated with decreased risk for HIV transmission.

* "Overall quality" is based on new evidence identified for this update plus previously reviewed evidence.
† Cost-effectiveness modeling studies are not included in this summary table.
‡ One RCT compared rapid versus standard testing, but it only identified one new infection.

CDC = Centers for Disease Control and Prevention; KQ = key question; RCT = randomized, controlled trial; USPSTF = U.S. Preventive Services Task Force.

Appendix A1. Search Strategies

All Key Questions

Database: EBM Reviews - Cochrane Database of Systematic Reviews
1 hiv.ti.
2 limit 1 to full systematic reviews
3 antiretroviral.mp. [mp=title, short title, abstract, full text, keywords, caption text]
4 haart.mp. [mp=title, short title, abstract, full text, keywords, caption text]
5 3 or 4
6 2 and 5
7 screen$.mp. [mp=title, short title, abstract, full text, keywords, caption text]
8 2 and 7
9 test$.mp. [mp=title, short title, abstract, full text, keywords, caption text]
10 2 and 9
11 6 or 8 or 10
12 limit 11 to last 8 years
13 pregnan$.mp. [mp=title, short title, abstract, full text, keywords, caption text]
14 12 not 13

Key Questions 1 and 2a-2f

Database: Ovid MEDLINE(R) without Revisions
1 exp AIDS Serodiagnosis/
2 exp HIV Seronegativity/
3 exp HIV Antigens/
4 exp HIV/
5 exp HIV Seroprevalence/
6 exp HIV Seropositivity/
7 exp HIV Antibodies/
8 or/2-7
9 exp Mass Screening/
10 8 and 9
11 1 or 10
12 (hiv adj1 screen$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
13 11 or 12
14 13 and (200406$ or 200407$ or 200408$ or 200409$ or 20041$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ed.
15 limit 14 to English language
16 limit 14 to abstracts
17 15 or 16
18 limit 17 to humans
19 universal.mp.
20 rapid.mp.
21 19 and 20
22 or/1-8
23 21 and 22
24 9 and 21

25 23 or 24
26 18 or 25

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 exp AIDS Serodiagnosis/
2 exp HIV Seronegativity/
3 exp HIV Antigens/
4 exp HIV/
5 exp HIV Seroprevalence/
6 exp HIV Seropositivity/
7 exp HIV Antibodies/
8 or/2-7
9 exp Mass Screening/
10 8 and 9
11 1 or 10
12 (hiv adj1 screen$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
13 11 or 12
14 limit 13 to yr="2004 -Current"
15 Pregnancy/
16 14 not 15

Key Questions 3a, 3b

Database: Ovid MEDLINE(R) without Revisions
1 HIV Seropositivity/
2 (hiv adj1 positive).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
3 1 or 2
4 exp Anti-HIV Agents/
5 exp Antiretroviral Therapy, Highly Active/
6 haart.mp.
7 5 or 6
8 or/3-5,7
9 Sexual Behavior/
10 Unsafe Sex/
11 Safe Sex/
12 Risk-Taking/
13 Needle Sharing/
14 or/9-13
15 8 and 14
16 Pregnancy/
17 15 not 16
18 limit 17 to English language
19 limit 17 to abstracts
20 18 or 19
21 limit 20 to humans

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 HIV Seropositivity/
2 (hiv adj1 positive).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 1 or 2
4 exp Anti-HIV Agents/
5 exp Antiretroviral Therapy, Highly Active/
6 haart.mp.
7 5 or 6
8 or/3-5,7
9 Sexual Behavior/
10 Unsafe Sex/
11 Safe Sex/
12 Risk-Taking/
13 Needle Sharing/
14 or/9-13
15 8 and 14
16 Pregnancy/
17 15 not 16
18 limit 17 to yr="2004 -Current"

Key Questions 4a, 4b

Database: Ovid MEDLINE(R) without Revisions
1 exp HIV Infections/dh, dt, pc, th [Diet Therapy, Drug Therapy, Prevention & Control, Therapy]
2 exp HIV Infections/tm [Transmission]
3 1 and 2
4 (hiv adj2 (transmission or transmit)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
5 3 or 4
6 exp Anti-HIV Agents/tu [Therapeutic Use]
7 haart.mp. or Antiretroviral Therapy, Highly Active/
8 6 or 7
9 8 and (2 or 4)
10 Counseling/
11 Patient Education as Topic/
12 10 or 11
13 12 and (2 or 4)
14 5 or 9 or 13
15 Pregnancy/
16 14 not 15
17 limit 16 to English language
18 limit 16 to abstracts
19 17 or 18
20 limit 19 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)")
21 limit 20 to yr="2004 - Current"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 exp HIV Infections/dh, dt, pc, th [Diet Therapy, Drug Therapy, Prevention & Control, Therapy]
2 exp HIV Infections/tm [Transmission]
3 1 and 2
4 (hiv adj2 (transmission or transmit)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
5 3 or 4
6 exp Anti-HIV Agents/tu [Therapeutic Use]
7 haart.mp. or Antiretroviral Therapy, Highly Active/
8 6 or 7
9 8 and (2 or 4)
10 Counseling/
11 Patient Education as Topic/
12 10 or 11
13 12 and (2 or 4)
14 5 or 9 or 13
15 Pregnancy/
16 14 not 15
17 limit 16 to yr="2004 -Current"

Key Question 4c

Database: Ovid MEDLINE(R) without Revisions
1 exp HIV Infections/dt, th [Drug Therapy, Therapy]
2 haart.mp. or Antiretroviral Therapy, Highly Active/
3 Anti-HIV Agents/ad, tu [Administration & Dosage, Therapeutic Use]
4 Anti-Retroviral Agents/ad, tu [Administration & Dosage, Therapeutic Use]
5 or/1-4
6 Viral Load/
7 CD4 Lymphocyte Count/
8 or/6-7
9 5 and 8
10 Drug Administration Schedule/
11 (treatment adj1 (tim$ or administration)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
12 10 or 11
13 9 and 12
14 Pregnancy/
15 13 not 14
16 limit 15 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)")
17 limit 16 to English language
18 limit 16 to abstracts
19 17 or 18
20 limit 19 to yr="2004 - Current"

Appendix A1. Search Strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 exp HIV Infections/dt, th [Drug Therapy, Therapy]
2 haart.mp. or Antiretroviral Therapy, Highly Active/
3 Anti-HIV Agents/ad, tu [Administration & Dosage, Therapeutic Use]
4 Anti-Retroviral Agents/ad, tu [Administration & Dosage, Therapeutic Use]
5 or/1-4
6 Viral Load/
7 CD4 Lymphocyte Count/
8 or/6-7
9 5 and 8
10 Drug Administration Schedule/
11 (treatment adj1 (tim$ or administration)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
12 10 or 11
13 9 and 12
14 Pregnancy/
15 13 not 14
16 limit 15 to yr="2004 -Current"

Key Question 4c Supplement

Database: Ovid MEDLINE(R) without Revisions
1 exp HIV Infections/dt, th [Drug Therapy, Therapy]
2 haart.mp. or Antiretroviral Therapy, Highly Active/
3 Anti-HIV Agents/ad, tu [Administration & Dosage, Therapeutic Use]
4 Anti-Retroviral Agents/ad, tu [Administration & Dosage, Therapeutic Use]
5 or/1-4
6 Viral Load/
7 CD4 Lymphocyte Count/
8 or/6-7
9 5 and 8
10 Drug Administration Schedule/
11 (treatment adj1 (tim$ or administration)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
12 10 or 11
13 9 and 12
14 Pregnancy/
15 13 not 14
16 limit 15 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)")
17 limit 16 to English language
18 limit 16 to abstracts
19 17 or 18
20 (treatment adj5 (tim$ or administration or initiation)).mp.
21 9 and 20
22 21 not 19
23 limit 22 to English language
24 23 not 14

25 limit 24 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)")
26 Prognosis/
27 9 and 26
28 27 not (19 or 22)
29 limit 28 to English language
30 limit 29 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)")
31 25 or 30

Key Question 5

Database: Ovid MEDLINE(R) without Revisions
1 haart.mp. or Antiretroviral Therapy, Highly Active/
2 (ae or co or de or mo).fs.
3 1 and 2
4 (harm$ or safe$ or adverse).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
5 1 and 4
6 3 or 5
7 Pregnancy/
8 6 not 7
9 limit 8 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)")
10 limit 9 to English language
11 limit 9 to abstracts
12 10 or 11
13 limit 12 to yr="2004 - Current"
14 13 not (letter or editorial or case reports).pt.

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 haart.mp. or Antiretroviral Therapy, Highly Active/
2 (ae or co or de or mo).fs.
3 1 and 2
4 (harm$ or safe$ or adverse).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
5 1 and 4
6 3 or 5
7 Pregnancy/
8 6 not 7
9 limit 8 to yr="2004 -Current"

Key Questions 6a, 6b

Database: Ovid MEDLINE(R) without Revisions
1 HIV Infections/tm [Transmission]
2 viremia.mp.
3 1 and 2
4 Risk-Taking/
5 Sexual Behavior/

6 Unsafe Sex/
7 Safe Sex/
8 or/4-7
9 1 and 8
10 risk reduction behavior/
11 (risk$ adj1 reduc$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
12 10 or 11
13 9 and 12
14 3 or 13
15 Pregnancy/
16 14 not 15
17 limit 16 to yr="2004 - Current"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 HIV Infections/tm [Transmission]
2 viremia.mp.
3 1 and 2
4 Risk-Taking/
5 Sexual Behavior/
6 Unsafe Sex/
7 Safe Sex/
8 or/4-7
9 1 and 8
10 risk reduction behavior/
11 (risk$ adj1 reduc$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
12 10 or 11
13 9 and 12
14 3 or 13
15 Pregnancy/
16 14 not 15
17 limit 16 to yr="2004 -Current"

Appendix A2. Inclusion and Exclusion Criteria per Key Question

	Include	Exclude
All Key Questions (KQs)		
Settings	Primary care or other settings generalizable to primary care (e.g., family planning clinics, school-based health clinics), other health care settings in which screening is commonly performed (e.g., emergency room or urgent care). Focus on studies conducted in the United States and other developed countries, unless studies are not available in those settings.	Developing countries, unless fair- or good-quality trials and studies in the United States are lacking
KQ 1. What are the benefits of universal or targeted HIV screening vs. no screening or each other in asymptomatic, nonpregnant adolescents and adults on disease transmission, morbidity, mortality, and quality of life?		
Populations	Asymptomatic adolescents and adults	Known HIV infection, on dialysis, post-transplant, occupational exposure
Interventions	Rapid or standard HIV testing	
Outcomes	Reduction in transmission rates of HIV; morbidity and mortality related to HIV infection and quality of life	
Comparisons	Universal or targeted HIV screening vs. no screening, or vs. one another	
Study designs	Randomized, controlled trials and controlled observational studies	Uncontrolled observational studies
KQ 2a. What is the yield (number of new diagnoses) of HIV screening at different intervals in nonpregnant adolescents and adults?		
Populations	Asymptomatic adolescents and adults	Known HIV infection, on dialysis, post-transplant, occupational exposure
Interventions	Rapid or standard HIV testing	
Outcomes	Number of positive test results	
Comparisons	Repeat HIV screening vs. one-time screening, or screening at one interval vs. another interval	
Study designs	Randomized, controlled trials and controlled observational studies	
KQ 2b. What are the effects of universal vs. targeted HIV screening on testing acceptability and uptake in nonpregnant adolescents and adults?		
Populations	Asymptomatic adolescents and adults	Known HIV infection, on dialysis, post-transplant, occupational exposure
Interventions	Rapid or standard HIV testing	
Outcomes	Testing acceptability and uptake	
Comparisons	Universal vs. targeted HIV screening	
Study designs	Any	
KQ 2c. What is the effect of opt-out vs. opt-in testing or different pre- or post-test HIV counseling methods on screening uptake or rates of followup and linkage to care in nonpregnant adolescents and adults?		
Populations	Asymptomatic adolescents and adults	Known HIV infection, on dialysis, post-transplant, occupational exposure
Interventions	Rapid or standard HIV testing	
Outcomes	Testing acceptability and uptake or rates of followup	
Comparisons	Opt-out vs. opt-in testing, or comparisons of different pre- or post-test HIV counseling methods	
Study designs	Any	
KQ 2d. What are the adverse effects (including false-positive results and anxiety) of rapid vs. standard HIV testing in nonpregnant adolescents and adults not known to be at higher risk?		
Populations	Asymptomatic adolescents and adults	High-risk; known HIV infection, on dialysis, post-transplant, occupational exposure
Interventions	Rapid or standard HIV testing	
Outcomes	False-positive results, anxiety, and effects of labeling; partner discord, abuse, or violence	
Comparisons	Rapid vs. standard HIV testing	
Study designs	Any	

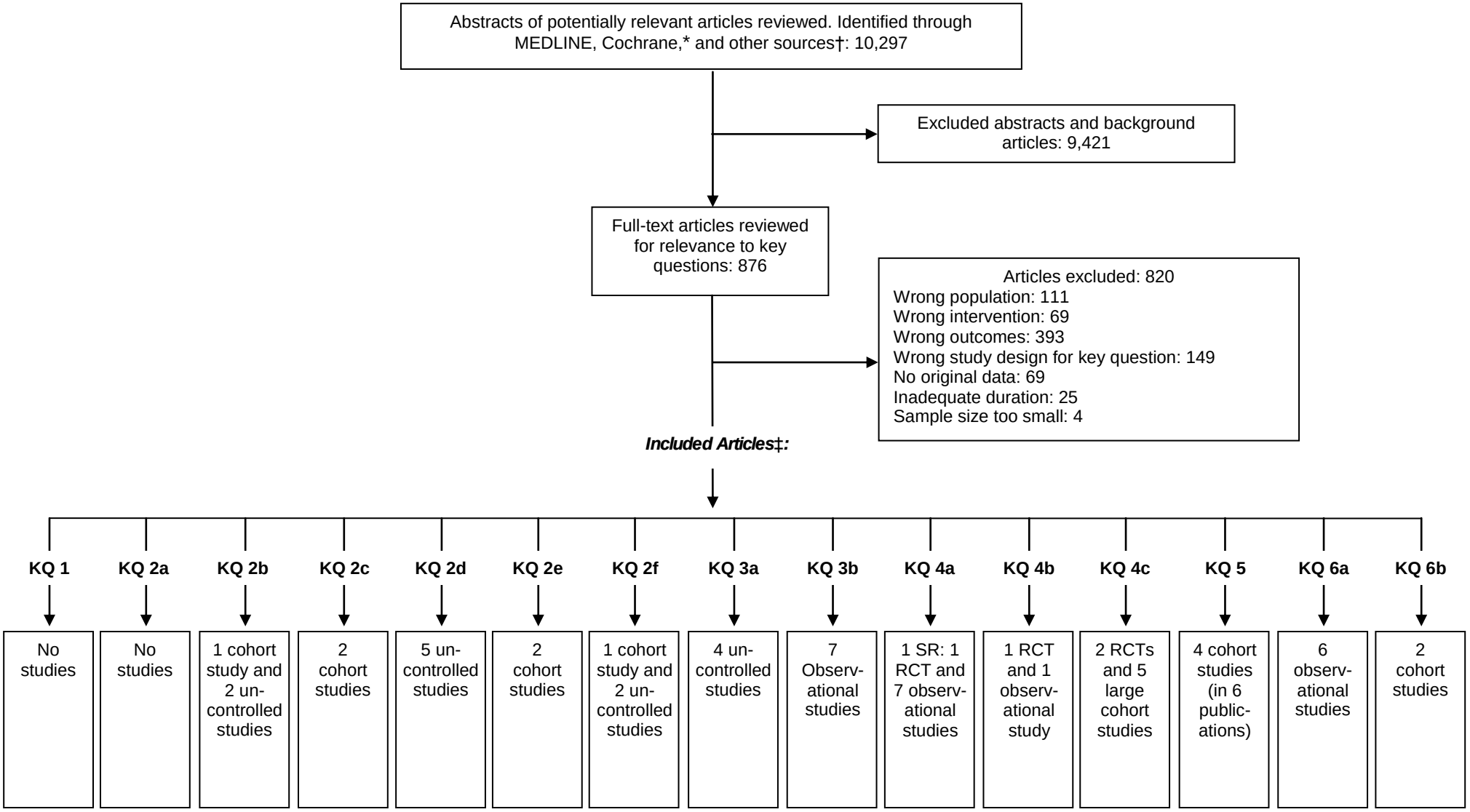
Appendix A2. Inclusion and Exclusion Criteria per Key Question

	Include	Exclude
KQ 2e. What are the effects of universal vs. targeted HIV screening on CD4 counts at the time of diagnosis?		
Populations	Asymptomatic adolescents and adults	Known HIV infection, on dialysis, post-transplant, occupational exposure
Interventions	Rapid or standard HIV testing	
Outcomes	CD4 count	
Comparisons	Universal or targeted HIV screening vs. no screening, or vs. one another	
Study designs	Randomized, controlled trials or controlled observational studies	
KQ 2f. What are the effects of universal vs. targeted HIV screening on rates of followup and linkage to care in nonpregnant adolescents and adults who screen positive?		
Populations	Asymptomatic adolescents and adults	Known HIV infection, on dialysis, post-transplant, occupational exposure
Interventions	Rapid or standard HIV testing	
Outcomes	Rates of followup and linkage to care	
Comparisons	Universal or targeted HIV screening	
Study designs	Randomized, controlled trials or controlled observational studies	
KQ 3a. To what extent does knowledge of HIV-positive status affect behaviors associated with increased risk for HIV transmission in nonpregnant adolescent and adults?		
Populations	Asymptomatic persons newly diagnosed with HIV infection	Already or previously taking antiretroviral therapy; acute HIV or subtypes
Comparisons	Knowledge of HIV-positive status vs. not aware	
Outcomes	Risky behaviors	
Study designs	Randomized, controlled trials or controlled observational studies	
KQ 3b. To what extent does use of antiretroviral therapy affect behaviors associated with increased risk for HIV transmission in nonpregnant adolescent and adults?		
Populations	Asymptomatic persons newly diagnosed with HIV infection	Already or previously taking antiretroviral therapy; acute HIV or subtypes
Comparisons	Use of antiretroviral therapy vs. no use of antiretroviral therapy	
Outcomes	Risky behaviors	
Study designs	Randomized, controlled trials or controlled observational studies	
KQ 4a. How effective is antiretroviral therapy in reducing transmission of HIV in nonpregnant adolescents and adults with chronic HIV infection?		
Populations	HIV-positive adolescents and adults	Acute HIV infection
Interventions	Use of antiretroviral therapy	
Comparisons	Use of antiretroviral therapy vs. no use of antiretroviral therapy	
Outcomes	Transmission rates	
Study designs	Randomized, controlled trials or controlled observational studies	
KQ 4b. How effective is behavioral counseling in reducing transmission of HIV in nonpregnant adolescents and adults with chronic HIV infection?		
Populations	HIV-positive adolescents and adults	Acute HIV infection
Interventions	Behavioral counseling interventions (pre- and post-test) to reduce risky sexual behaviors or enhance protective sexual behaviors for those who are asymptomatic and identified through screening	
Comparisons	Counseling vs. usual care	
Outcomes	Transmission rates	
Study designs	Randomized, controlled trials or controlled observational studies	
KQ 4c. In asymptomatic, nonpregnant adolescents and adults with chronic HIV infection, what are the effects of initiating antiretroviral therapy at different CD4 counts or viral load thresholds on morbidity, mortality, and quality of life?		
Populations	HIV-positive adolescents and adults	Acute HIV infection
Interventions	Antiretroviral regimens	
Comparisons	Initiation of antiretroviral therapy earlier vs. initiation later	
Outcomes	Morbidity and mortality related to HIV infection and quality of life	
Study designs	Randomized, controlled trials or controlled observational studies	

Appendix A2. Inclusion and Exclusion Criteria per Key Question

	Include	Exclude
KQ 5. What are the longer-term harms associated with antiretroviral therapy in nonpregnant adolescents and adults with chronic HIV infection?		
Populations	HIV-positive adolescents and adults	Already or previously taking antiretroviral therapy; acute HIV infection
Interventions	Antiretroviral regimens	
Outcomes	Cardiovascular harms	
Study designs	Any	
Timing	Long-term followup defined as ≥2 years	
KQ 6a. To what extent are improvements in viremia associated with reductions in HIV transmission rates in nonpregnant adolescents and adults?		
Populations	HIV-positive adolescents and adults	Acute HIV or subtypes
Comparisons	Differences in improvements in viral load	
Outcomes	HIV transmission rates	Risk perception
Study designs	Randomized, controlled trials or controlled observational studies	
KQ 6b. To what extent are improvements in risky behaviors associated with reductions in HIV transmission rates in nonpregnant adolescents and adults?		
Populations	HIV-positive adolescents and adults	Acute HIV or subtypes
Comparisons	Differences in self-reported risky behaviors	
Outcomes	HIV transmission rates	Risk perception
Study designs	Randomized, controlled trials or controlled observational studies	

Appendix A3. Literature Flow Diagram



*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
†Other sources include reference lists, suggested by peer reviewers, etc.
‡ Some articles are included for more than one key question.
Abbreviations: RCT = randomized, controlled trial; SR = systematic review.

Wrong population

Antiretroviral Therapy Cohort Collaboration. Importance of baseline prognostic factors with increasing time since initiation of highly active antiretroviral therapy: collaborative analysis of cohorts of HIV-1-infected patients. *J Acquir Immune Defic Syndr.* 2007;15;46(5):607-15. PMID: 18043315.

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Beckwith CG, Liu T, Bazerman LB, DeLong AK, Desjardins SF, Poshkus MM, et al. HIV risk behavior before and after HIV counseling and testing in jail: a pilot study. *J Acquir Immune Defic Syndr.* 2010;53(4):485-90. PMID: 20035232.

Bini EJ, Currie SL, Shen H, Brau N, Schmidt W, Anand BS, et al. National multicenter study of HIV testing and HIV seropositivity in patients with chronic hepatitis C virus infection. *J Clin Gastroenterol*. 2006;40(8):732-9. PMID: 16940888.

Bower M, Weir J, Francis N, Newsom-Davis T, Powles S, Crook T, et al. The effect of HAART in 254 consecutive patients with AIDS-related Kaposi's sarcoma. *AIDS*. 2009;23(13):1701-6. PMID: 19550283.

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Cabie A, Bissuel F, Abel S, Huc P, Paturel L, Pierre-Francois S. Use of HIV rapid tests in free and anonymous screening consultations in the French West Indies. *Med Mal Infect*. 2009;39(6):370-4. PMID: 19346089.

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Casula M, Weverling GJ, Wit FW, Timmermans EC, Stek M, Lange JM, et al. Mitochondrial DNA and RNA increase in peripheral blood mononuclear cells from HIV-1–infected patients randomized to receive stavudine-containing or stavudine-sparing combination therapy. *J Infect Dis.* 2005;192(10):1794-800. PMID: 16235179.

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Celum CL, Buchbinder SP, Donnell D, Douglas JM Jr, Mayer K, Koblin B, et al. Early human immunodeficiency virus (HIV) infection in the HIV Network for Prevention Trials Vaccine Preparedness Cohort: risk behaviors, symptoms, and early plasma and genital tract virus load. *J Infect Dis.* 2001;183(1):23-35. PMID: 11106536.

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Appendix A4. Excluded Studies List

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Randomized Controlled Trials (RCTs) and Cohort Studies

Criteria:

- Initial assembly of comparable groups: RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of ratings based on above criteria:

Good: Meets all criteria: comparable groups are assembled initially and maintained throughout the study (followup at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Source: Harris et al, 2001[66]

Each criterion was given an assessment of yes, no, unclear, or not applicable:

1. *Was an a priori design provided?* The research question and inclusion criteria should be established before the conduct of the review.
2. *Was there duplicate study selection and data extraction?* There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.
3. *Was a comprehensive literature search performed?* At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and, where feasible, the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.
4. *Was the status of publication (i.e., gray literature) used as an inclusion criterion?* The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language, etc.
5. *Was a list of studies (included and excluded) provided?* A list of included and excluded studies should be provided.
6. *Were the characteristics of the included studies provided?* In an aggregated form, such as a table, data from the original studies should be provided on the participants, interventions, and outcomes. The ranges of characteristics in the studies analyzed, such as age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases, should be reported.
7. *Was the scientific quality of the included studies assessed and documented?* A priori methods of assessment should be provided (e.g., for effectiveness studies if the authors chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies, alternative items will be relevant.
8. *Was the scientific quality of the included studies used appropriately in formulating conclusions?* The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating the recommendations.
9. *Were the methods used to combine the findings of studies appropriate?* Reviews should not combine or pool dissimilar studies. If studies are pooled using a fixed effects model, there should be a clear rationale for doing so. A test should be done to assess for statistical heterogeneity (i.e., chi-square test for homogeneity, I^2).
10. *Was the likelihood of publication bias assessed?* An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test). If assessment of publication bias is not possible, the review should provide justification (e.g., small numbers of studies, too much heterogeneity, poor quality).
11. *Was the conflict of interest stated?* Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

Definition of ratings based on above criteria:

Good: Recent, comprehensive review that uses explicit criteria to identify and select studies for inclusion, uses appropriate methods to assess quality of primary studies appropriately, and uses appropriate methods for synthesizing or combining results.

Fair: Systematic methods for identifying studies but does not meet one or more of the criteria listed above.

Poor: No systematic methods for identifying studies, major selection bias, or inappropriate methods for combining or pooling data.

Source: Harris et al, 2001[66]

Appendix A7. Expert Reviewers of the Draft Report

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Appendix B1. Key Question 2b: Evidence Table of Studies of Acceptability/Uptake of Universal or Targeted HIV Testing

Author, Year	Study design	Location/setting/high or low prevalence population (based on 0.1% prevalence rate)	Study time frame	Comparison groups/ intervention	Baseline population characteristics	Eligibility criteria	Exclusion criteria
Cunningham et al, 2009[70]	Cross-sectional	Acceptance of opt-out standard testing implemented in an urban FQHC, New York City	July 2007 to March 2008	Characteristics of those accepting testing (n=105) compared with those not accepting testing (n=195)	Mean age, 53 years (range, 18–92); 70.2% female; 55.7% black, 37.7% Hispanic; 66.0% public insurance	Patients seeing 1 of 5 participating providers; age ≥18 years; English-speaking; not pregnant; not known to be HIV-infected	None
Haukoos et al, 2010[68]	Quasi-experiment with sequential time samples (cohort study)	Large urban ED (Denver) where rapid HIV testing (Uni-Gold Recombigen) performed as opt-out x 3 months vs. diagnostic (physician-directed) testing x 4 months over 2 years (3 cycles each); local estimated HIV prevalence, 0.7%	April 15, 2007 to April 15, 2009	Opt-out vs. diagnostic (physician-directed) timeframes	During opt-out phase: mean age, 36 years; 56% male; 40% white; 37% Hispanic; 14% black During diagnostic phase: mean age, 36 years; 57% male; 41% white; 37% Hispanic; 14% black	All ED patients age ≥16 years and capable of providing consent for emergency medical care	If unable to provide consent for HIV testing; detainees/ prisoners; seeking care after sexual assault; seeking care after occupational exposure; self-identified as HIV-infected; left ED prior to being placed in treatment room
Weis et al, 2009[69]	Cross-sectional	Feasibility study of rapid HIV testing (Oraquick Advance Rapid HIV-1/2 with oral fluid or Uni-Gold Recombigen with finger stick) implementation in 3 rural primary care FQHCs in Aiken County, SC; low prevalence (estimated 0.01%; actual prevalence during study 0%)	Dec 2006 to July 2007	Not relevant (descriptive report of screening acceptability)	Mean age not reported; 43% age ≥50 years; 71% female; 59% black; 36% white; 52% self-pay/no insurance; 29% public insurance	All patients age ≥13 years presenting for care at participating FQHCs during first 8 months after rapid HIV testing implementation; multiple tests allowed	Patients missing demographic data (n=36; 4% of 990 unique patients attending clinic during this period)

Author, Year	Number screened/ acceptibility	Adjusted variables for statistical analysis	Clinical outcomes	Adverse events	Linkage to care	CD4 count at HIV diagnosis	Quality rating	Funding source
Cunningham et al, 2009[70]	300 of 319 eligible patients approached (94%) 105/300 (35%) agreed to be HIV-tested	Age, race, HIV tester, other blood test during visit	105/300 (35%) eligible patients approached agreed to screening. In multivariate models, younger age (AOR, 0.97 [95% CI, 0.96-0.99]), Hispanic race (AOR, 1.78 [CI, 1.01-3.14]), and having other blood tests done during visit (AOR, 6.36 [CI, 3.58-11.28]) were associated with test acceptance. 0 HIV-positive tests.	Not reported	N/A (no one confirmed HIV positive)	N/A (no confirmed positives)	Uncontrolled study - not rated	RWJ, New York Academy of Medicine, NIH, Center for AIDS Research at Albert Einstein College of Medicine, Montefiore Medical Center

Appendix B1. Key Question 2b: Evidence Table of Studies of Acceptability/Uptake of Universal or Targeted HIV Testing

Author, Year	Number screened/ acceptibility	Adjusted variables for statistical analysis	Clinical outcomes	Adverse events	Linkage to care	CD4 count at HIV diagnosis	Quality rating	Funding source
Haukoos et al, 2010[68]	During opt-out phase: 6702 of 28,043 eligible patients (24%) screened; during diagnostic phase: 243 of 29,925 eligible patients (0.8%) tested	Unclear. Adjusted for "potential variation between study groups"	Universal opt-out rapid screening vs. physician-directed targeted rapid screening: Testing: 24.7% or 6933/28,043 vs. 0.8% or 243/29,925; RR, 30 [CI, 26-34] Testing uptake: not reported	Across both phases, 6/7656 tests performed were false-positive tests (0.08%). PPV: 82.4%	During opt-out phase: 30/31 (96.8%) of preliminary positives attended at least 1 appt. in HIV clinic. During diagnostic phase: 5/5 (100%) preliminary positives attended initial HIV clinic visit.	During opt-out phase: median CD4 count, 0.069 x 10^9 cells/L (IQR, 0.017-0.430 x 10^9 cells/L). During diagnostic phase: median CD4 count, 0.013 (IQR, 0.011-0.015 x 10^9 cells/L; p=0.02). Of 15 confirmed HIV infections identified during opt-out testing, 9 (60% [CI, 32%-84%]) had an initial CD4 count <0.200 x 10^9 cells/L whereas all 4 confirmed HIV infections (100% [CI, 40%-100%]) had an initial CD4 count <0.200 x 10^9 cells/L.	Fair	CDC, AHRQ
Weis et al, 2009[69]	954/954 (100%) eligible patients offered screening during 985 visits; 574 (58%) visits accepted HIV screening	Center, gender, race/ethnicity, age, insurance, and history of prior HIV testing	574 (58%) visits accepted screening; 411 (42%) visits declined screening; in multivariate models of test acceptance, African American race (AOR, 1.53 [CI, 1.15-2.04]), age ≥50 years (AOR, 0.28 [CI, 0.28-0.98]), and Medicare insurance (vs. self-pay) (AOR, 0.61 [CI, 0.40-0.94]) associated with acceptance of HIV testing.	3/3 (100%) preliminary HIV-positive tests were false-positive (PPV=0); all in the first month of testing.	N/A (no one confirmed HIV positive)	N/A (no one confirmed positive)	Uncontrolled study - not rated	CDC

AHRQ = Agency for Healthcare Research and Quality; AOR = adjusted odds ratio; CDC = Centers for Disease Control and Prevention; CI = confidence interval; ED = emergency department; FQHC = Federally Qualified Health Center; NIH = National Institutes of Health; PPV = positive predictive value; RWJ = Robert Wood Johnson Foundation.

Appendix B2. Key Question 2b: Quality Assessment of a Cohort Study

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified, defined, and ascertained using accurate methods?	Quality rating
Haukoos et al, 2010[68]	Yes	Yes	Not applicable	Yes	Unclear	Not applicable	Yes	Not applicable	Yes	Fair

Appendix B3. Key Question 2c: Evidence Table of Studies of Testing Rates of Opt-Out Versus Opt-In HIV Testing

Author, Year	Study design	Comparison groups	Location/setting/high or low prevalence population (based on 0.1% prevalence rate)	Study timeframe	Baseline population characteristics	Eligibility criteria	Exclusion criteria
Haukoos et al, 2012[72]	Prospective quasi-experiment (cohort study)	A: Patients offered opt-out rapid testing B: Patients offered opt-in rapid testing	Evaluation of patient acceptance and understanding of opt-out and opt-in rapid HIV screening in the emergency department of an urban hospital in Denver/low prevalence	October to December 2009	A vs. B Age: 36 vs. 25 years Male sex: 45% vs. 45% Race: 52% Hispanic, 26% white, 16% black, 3% unknown/missing, 2% Asian, 1% other vs. 44% Hispanic, 29% white, 21% black, 3% unknown/missing, 2% other, 1% Asian	Ambulatory patients presenting for care who were ≥13 years and able to provide informed consent	None (reported as inverse of inclusion: younger than age 13 years, arrived by ambulance, unable to consent)
White et al, 2011[73]	Cohort study	Opt-in period: screening offered by providers (Feb 1, 2007–July 31, 2007; n=23,236) vs. opt-out period: screening offered by registration staff (Aug 1, 2007–January 31, 2007; n=26,757).	Pre-post evaluation of opt-In vs. Opt-Out testing implementation on screening rates and acceptance of rapid oral HIV screening in Oakland, CA ED.	February 1, 2007 to January 31, 2008	Demographic data available only for patients offered testing: Opt-in phase (n=6479): mean age, 39 (SD, 13); 53% male; 43% black, 27% Hispanic, 15% white Opt-out phase: mean age, 42 (SD, 14); 45% female; 45% black, 26% Hispanic, 15% white	Age ≥15 years; medically stable; able to consent for HIV testing (opt-in phase) or complete general consent (opt-in and opt-out phase)	Patients requiring immediate medical evaluation or if staff deemed patient "too ill"

Author, Year	Number screened/ acceptibility	Clinical outcomes	Adverse events	Linkage to care	CD4 count at HIV diagnosis	Quality rating	Funding source
Haukoos et al, 2012[72]	A vs. B 6842 eligible/3993 agreed/886 screened vs. 5985 eligible/930 agreed/389 screened	A vs. B Difference in completed screening: 13% vs. 7% (6% difference [95% CI, 5 to 8]) Eligible patients agreeing to testing: 44% difference (95% CI, 43 to 46) Agreed patients completing screening: -21% difference (95% CI, -17 to -27) Screened patients newly diagnosed with HIV: 2 (0.2 [95% CI, 0.02 to 0.8]) vs. 0 (0% [95% CI, 0 to 0.9) Self-reported not being informed about HIV test: 54% vs. 3% (absolute difference, 35% [95% CI, 44 to 59]) Agreed (or neglected to opt out) but self-report not agreeing to an HIV test: 38% vs. 3% (absolute difference, 35% [95% CI, 24 to 46%)	Not reported	Newly diagnosed patients linked to care: 2/2 (100%, both from opt-out group)	CD4 counts: 0.047 and 0.085 x 10^9 cells/L Viral load: 184,272 and 206,878 copies/mL	Fair	Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality, Colorado HIV/AIDS Prevention Program
White et al, 2011[73]	Opt-in phase: 6479/23,236 eligible (62.9%) offered screening; 4061/6479 (62.7%) accepted screening. Opt-out phase: 20,280/26,757 (75.8%) offered screening; 6273/20,280 (30.9%) accepted screening	Opt-in phase: 21/4053 preliminary positive rapid tests; 10/4053 confirmed positive (0.25% prevalence). Opt-out phase: 28/4679 preliminary positive; 28/4679 confirmed positive (0.60%). When previously known HIV-positive subjects excluded, opt-in identified 8 new cases (0.2% of tested) and opt-out identified 21 new cases (0.4%); p=0.04	11/21(52.4%) false-positive preliminary rapid tests; all occurred during first 2 months of study (opt-in phase); cause unknown	75% of opt-in and 77% of opt-out newly diagnosed cases linked to care within 90 days of diagnosis	Mean CD4 (opt-in): 0.415 x 10^9 (SD, 0.237 x 10^9). Mean CD4 (opt-out): 0.307 x 10^9 (SD, 0.274 x 10^9). 25% of opt-in and 48% of opt-out newly diagnosed patients had CD4 count <0.200 x 10^9	Fair	Centers for Disease Control and Prevention

Appendix B4. Key Question 2c: Quality Assessment of Cohort Studies

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified, defined, and ascertained using accurate methods?	Quality rating
Haukoos et al, 2012[72]	Yes	Yes	Not applicable	Yes	Unclear	Not applicable	No	Not applicable	Yes	Fair
White et al, 2011[73]	Yes	Yes; differ only on acuity rating	Not applicable	Yes	Yes	Not applicable	Unclear; states bivariate analysis completed but not shown	Not applicable	Yes	Fair

Appendix B5. Key Question 2e: Evidence Table of Studies of Universal Versus Targeted HIV Screening and CD4 Counts at Time of Diagnosis

Author, Year	Study design	Location/setting/high or low prevalence population (based on 0.1% prevalence rate)	Study timeframe	Comparison groups	Baseline population characteristics	Eligibility criteria	Exclusion criteria
Haukoos et al, 2010[68]	Quasi-experiment with sequential time samples (cohort study)	Large urban ED (Denver) where rapid HIV testing (Uni-Gold Recombigen) performed as opt-out x 3 months vs. diagnostic (physician-directed) testing x 4 months over 2 years (3 cycles each); local estimated HIV prevalence, 0.7%	April 15, 2007 to April 15, 2009	Opt-out vs. diagnostic (physician-directed) timeframes	During opt-out phase: mean age, 36 years; 56% male; 40% white, 37% Hispanic, 14% black During diagnostic phase: mean age, 36 years; 57% male; 41% white, 37% Hispanic, 14% black	All ED patients ages ≥16 years and capable of providing consent for emergency mediare care	If unable to provide consent for HIV testing; detainees/prisoners; seeking care after sexual assault; seeking care after occupational exposure; self-identified as HIV-infected; left ED prior to being placed in treatment room
White et al, 2011[73]	Cohort study	Pre-post evaluation of opt-in vs. opt-out testing implementation on screening rates and acceptance of rapid oral HIV screening in an ED in Oakland, California	February 1, 2007 to January 31, 2008	Opt-in period: screening offered by providers (February 1, 2007–July 31, 2007; n=23,236) vs. opt-out period: screening offered by registration staff (Aug 1, 2007–January 31, 2007; n=26,757)	Demographic data available only for patients offered teting: Opt-in phase (n=6479): Mean age, 39 years (SD, 13); 53% male; 43% black, 27% Hispanic, 15% white Opt-out phase: Mean age, 42 years (SD, 14); 45% female, 45% black, 26% Hispanic, 15% white	Ages ≥15 years; medically stable; ablet to consent for HIV testing (opt-in phase) or complete general consent (opt-in and opt-out phase)	Patients requiring immediate medical evaluation or if staff deemed patient "too ill"

Author, Year	Number screened/ acceptibility	Adverse events	Linkage to care	CD4 count at HIV diagnosis	Quality rating	Funding source
Haukoos et al, 2010[68]	During opt-out phase: 6702/28,043 eligible patients (24%) screened During diagnostic phase: 243/29,925 eligible patients (0.8%) tested	Across both phases, 6/7656 tests performed were false-positive tests (0.08%). PPV, 82.4%	During opt-out phase: 30/31 (96.8%) of preliminary positives attended at least 1 appt in HIV clinic During diagnostic phase: 5/5 (100%) of preliminary positives attended initial HIV clinic visit	During opt-out phase: median CD4 count was 0.069 x 10^9 cells/L (IQR, 0.017–0.430 x 10^9) During diagnostic phase: median CD4 count was 0.013 x 10^9 cells/L (IQR, 0.011–0.015 x 10^9; p=0.02). Of 15 confirmed HIV infections identified during opt-out testing, 9 (60% [95% CI, 32%–84%]) had an initial CD4 count <0.200 x 10^9 cells/L whereas all 4 confirmed HIV infections (100% [95% CI, 40%–100%]) has an initial CD4 count <0.200 x 10^9 cells/L	Fair	CDC, AHRQ
White et al, 2011[73]	Opt-in phase: 6479/23,236 eligible (62.9%) offered screening; 4061/6479 (62.7%) accepted screening Opt-out phase: 20,280/26,757 (75.8%) offered screening; 6273/20,280 (30.9%) accepted screening	11/21(52.4%) false-positive preliminary rapid tests; all occurred during first 2 months of study (opt-in phase); cause unknown	75% of opt-in and 77% of opt-out newly diagnosed cases linked to care within 90 days of diagnosis	Universal opt-in screening offered by ED triage nurses and providers vs. universal opt-out screening offered by ED front desk registration staff: mean CD4 count of 0.415 x 10^9 cells/L (SD, 0.237) in 8 new confirmed HIV infections (0.2% prevalence) vs. 0.307 x 10^9 cells/L (SD, 0.274) in 21 new confirmed HIV infections (0.4% prevalence) 25% of opt-in and 48% of opt-out newly diagnosed patients had CD4 count <0.200 x 10^9 cells/L	Fair	CDC

AHRQ = Agency for Healthcare Research and Quality; CDC = Centers for Disease Control and Prevention; CI = confidence interval; ED = emergency department; IQR = interquartile range; PPV = positive predictive value.

Appendix B6. Key Question 2e: Quality Assessment of Cohort Studies

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified, defined, and ascertained using accurate methods?	Quality rating
Haukoos et al, 2010[68]	Yes	Yes	Not applicable	Yes	Unclear	Not applicable	Yes	Not applicable	Yes	Fair
White et al, 2011[73]	Yes	Yes; differ only on acuity rating	Not applicable	Yes	Yes	Not applicable	Unclear; states bivariate analysis completed but not shown	Not applicable	Yes	Fair

Appendix B7. Key Question 2f: Evidence Table of Studies Reporting Linkage to Care Following HIV Testing

Author, Year	Type of study/location/ setting/high or low prevalence population (based on 0.1% prevalence rate)	Study timeframe	Comparison groups	Baseline population characteristics	Eligibility criteria	Exclusion criteria
Haukoos et al, 2010[68]	Quasi-experiment with sequential time samples in large urban ED (Denver) where rapid HIV testing (Uni-Gold Recombigen) performed as opt-out x 3 months vs. diagnostic (physician-directed) testing x 4 months over 2 years (3 cycles each); local estimated HIV prevalence, 0.7%	April 15, 2007 to April 15, 2009	Opt-out vs. diagnostic (physician-directed) timeframes	During opt-out phase: mean age, 36 years; 56% male, 40% white, 37% Hispanic, 14% black During diagnostic phase: mean age, 36 yrs; 57% male, 41% white, 37% Hispanic, 14% black	All ED patients ages ≥16 years and capable of providing consent for emergency mediare care	If unable to provide consent for HIV testing; detainees/ prisoners; seeking care after sexual assault; seeking care after occupational exposure; self-identified as HIV-infected; left ED prior to being placed in treatment room
Myers et al, 2009[76]	Pre-post testing intervention in FQHCs in North Carolina, South Carolina, and Mississippi; 0.16% HIV prevalence	2007 to 2008 (13 months)	HIV testing rate before/after routine rapid HIV test staff training intervention	66% female; 30% African American, 37% Latino, 26% white; 45% uninsured	Patients ages 13–64 years seen at 6 participating FQHCs	Excluded previously diagnosed HIV-positive patients
White et al, 2011[73]	Pre-post evaluation of opt-in vs. opt-out testing implementation on screening rates and acceptance of rapid oral HIV screening in an ED in Oakland, California	February 1, 2007 to January 31, 2008	Opt-in period: screening offered by providers (February 1, 2007–July 31, 2007; n=23,236) vs. opt-out period: screening offered by registration staff (August 1, 2007– January 31, 2007; n=26,757)	Demographic data available only for patients offered testing: opt-in phase (n=6479): mean age, 39 years (SD, 13); 53% male; 43% black, 27% Hispanic, 15% white Opt-out phase: mean age, 42 years (SD, 14); 45% female; 45% black, 26% Hispanic, 15% white	Ages ≥15 years; medically stable; able to consent for HIV testing (opt-in phase) or complete general consent (opt-in and opt-out phase)	Patients requiring immediate medical evaluation or if staff deemed patient "too ill"

Author, Year	Number screened/ Acceptibility	Clinical outcomes	Adverse events	Linkage to care	CD4 count at HIV diagnosis	Quality Rating	Funding Source
Haukoos et al, 2010[68]	During opt-out phase: 6762/28,043 eligible patients (24%) screened; during diagnostic phase: 243/29,925 eligible patients (0.8%) tested	During opt-out phase: 16 confirmed HIV infections diagnosed (0.24% of tests); during diagnostic phase: 5 confirmed HIV infections diagnosed (2.1% of tests)	Across both phases, 6/7656 tests performed were false-positive tests (0.08%). PPV, 82.4%	During opt-out phase: 30/31 (96.8%) of preliminary positives attended at least 1 appt in HIV clinic; during diagnostic phase: 5/5 (100%) preliminary positives attended initial HIV clinic visit	During opt-out phase: median CD4 count was 0.069 x 10^9 cells/L (IQR, 0.017–0.430 x 10^9); during diagnostic phase: median CD4 count was 0.013 x 10^9 cells/L (IQR, 0.011–0.015 x 109; p=0.02)	Fair	CDC, AHRQ
Myers et al, 2009[76]	16,148/58,619 eligible patients (28%) offered screening; 10,769/16,148 (67%) offered screening	HIV testing rates increased from 3% in year preceding intervention to 18% of those eligible during intervention year; preliminary positive: 39/10,769 (0.36%); confirmed newly diagnosed HIV infection: 17/10,769 (0.16%)	19/36 (52.8%) who received confirmatory testing were confirmed or probable false-positive rapid HIV tests	14/17 (82%) confrmed positives linked to care	No data presented	Uncontrolled study; not rated	CDC; Gilead Sciences, Inc.

Appendix B7. Key Question 2f: Evidence Table of Studies Reporting Linkage to Care Following HIV Testing

Author, Year	Number screened/ Acceptibility	Clinical outcomes	Adverse events	Linkage to care	CD4 count at HIV diagnosis	Quality Rating	Funding Source
White et al, 2011[73]	Opt-in phase: 6479/23,236 eligible (62.9%) offered screening; 4061/6479 (62.7%) accepted screening; opt-out phase: 20,280/26,757 (75.8%) offered screening; 6273/20,280 (30.9%) accepted screening	Opt-in phase: 21/4053 preliminary positive rapid tests; 10/4053 confirmed positive (0.25% prevalence); opt-out phase: 28/4679 preliminary positive; 28/4679 confirmed positive (0.60%). When previously known HIV-positive subjects excluded, opt-in identified 8 new cases (0.2% of tested) and opt-out identified 21 new cases (0.4%); p=0.04	11/21(52.4%) false-positive preliminary rapid tests; all occurred during first 2 months of study (opt-in phase); cause unknown	75% of opt-in and 77% of opt-out newly diagnosed cases linked to care within 90 days of diagnosis	Mean CD4 count (opt-in): 0.415 x 10^9 cells/L (SD, 0.237 x 10^9); mean CD4 count (opt-out): 0.307 x 10^9 cells/L (SD, 0.274 x 10^9); 25% of opt-in and 48% of opt-out newly diagnosed patients had CD4 count <0.200 x 10^9 cells/L	Analyzed as uncontrolled study for this key question; not rated	CDC

AHRQ = Agency for Healthcare Research and Quality; CDC = Centers for Disease Control and Prevention; ED = emergency department; FQHC = Federally Qualified Health Center; IQR = interquartile range; PPV = positive predictive value; SD = standard deviation.

Appendix B8. Key Question 2f: Quality Assessment of a Cohort Study

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified, defined, and ascertained using accurate methods?	Quality rating
Haukoos et al, 2010[68]	Yes	Yes	Not applicable	Yes	Unclear	Not applicable	Yes	Not applicable	Yes	Fair

Appendix B9. Key Question 3a: Evidence Table of Studies of Effect of Knowledge of HIV-Positive Status or Use of Highly Active Antiretroviral Therapy on Risky Behaviors

Author, year	Type of study	Location/setting/ high or low prevalence population (based on 0.1% prevalence rate)	Study duration/ followup	Comparison groups	Demographics/baseline disease
Amaro et al, 2005[84]	Before-after observational	Massachusetts; HIV counseling and testing sites; high-risk sites (seroprevalence ≥2%), low risk sites (seroprevalence <2%)	May 1996 to February 1997; 3 months	Before HIV test vs. after HIV test (3 months after testing)	48.9% male Males: mean age, 35.9 years (SD, 9.74); 38.7% white, 31.7% black, 24.5% Hispanic, 5% other; 12.8% married, 4.0% same sex partner, 38.3% different sex partner, 44.2% not in special relationship; 55.1% history of partner HIV risk (sex partner in last 5 years who was IDU, had sex outside the relationship, was HIV positive, or had an STD); 2.9% exchanged sex for drugs (35% unknown); 32.5% history of IDU; 61.3% previous HIV test; 4.7% positive HIV test result Females: mean age, 31.5 years (SD, 9.23); 53.2% white, 16.4% black, 22.0% Hispanic, 8% other; 11.5% married, 3.1% same sex partner, 47.9% different sex partner, 36.4% not in special relationship; 62.2% history of partner HIV risk (sex partner in last 5 years who was IDU, had sex outside the relationship, was HIV positive, or had an STD); 7.7% exchanged sex for drugs (35% unknown); 17.8% history of IDU; 64.0% previous HIV test; 1.0% positive HIV test result
Brogly et al, 2002[85]; Bruneau et al, 2001[88]	Before-after observational	Montreal, Canada; self-referral, hospital detoxification unit, IDU centers; high; prevalence in original study cohort 11.1% (Bruneau, 2001)	January 1996 to July 1999 (source cohort recruiting began 1988 [Bruneau, 2001]); first followup visit planned at 3 months, subsequent every 6 months (although participants did not adhere to this schedule and eligibility changed to minimum of 1 month between time of HIV-positive notification and next study visit)	Before HIV diagnosis vs. after HIV diagnosis (at least 1 month after diagnosis) Also had HIV-positive vs. HIV-negative group	93% male; 79% French speaking; mean and median age, 38 years Comparing IDU who test positive for HIV vs. those who test negative: Currently have no stable home: 56/2% vs. 36.5%; p=0.003 In drug treatment since last visit: 32.9% vs. 47.9%; p=0.025 Perceived current health status >6 (1=very bad, 9=perfect): 43.8% vs. 62.1%; p=0.006 Mean (SD) number of cocaine injections per day in past 4 weeks: 7.9 (8.8) vs. 4.2 (6.3); p<0.001 Mean (SD) number of heroin injections per day in the past 4 weeks: 0.2 (0.5) vs. 0.6 (1.3); p=0.040 Lent needles in past 4 weeks: 35.6% vs. 22.8%; p=0.031 Borrowed needles in past 4 weeks: 50.7% vs. 32.0%; p=0.004 Shared needles with an HIV-positive partner since last visit: 45.2% vs. 13.2%; p<0.0111 Used needle exchange program to obtain clean needles in the past 3 months: 61.6% vs. 45.7%; p=0.018
Camoni et al, 2009[86]	Before-after observational (retrospective)	5 large cities in Italy; infectious disease and sexually transmitted infection clinics; not reported	2006; not applicable	Before HIV diagnosis vs. after HIV diagnosis (at least 2 years after diagnosis)	65.5% male; median age, 40 years (range, 34–45); 85.2% Italian; HIV exposure category: 43.4% heterosexual contact, 27.2% homosexual contact, 20.6% IDU; 52.5% clinical stage A upon enrollment; n=138/253 IDU
Fox et al, 2009[87]	Before-after observational	London, UK; HIV clinic; not reported	January 2002 to January 2004; 3 months	Before HIV diagnosis vs. after HIV diagnosis (at 12 weeks ± 5 days after diagnosis)	96% Caucasian, 1% black Caribbean, 2% Asian, 1% other; median age, 33 years (range, 20–59); 88% had seroconversion symptoms; 26% had STD at HIV diagnosis; 51% had unprotected insertive anal sex with casual partner, 64% had unprotected receptive anal sex with casual partner, 38% ever received payment for sex, 10% had no casual sex partner in past 3 months, 38% had 1–5 casual sex partners in past 3 months, 17% had 6–10 casual sex partners in past 3 months, 35% had >10 casual sex partners in past 3 months

Appendix B9. Key Question 3a: Evidence Table of Studies of Effect of Knowledge of HIV-Positive Status or Use of Highly Active Antiretroviral Therapy on Risky Behaviors

Author, year	Eligibility criteria	Exclusion criteria	Number screened/ eligible/enrolled/ withdrawals/% analyzed	Virologic response	CD4 count response	Adjusted variables for statistical analysis
Amaro et al, 2005[84]	Ages ≥18 years, speaker of English or Spanish, ability to give informed consent, attending 1 of 13 study sites	Exclusively homosexual behavior	1286 eligible; 939 (73%) enrolled, completed pretest questionnaire; 672 completed posttest questionnaire (72% followup rate); 560 analyzed overall; 16 HIV-positive	Not reported	Not reported	Multinomial logistic regression analysis used to examine effects of HIV serostatus and counseling services, sociodemographic, behavioral predictors, on post-HIV test stage of change for condom use with main partners, stratified by stage of change and condom use at pretest
Brogly et al, 2002[85]; Bruneau et al, 2001[88]	Cohort eligibilty: ages ≥14 years, residing in Montreal, having injected drugs in past 6 months, having provided informed consent Current investigation: injected drugs in past 6 months, unaware of HIV-positive status at enrollment Current analysis: aware of HIV diagnosis for at least 1 month before study visit for those testing positive	For particular behavior change analysis, only participants that were aware of their status for relevant amount of time were included (e.g., those who knew of status for past 3 months included for behaviors covering past 3 months) and individuls had to be aware of HIV seropositivity for a minimum of 70% of time period over which behavior change was assesed; only those who could augment or diminish behavior as measured by questionnaire were included; changes in sexual behavior assessed in male subjects only due to small number of females	103 HIV-positive eligible; 73 HIV-positive analyzed, 219 HIV-negative analyzed	Not reported	Not reported	No adjustments
Camoni et al, 2009[86]	Ages ≥18 years, diagnosed at least 2 years prior to study	Not reported	497 eligible; 487 enrolled; 487 analyzed for sexual behavior, 253 analyzed for drug use behavior	Not reported	Not reported	No adjustments
Fox et al, 2009[87]	Men who have sex with men, diagnosed with primary HIV infection	Not reported	104 eligible; 98 analyzed (100% followup)	Not reported	Not reported	No adjustments

Author, year	Outcomes	Adverse events	Funding source and role	Quality rating
Amaro et al, 2005[84]	All HIV-positive participants adopted safer behavior with main and nonmain partners at posttest, indicating that HIV status was the most significant factor determining stage of change for condom use at posttest. Posttest questionnaire given at 3 month followup visit (statistics for this group not reported)	Not reported	Centers for Disease Control and Prevention	Fair
Brogly et al, 2002[85]; Bruneau et al, 2001[88]	Behavior change in IDUs who received positive test result: 26.2% (11/42) stopped injecting, 49.3% (36/73) decreased number of injections by 20%, 62.5% (5/8) decreased injection heroin use, 73.1% (19/26) stopped lending needles, 62.2% (23/37) stopped borrowing needles, 70.6% (12/17) stopped sharing needles with HIV-positive partner, 34.2% (25/73) increased number of needles from needle exchange program by 25%, 37.5% (27/72) increased use of needle exchange program, 50.0% (9/18) of males stopped sexual realtions, 100% (5/5) of men stopped sex work. For majority of behaviors examined, significantly higher proportion of HIV-positive IDUs adopted protective vs. risky behaviors (data not shown). Considering behavior change among HIV-positive individuals only, substantial number of IDUs responded to HIV diagnosis by engaging in lower risk behaviors.	Not reported	National Health Research and Development Program of Health Canada; National Institute of Drug Abuse	Fair

Appendix B9. Key Question 3a: Evidence Table of Studies of Effect of Knowledge of HIV-Positive Status or Use of Highly Active Antiretroviral Therapy on Risky Behaviors

Author, year	Outcomes	Adverse events	Funding source and role	Quality rating
Camoni et al, 2009[86]	Comparing drug use before HIV diagnosis vs. after HIV diagnosis Injecting drug use: yes, n=138 (54.5%) vs. n=82 (32.4%); no, n=114 (45.1%) vs. n=164 (64.8%); no answer, n=1 (0.4%) vs. n=7 (2.8%); McNemar chi=42.9; p<0.0005 Syringe exchange: yes, n=113 (44.7%) vs. n=40 (15.8%); no, n=104 (41.1%) vs. n=160 (63.3%); no answer, n=36 (14.2%) vs. n=53 (20.9%); McNemar chi=53.7; p<0.0005 Comparing sexual behavior before HIV diagnosis vs. after HIV diagnosis Number of sex partners: <2, n=81 (16.6%) vs. n=219 (45.0%); >2, n=405 (83.2%) vs. n=264 (54.2%); no answer, n=1 (0.2%) vs. n=4 (0.8%); McNemar chi=113.47; p<0.0005 Sex for money or drugs: yes, n=64 (13.1%) vs. n=33 (6.8%); no, n=413 (84.8%) vs. n=433 (88.9%); no answer, n=10 (2.1%) vs. n=21 (4.3%); McNemar chi=16.68; p<0.0005 Sex with sex workers: yes, n=78 (16.0%) vs. n=35 (7.2%); no, n=381 (78.25) vs. n=416 (85.4%); no answer, n=28 (5.8%) vs. n=36 (7.4%); McNemar chi=22.37; p<0.0005 Comparing sexual behavior with stable partner and occasional partner before HIV diagnosis vs. after HIV diagnosis Stable partner: yes, n=434 (89.1%) vs. n=377 (77.4%); no, n=53 (10.9%) vs. n=110 (22.6%); McNemar chi=27.75; p<0.0005 Condom use, vaginal sex: always, n=24 (5.5%) vs. n=150 (39.8%); not always/never, n=323 (74.5%) vs. n=122 (32.4%); no answer, n=87 (20.0%) vs. n=105 (27.8%); McNemar chi=118.07; p<0.0005 Condom use, anal sex: always, n=18 (4.1%) vs. n=120 (31.8%); not always/never, n=292 (67.3%) vs. n=126 (33.5%); no answer, n=124 (28.6%) vs. n=131 (34.7%); McNemar chi=86.49; p<0.0005 Condom use, oral-genital sex: always, n=4 (0.9%) vs. n=34 (9.0%); not always/never, n=372 (85.7%) vs. n=273 (72.4%); no answer, n=58 (13.4%) vs. n=70 (18.6%); McNemar chi=26.03; p<0.0005 Occasional partners: yes, n=400 (82.1%) vs. n=283 (58.1%); no, n=87 (17.9%) vs. n=204 (41.9%); McNemar chi=89.11; p<0.0005 Condom use, vaginal sex: always, n=41 (10.3%) vs. n=107 (37.8%); not always/never, n=254 (63.5%) vs. n=65 (23.0%); no answer, n=105 (26.2%) vs. n=111 (39.2%); McNemar chi=65.33; p<0.0005 Condom use, anal sex: always, n=42 (10.5%) vs. n=115 (40.6%); not always/never, n=267 (66.8%) vs. n=91 (32.2%); no answer, n=91 (22.7%) vs. n=77 (27.2%); McNemar chi=68.36; p<0.0005 Condom use, oral-genital sex: always, n=11 (2.7%) vs. n=49 (17.3%); not always/never, n=329 (82.3%) vs. n=188 (66.4%); no answer, n=60 (15.0%) vs. n=46 (16.3%), McNemar chi=31.24, p<0.0005	Not reported	VI Programma Nazionale di Ricerca sull'AIDS 2005	Fair
Fox et al, 2009[87]	Risk for onward transmission: unprotected anal intercourse with regular partner of unknown or negative HIV status, unprotected anal intercourse with casual male partners, or incident sexually transmitted infection Significant changes in risk behavior in the 12 weeks following HIV diagnosis, n=74/98 (76%) posing no risk for onward transmission during that period. Overall shift to fewer sex partners in cohort with 65 men decreasing number of partners, 26 staying same, 7 increasing number (Wilcoxon test Z, -6.302; p<0.001) (visual representation). Proportion always using condoms during receptive anal intercourse with casual partners increased from n=13/76 (17%) to 29/45 (64%) (p<0.001) and for insertive anal intercourse from n=22/72 (31%) to 28/46 (61%) (p<0.01). Paired analysis for receptive anal intercourse showed 23 men increased condom use, 16 stayed the same, 2 used condoms less (Wilcox test Z, -4.097; p<0.001). Paired analysis for insertive anal intercourse showed 15 men increased condom use, 19 stayed the same, 5 reduced use (Wilcox test Z, -2.294; p=0.024). 24 men reported behaviors that posed a continuing risk for transmission to others post-HIV diagnosis, although this group significantly decreased their numbers of sex partners post-diagnosis (14/24 reduced number of partners, 8/24 stayed the same, 2/24 increased number; Wilcox test Z, -2.610; p<0.009)	Not reported	United Kingdom Medical Research Council, UNAIDS	Good

IDU = injection drug user; SD = standard deviation; STD = sexually transmitted disease.

Appendix B10. Key Question 3a: Quality Assessment of Cohort Studies

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified, defined, and ascertained using accurate methods?	Quality rating
Amaro et al, 2005[84]	Yes	Not relevant; pre-post design, one group	Not relevant; pre-post design	Yes	Unclear	Yes	Yes	Yes; 72% followup	Yes	Fair
Brogly et al, 2002[85]; Bruneau et al, 2001[88]	Yes	Not relevant; pre-post design, one group	Not relevant; pre-post design	Yes	Unclear	No	Yes	Unclear; no followup proportion given	Yes	Fair
Camoni et al, 2009[86]	Yes	Not relevant; pre-post design, one group	Not relevant; pre-post design	Yes	Unclear	Not relevant; retrospective	Yes	Not relevant; retrospective	Yes	Fair
Fox et al, 2009[87]	Yes	Not relevant; pre-post design, one group	Not relevant; pre-post design	Yes	Unclear	Yes	Yes	No	Yes	Good

Appendix B11. Key Question 3b: Evidence Table of Studies of Effect of Knowledge of HIV-Positive Status or Use of Highly Active Antiretroviral Therapy on Risky Behaviors

Author, year	Type of study	Location/setting/high or low prevalence population (based on 0.1% prevalence rate)	Study duration/ followup	Comparison groups	Demographics/baseline disease
Del Romero et al, 2010[93]	Cross sectional and prospective cohort	Madrid, Spain; HIV clinic; high; no ART 9.2%, ART 8.7%; 9% HIV prevalence among partners whose index partner was not on ART, 0% in those on ART	1989–2008; 1355 couple-years accrued in prospective cohort	ART vs. no ART	Index cases 83% male; female median age, 29 years; male median age, 32 years; median CD4 count, 500 x 10^9 cells/L (IQR, 295–700); median plasma HIV RNA, 200 copies/mL (IQR, nondetectable to 8876); 54% detectable viral load; median known duration of HIV infection, 29 months (IQR, 3–94)
Diamond et al, 2005[94]	Cross sectional of patients randomly selected for clinic trial	California; HIV clinic; not reported	October 1998 to September 1999; baseline visit data	ART vs. no ART	45% ages <37 years; 88% male; 39% white, 37% Latino, 16% black, 8% Asian/Pacific Islander/American Indian/Alaska native/other; HIV exposure: 62% homosexual sex, 16% heterosexual sex, 10% injection drug use, 9% both homosexual sex and injection drug use, 3% transfusion/other/don't know; 22% current CD4 count 0–199 x 10^9 cells/L, 45% current CD4 count 200–499 x 10^9 cells/L, 32% current CD4 count ≥500 x 10^9 cells/L; 42% recent undetectable viral load; 65% with 1 sex partner in past 3 months, 13% with 2 sex partners in past 3 months, 22% with ≥3 sex partners in past 3 months; 48% sex with main partner only in past 3 months, 46% sex with casual exchange partner in past 3 months, 6% sex with exchange partner in past 3 months; 34% unprotected anal/vaginal intercourse in past 3 months; 79% using ART; 74% taking ≥95% of medication; median time from diagnosis of HIV infection, 6 years (range, 0–18)
Elford et al, 2007[95]; Elford et al, 2006[100]	Cross sectional	London, UK; HIV clinic; 17,000 gay men, 13,000 black African heterosexual men and women with HIV (Elford 2006)	4–6 month period in 2004–2005; once only data	ART use vs. no ART use	Gay men: median age, 39 years (range, 18–72); 85% white; 70.7% on ART; 61.2% undetectable viral load; median CD4 count, 350 x 10^9 cells/L (range, 0–999); 42.5% recreational drug use; median time since diagnosis, 6 years (range, 0–21) Black African heterosexual: median age, 39 years (range, 18–69); 85.5% on ART; 59.2% undetectable viral load; median CD4 count, 150 x 10^9 cells/L (range, 0–999); 0% recreational drug use; median time since diagnosis, 3 years (range, 0–18) Black African heterosexual women: median age, 36 years (range, 18–67); 75% on ART; 62.3% undetectable viral load; median CD4 count, 200 x 10^9 cells/L (range, 0–999); 0.2% recreational drug use; median time since diagnosis, 3 years (range, 0–20) **Significant differences between groups on age, use of ART, CD4 count, years since diagnosis, employment status, education, birth in the U.K., number of years in the U.K., relationship status, knowledge of partner's HIV status, partner's knowledge of index case's HIV status, access to the Internet, use of Internet to look for sexual partners, HIV treatment optimism
Miguez-Burbano et al, 2002[96]	Cross sectional embedded in RCT	Miami; community health and research clinic; not reported	RCT 1998–2001; behavioral questionnaire approved in 2000; RCT cohort followed 1998–2001	ART use vs. no ART use	Mean age, 39.1 years (SD, 6); 57.6% male; 78% African American, 4% Caucasian, 17% Hispanic, 1% other (Haitian); 67% drug use (65% past use of injecting heroin, 46% past use of injecting cocaine); 65% heterosexual, 11% homosexual, 24% bisexual; 91% single, 9% stable partner; 31% not on ART, 47% on ART, 22% on ART but not taking it; 68% diagnosed before 1995, 8% diagnosed after 1999 (range, 1981–2000 [questionnaire approved in 2000])

Appendix B11. Key Question 3b: Evidence Table of Studies of Effect of Knowledge of HIV-Positive Status or Use of Highly Active Antiretroviral Therapy on Risky Behaviors

Author, year	Type of study	Location/setting/high or low prevalence population (based on 0.1% prevalence rate)	Study duration/ followup	Comparison groups	Demographics/baseline disease
Morin et al, 2007[97]	Cross sectional	Various clinics throughout U.S.; Ryan White-funded clinics; not reported	April 2004 to December 2006; baseline interview data	ART vs. no ART	MSM: 51% white, 29% black/African American, 15% Hispanic/Latino, 5% other; 84% homosexual, 13% bisexual, 1% heterosexual, 2% unknown/no answer; 41% ages <39 years, 59% ages >40 years; 15% CD4 count <200 x 10^9 cells/L, 66% CD4 count ≥200 x 10^9 cells/L, 18% unknown CD4 count; 57% most recent viral load undetectable, 33% most recent viral load detectable, 10% most recent viral load unknown/no answer; 14% not currently on ART, 69% currently on ART, 18% unknown/no answer; 40% unprotected anal or vaginal sex in last 6 months; 4% injected any drug in last 30 days Women: 16% white, 68% black/African American, 11% Hispanic/Latino, 4% other; 3% homosexual, 5% bisexual, 89% heterosexual, 3% unknown/no answer; 41% ages <39 years, 59% ages >40 years; 14% CD4 count <200 x 10^9 cells/L, 57% CD4 count ≥200 x 10^9 cells/L, 29% unknown CD4 count; 52% most recent viral load undetectable, 34% most recent viral load detectable, 14% most recent viral load unknown/no answer; 18% not currently on ART, 60% currently on ART, 22% unknown/no answer; 27% unprotected anal or vaginal sex in last 6 months; 3% injected any drug in past 30 days MSW: 15% white, 68% black/African American, 15% Hispanic/Latino, 2% other; <1% homosexual, 2% bisexual, 96% heterosexual, 1% unknown/no answer; 20% ages <39 years, 80% ages >40 years; 19% CD4 count <200 x 10^9 cells/L, 52% CD4 count ≥200 x 10^9 cells/L, 29% unknown CD4 count; 53% most recent viral load undetectable, 36% most recent viral load detectable, 11% most recent viral load unknown/no answer; 11% not currently on ART, 71% currently on ART, 18% unknown/no answer; 20% unprotected anal or vaginal sex in last 6 months; 7% injected any drug in last 30 days; no data on duration of HIV infection
Smit et al, 2006[98]; van Haastrecht et al, 1991[101]	Prospective cohort	Amsterdam; methadone maintenance outposts, sexually transmitted diseases clinic, word of mouth; assumed high prevalence (homosexual drug users in Amsterdam); high; adjusted prevalence rate was 34.1% among IDUs participating in study 1986–1989 (van Haastrecht, 1991)	December 1985 to ongoing Treatment, 8.08 years (range, 4.6–10.2) Control: 7.98 years (range, 4.2–10.0)	ART use vs. no ART use	Treatment: 73% male; mean age, 40 years; 87% methadone users; 51% naive; median CD4 count, 185 x 10^9 cells/L Control: 71% male; mean age, 38 years; 95% methadone users; 58% naive; median CD4 count, 0.200 x 10^9 cells/L; no data on duration of HIV diagnosis
Tun et al, 2004[99]; Vlahov et al, 1991[102]; Vlahov et al, 2001[103]	Before-after derived from prospective cohort	Baltimore; community outreach recruitment; high; 24% in population enrolled from 1988–1989 (Vlahov, 2001)	ALIVE cohort recruitment 1988–1989 and 1994 Present analysis: enrolled July 1996 to November 2000; followup to August 2001, occurrence of behavioral outcome or last study visit (variable durations)	ART vs. no ART	70.5% male; 95.3% African American; median age at ART initiation, 44 years (IQR, 40–47); median CD4 count, 0.260 x 10^9 cells/L (IQR, 0.129–0.358 x 10^9); median HIV RNA level for 64% of sample, 23,709 copies/mL (2,184–10,4544); 20.0% with AIDS diagnosis prior to ART; 66.3% engaged in any sex 1 year prior to ART; 22.1% engaged in unprotected sex 1 year prior to ART; 52.6% injected drugs 1 year prior to ART; 20% shared needles 1 year prior to ART; no data on duration of HIV diagnosis

Appendix B11. Key Question 3b: Evidence Table of Studies of Effect of Knowledge of HIV-Positive Status or Use of Highly Active Antiretroviral Therapy on Risky Behaviors

Author, year	Eligibility criteria	Exclusion criteria	Number screened/ eligible/enrolled/ withdrawals/% analyzed	Virologic response	CD4 count response
Del Romero et al, 2010[93]	All heterosexual couples who had an ongoing sexual relationship over the preceding 6 months, were serodiscordant for HIV, and returned for at least 1 followup visit	Non-index partner with previous HIV diagnosis or known risk exposures other than relationship with index partner	648 eligible; 602 serodiscordant at first visit; 625 analyzed (first visit data); 424 with followup	Detectable viral load in 111/120 (93%) not taking ART vs. 30/145 (21%) taking ART (p<0.001)	Not reported
Diamond et al, 2005[94]	Patients enrolled in trial of clinic-based safer sex interventions at 6 public HIV clinics, ages ≥18 years, HIV infection diagnosed for at least 3 months, sexually active during past 3 months, English or Spanish speaking, and expecting to continue care at clinic for next year	Missing information on unprotected sex (n=1), women who had sex with women only (n=11)	2027 approached; 1840 screened; 1278 eligible; 886 enrolled (69% of patients screened and eligible); 874 analyzed	Not reported	Not reported
Elford et al, 2007[95]; Elford et al, 2006[100]	People ages ≥18 years diagnosed with HIV infection and receiving treatment and care in 6 East London public hospitals. Ineligible = limited command of English, too ill or too distressed to complete questionnaire	Bisexual women, lesbians; analysis included only gay or bisexual men, black African heterosexual men and women (87% of respondents), other groups excluded due to small sample size	2680 screened; 2299 eligible; 1687 completed questionnaire (gay men, n=758; black African heterosexual men, n=224; black African heterosexual women, n=480; response rate, 73% eligible attenders)	Not reported	Not reported
Miguez-Burbano et al, 2002[96]	RCT enrolled HIV-1 infected drug abusers at University of Miami clinic	Not reported	87 screened; 85 enrolled, participated	Among those on ART, men were 7 times less likely to achieve positive virological response (undetectable viral loads after 6 months of treatment) compared with HIV-infected women (95% CI, 1–12.4; p=0.03). No gender differences in viral load for those not on ART	Not reported
Morin et al, 2007[97]	HIV-infected status, receipt of primary care at clinic, ages ≥18 years, ability to provide informed consent.	Transgendered individuals	# screened not reported; # eligible not reported; 4016 enrolled: n=2109 (52.5%) MSM; n=1104 (27.5%) women; n=803 (20.0%) MSW	Not reported	Not reported

Appendix B11. Key Question 3b: Evidence Table of Studies of Effect of Knowledge of HIV-Positive Status or Use of Highly Active Antiretroviral Therapy on Risky Behaviors

Author, year	Eligibility criteria	Exclusion criteria	Number screened/ eligible/enrolled/ withdrawals/% analyzed	Virologic response	CD4 count response
Smit et al, 2006[98]; van Haastrecht et al, 1991[101]	HIV-positive homosexual drug users Treatment: use of ART regimen, including a combination of ≥2 antiretrovirals with ≥1 protease inhibitor or nonnucleoside reverse transcriptase inhibitor	Not reported	202 screened; 68 eligible; 67 enrolled on ART, 130 not on ART	During first 1.5 months after ART initiation, strong decline seen in HIV RNA levels among IDUs on ART and homosexual men on ART. Differed significantly from IDUs not on ART. After 1.5 months, decrease in HIV RNA was not significant in either ART group and increased nonsignicantly in IDUs on ART.	In first 3 months after therapy initiation, CD4 cell counts increased significantly in both ART- treated IDUs and homo-sexual men. After 3 months, CD4 cell counts continued to increase significantly among ART-treated homosexual men, remained stable among IDUs. CD4 cell counts contin-ued to decrease significantly among IDUs not on ART but slope differences compared with IDUs on ART were insignificant.
Tun et al, 2004[99]; Vlahov et al, 1991[102]; Vlahov et al, 2001[103]	ALIVE cohort participants had to be ages >18 years, report history of illicit drug injection within previous 11 years, and be AIDS-free at time of enrollment Present analysis: Initiated ART between July 1996 and November 2000, had CD4 count obtained at visit immediately prior to ART initiation, had at ≥1 semiannual visit after ART initiation	Present analysis included those starting ART between July 1996 and November 2000 with CD4 count data for visit prior to ART inititiation and 1 visit after ART initiation, others excluded	3360 enrolled in cohort; 693 HIV-positive enrolled 1996–2000; 276 initiated ART during study period; 190 analyzed	Not reported	Not reported

Author, year	Adjusted variables for statistical analysis	Outcomes	Adverse events	Funding source and role	Quality rating
Del Romero et al, 2010[93]	No adjustments	Proportion engaging in unprotected sexual intercourse in past 6 months, no ART vs. ART 273/476 (57%) vs. 69/149 (46%); p=0.019 Proportion of couples with previous pregnancies, no ART vs. ART 226/476 (47%) vs. 53/149 (36%); p=0.011 Characteristics of couples and events during followup based on ART of index partner, no treatment vs. mono/dual therapy vs. combined treatment Couples with unprotected sexual contacts: n=187 (55%) vs. n=24 (51%) vs. n=101 (70%) Couples with unprotected penile-anal contacts: n=13 vs. n=4 vs. n=11 Estimated number of risky sexual exposures: 11,000 vs. 1600 vs. 7400 **Sexual risk exposures include penile-vaginal or penile-anal contacts without a condom and condoms breaking or slipping during intercourse	Not reported	Grant from FIPSE (foundation formed by Spanish Ministry of Health and Consumer Affairs and multiple pharmaceutical companies), and Spanish Network for Research on AIDS	Fair

Appendix B11. Key Question 3b: Evidence Table of Studies of Effect of Knowledge of HIV-Positive Status or Use of Highly Active Antiretroviral Therapy on Risky Behaviors

Author, year	Adjusted variables for statistical analysis	Outcomes	Adverse events	Funding source and role	Quality rating
Diamond et al, 2005[94]	Age, sex, race, HIV exposure category, years since HIV diagnosis, current CD4 count, number of sex partners in past 3 months, type of sex partners in past 3 months, use of illicit drugs or alcohol in past 3 months, depression and health beliefs, clinical site, frequency of missed appointments, duration of clinic attendance	Unprotected anal or vaginal sex: anal or vaginal intercourse without a condom within past 3 months. Amphetamine use variable included any route, including injection. Proportion engaging in unprotected sexual intercourse, ART vs. no ART 215/689 (31%) vs. 86/185 (46%); OR, 0.5 (95% CI, 0.4–0.7), p<0.001 Proportion engaging in unprotected sexual intercourse with ART adherence data, >95% ART adherence vs. <95% ART adherence 142/683 (28%) vs. 72/175 (41%); OR, 0.6 (95% CI, 0.4–0.8); p<0.001 Stratified analysis results: ART was significantly associated with decreased unprotected anal and vaginal intercourse across ages and sexes in whites, Latinos, MSM, and injection drug users, those diagnosed with HIV for <4 or >8 years, those with CD4 counts >200 x 10^9 cells/L, those with detectable viral loads, 1 sexual partner in past 3 months, main and casual sex partners in past 3 months, no use of marijuana, amphetamines, or nitrates (OR and CI available for these associations, more variables described in Table 3) **Among those with exchange partners, unprotected intercourse was higher in those on ART than not on ART, only such group but nonsignificant result Multivariate analysis: negative relationship between ART use and unprotected intercourse remained after adjusting for race/ethnicity, marijuana use, alcohol use, symptomatic depression, clinic site, duration of clinic attendance (adjusted OR, 0.70 [95% CI, 0.50–1.0] p<0.04)	Not reported	Supported by National Institute of Mental Health grant, California Collaborative Treatment Group funded by universitywide AIDS research program of State of California, CDC, NCI grant	Fair
Elford et al, 2007[95]; Elford et al, 2006[100]	Age, number of years since diagnosis, CD4 count, employment, education, relationship, ART use, viral load, recreational drug use, seeking sex through Internet, HIV optimism (no significant differences found between black African heterosexual men and women on any sexual behavior outcomes [p>0.3], so combined for analysis)	Alpha=0.01. Unprotected intercourse: vaginal or anal intercourse without a condom in previous 3 months. In multivariate analysis, no significant association found between being on ART and unprotected intercourse with a casual partner of unknown or negative HIV status among gay men (p>0.01); in multivariate model, no variables other than seeking sex through Internet and recreational drug use were associated with unprotected intercourse with a casual partner who was HIV-positive among gay men (p>0.1); in multivariate analysis, no variables associated with unprotected intercourse with main partner of unknown or negative HIV status among gay men (p>0.1); in multivariate analysis there was no significant association between any variables and unprotected intercourse with main partner who was HIV-positive, -negative, or unknown for African men and women (p>0.05); abstract: neither viral load nor being on ART were significantly associated with unprotected intercourse among gay men or black African heterosexual men and women (p>0.05)	Not reported	Sponsorship: St. Bartholomew's and the Royal London Charitable Foundation Research Advisory Board, City University London, Institute of Health Sciences, St. Bartholomew School of Nursing and Midwifery	Fair
Miguez-Burbano et al, 2002[96]	Unclear; states that multivariate analysis was performed but no details	Risk-taking behavior and HIV treatment Contaminated needles used by 18 participants; 85% of this group was receiving ART Men receiving ART tended to have unprotected anal sex compared with those not on ART; OR, 2 (95% CI, 0.47–11.73; p=0.067)	Not reported	NIDA, NIH-Fogarty	Fair

Appendix B11. Key Question 3b: Evidence Table of Studies of Effect of Knowledge of HIV-Positive Status or Use of Highly Active Antiretroviral Therapy on Risky Behaviors

Author, year	Adjusted variables for statistical analysis	Outcomes	Adverse events	Funding source and role	Quality rating
Morin et al, 2007[97]	For transmission risk acts: sexual identity, education, age, employment, alcohol use, stimulant use, ART use, race Results separated by sex (CD4 count and viral load were not associated with risk in univariate analysis, so not used in multivariate)	Sexual behavior over 6-month period Unprotected sex: any act of insertive or receptive anal or vaginal intercourse in which a participant did not use a condom Predictors of transmission risk sex, ART vs. no ART MSM: transmission rate, 19% vs. 28%; adjusted OR, 0.73 (95% CI, 0.54–1.00); p=0.05 Women: transmission rate, 14% vs. 21%; adjusted OR, 0.75 (95% CI, 0.49–1.16); p=0.19 MSW: transmission rate, 10% vs. 12%; adjusted OR, 0.81 (95% CI, 0.39–1.67); p=0.56	Mathematical modeling analyses among 4016 participants with HIV: total infections, 36.6; mean infections per participant, 0.009; infections per sexually active participant, 0.012	Health Resources and Services Administration Special Projects of National Significance Program grant	Fair
Smit et al, 2006[98]; van Haastrecht et al, 1991[101]	No adjustments	At reference visit, 42% of ART users had injected drugs since previous visit, declining to 30% by third visit. At reference visit, 61% of nonART users had injected drugs since previous visit, declining to 44% by third visit. The proportion of IDUs that reported injecting drugs was significantly lower among ART users than nonART users at all visits (p<0.05), except the last 2. Modelled piecewise, ART users and nonART users showed nonsignificant declines in injecting drugs over time, which did not change after ART initiation. At reference visit, 15% of ART users and 13% of nonART users had engaged in unprotected sex. Significant differences between ART users and nonusers were seen at every visit (p<0.05). ART users reported significantly more unprotected sex than nonART users at reference visit, visit prior, and visit after reference visit (p<0.05). Modelled piecewise, sexual risk behavior nonsignificantly increased before ART initiation (OR, 1.67 per year [95% CI, 0.98–2.83]; p=0.06), and changed after initiation, nonsignificantly (OR, 0.33 per year [95% CI, 0.10–1.08]; p=0.07). Sexual risk behavior did not change over time for nonART users.	Not reported	Netherlands Organization for Health Research and Development; Ministry of Health, Welfare, and Sport; and the Dutch AIDS Fund	Fair
Tun et al, 2004[99]; Vlahov et al, 1991[102]; Vlahov et al, 2001[103]	Change in CD4 count from baseline, baseline CD4 count at visit prior to ART initiation, AIDS diagnosis prior to ART initiation, engaging in relevant risk behavior in the year prior to ART initiation or year of ART initiation, age at ART initiation, biological sex. Some analyses adjusted for past behavior	Unprotected sexual intercourse: engaging in vaginal or anal sex without using a condom (assessed in preceeding 6 months of each semiannual visit). Proportion of participants who engaged in any sexual intercourse (66.3%–71.6%), unprotected sex (22.9%–26.2%), any drug injection (52.7%–49.0%), and/or needle sharing (20%–26.3%) remained stable or increased slightly from before to after ART initiation, not significant (figure shows proportion who initiated, discontinued, or continued each behavior); at individual level, about 6%–11% discontinued any 1 of the behaviors and about 7%–14% initiated any 1 of the behaviors after starting ART, about 80% continued same behaviors before and after ART Unprotected sex: 26.3% had engaged in unprotected sex after ART initiation, 48% of whom had not engaged in unprotected sex in year prior to ART initiation Drug injection: after followup, 48.9% reported injecting drugs, 15.1% of whom had not injected drugs in year prior to ART initiation; 26.3% shared needles after ART, 52% of whom had not shared needles in year prior to ART	Not reported	National Institute on Drug Abuse grants and National Research Service Award from National Institute of Mental Hygiene	Fair

ART = antiretroviral therapy; CDC = Centers for Disease Control and Prevention; CI = confidence interval; IDU = injection drug user; IQR = interquartile range; MSM = men who have sex with men; MSW = men who have sex with women; NCI = National Cancer Institute; NIDA = National Institute on Drug Abuse; NIH = National Institutes of Health; OR = odds ratio; RCT = randomized, controlled trial; SD = standard deviation.

Appendix B12. Key Question 3b: Quality Assessment of Cohort Studies

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Was there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified, defined, and ascertained using accurate methods?	Quality rating
Del Romero et al, 2010[93]	Yes	No	Not relevant, cross sectional	Yes	Unclear	Not relevant, cross sectional	No	Not relevant, cross sectional	Yes	Fair
Diamond et al, 2005[94]	Yes	Unclear	Not reported	Yes	Unclear	Not reported	Yes	No	Yes	Fair
Elford et al, 2007[95]	Yes	Unclear	Not reported	Yes	Unclear	Not reported	Partially	No	Yes	Fair
Miguez-Burbano et al, 2002[96]	Yes	Unclear	Not relevant, cross sectional	Yes	Unclear	Not relevant, cross sectional	Unclear, states multivariate analysis was performed but no details	Not relevant, cross sectional	Yes	Fair
Morin et al, 2007[97]	Yes	Unclear	Not reported	Yes	Unclear	Not reported	Yes	No	Yes	Fair
Smit et al, 2005[98]	Yes	Yes	Yes	Yes	Unclear	No	Partially	Unclear	Yes	Fair
Tun et al, 2004[99]	Yes	Not reported	Not reported	Yes	Unclear	No	Yes	Unclear	Yes	Fair

Appendix B13. Key Question 4a: Evidence Table of a Systematic Review of Effects of Counseling or Antiretroviral Therapy Use on HIV Transmission

Author, Year	Purpose of study	Databases searched, date of last search	Number of studies	Types of studies included/ limitations of primary studies	Methods for rating methodological quality of primary studies	Methods for synthesizing results of primary studies	Number of patients (treatment and control)	Interventions	Results	Adverse events	Quality rating
Anglemyer et al, 2011[108]	To determine if ART use by the HIV-infected partner in a serodiscordant relationship is associated with lower risk for transmission to the uninfected partner	PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science, LILACS, Aegis archive of conference abstracts, CROI, International AIDS Society Web site Last search: February 1, 2011	8	1 RCT and 7 cohorts; limited by small numbers of transmissions; only 3 included studies adjusted odds ratios for age, sex, or frequency of sex; only 4 studies described loss to followup	Quality rating assessed randomization, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases	Data pooled using fixed and random-effects models. Heterogeneity assessed using subgroup analyses, and sensitivity analysis performed to identify outlying studies	11,478 serodiscordant couples	Use of antiretroviral drugs in HIV-infected members of serodiscordant couples	ART vs. no ART Total seroconversions: 71 vs. 365; pooled HR, 0.34 (95% CI, 0.13–0.92); adjusted HRs, 0.16 (95% CI, 0.07–0.35) after removing studies responsible for statistical heterogeneity, 0.06 (95% CI, 0.01–0.54) after restricting analysis to couples in which HIV-infected partner had CD4 count <200 x 10^9 cells/L, 0.02 (95% CI, 0.00–0.89) in couples in which index case was male, 0.24 (95% CI, 0.06–1.03) in couples residing in low-/middle-income countries	Not reported	Good

ART = antiretroviral therapy; HR = hazard rate; RCT = randomized, controlled trial.

Appendix B14. Key Question 4a: Quality Assessment of a Systematic Review

Study, Year	A priori design provided?	Duplicate study selection and data extraction?	Comprehensive literature search performed?	Status of publication used as an inclusion criteria?	List of studies (included and excluded) provided?	Characteristics of included studies provided?	Scientific quality of included studies assessed and documented?	Scientific quality of included studies used appropriately in formulating conclusions?	Methods used to synthesize the findings of studies appropriate?	Likelihood of publication bias assessed?	Conflict of interest stated?	Quality rating
Anglemyer et al, 2011[108]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Systematic review: yes Individual studies: no	Good

Appendix B15. Key Question 4a: Evidence Table of Studies of Effects of Counseling or Antiretroviral Therapy Use on HIV Transmission

Author, Year	Type of study	Location/setting/ high or low prevalence population (based on 0.1% prevalence rate)	Study duration/ followup	Treatment groups (or comparision groups if observational study)	Demographics/ baseline disease	Eligibility criteria	Exclusion criteria	Number screened/eligible/ enrolled/withdrawals/ % analyzed
Cohen et al, 2011[109]	RCT	Botswana, Kenya, Malawi, South Africa, Zimbabwe, India, Brazil, Thailand, and United States	Median followup, 42 months	Treatment: immediate ART Comparison: delayed ART initiated after decline in CD4 count to ≤250 x 10^9 cells/mL or onset of AIDS-related illness	61% of participants ages 26 to 40 years Median CD4 count: 0.442 x 10^9 cells/L for early-therapy group, 0.428 x 10^9 cells/L for delayed therapy group	Couples in which 1 partner was HIV-1 positive and the other negative; CD4 counts 0.350–0.550 x 10^9 cells/L; in a stable relationship for ≥3 months; reported ≥3 instances of vaginal or anal intercourse; willing to disclose serostatus to partner	HIV-positive participants who had previously received ART (with exception of short-term prevention of mother-to-child transmission)	10,838 screened; 1763 couples enrolled
Del Romero et al, 2010[93]	Prospective cohort	Madrid, Spain; HIV clinic; high prevalence (no ART: 9.2%, ART: 8.7%)	1355 couple-years	ART vs. no ART	Index cases 83% male; women median age, 29 years; men median age, 32 years;, median CD4 count, 0.500 x 10^9 cells/L (IQR, 0.295–0.700 x 10^9); median pasma HIV RNA, 200 copies/mL (IQR, ND to 8876); 54% detectable viral load	All heterosexual couples who had an ongoing sexual relationship over preceding 6 months, were serodiscordant for HIV, and returned for ≥1 followup visit	Nonindex partner with previous HIV diagnosis or known risk exposures other than relationship with index partner	648 eligible; 602 serodiscordant at first visit; 424 with followup
Donnell et al, 2010[110]	Pre-post analysis of prospective cohort data	14 sites in 7 African countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia)	Median study duration at ART initiation, 13 months	PreART transmission vs. postART transmission	HIV-infected partner vs. HIV-susceptible partner Mean age: 32 vs. 33 years Female sex: 68% vs. 32% HSV-2 positive: 100% vs. 68%	HIV-1 and HSV-2 serodiscordant couples reporting ≥3 episodes of vaginal intercourse during previous 3 months, with seropositive partner ages ≥18 years, CD4 count ≥0.250 x 10^9 cells/L	History of AIDS-defining condition, receiving ART	3408 enrolled; 3381 analyzed Note: 27 couples' baseline serology did not confirm HIV-1 and HSV-2
Goncalves Melo et al, 2008[111]	Retrospective cohort	Urban HIV/AIDS referral center in Porto Alegre, Brazil; assumed high prevalence	Median followup transmitters: 25.5 months nontransmitters: 22.3 months	Transmitters vs. nontransmitters	72% women (index cases); 57.7% IDUs; 91% unprotected sex; 23.6% STD diagnosis	ART-naive HIV-1 infected people with uninfected, steady, opposite-sex partners	None	4500 screened retrospectively; 56 enrolled retrospectively and 37 enrolled prospectively (93 total enrolled)
Musicco et al, 1994[107]	Prospective cohort	Multicenter; Italy; assumed high prevalence (high risk)	Mean followup, 2 years (740 person-years)	Zidovudine vs. no zidovudine	Mean age, 26 years; 100% female; median duration of relationship with HIV-positive partner, 3 years; 56% consistent condom use; 53% regular sexual intercourse; 15% anal sex; 48% oral sex	Serodiscordant women identifyed through partner's attendance at specialty clinic with ≥1 followup visit	None	Not reported; 525 eligible; 436 enrolled; unclear; unclear Data from 103 person-years excluded

Appendix B15. Key Question 4a: Evidence Table of Studies of Effects of Counseling or Antiretroviral Therapy Use on HIV Transmission

Author, Year	Type of study	Location/setting/ high or low prevalence population (based on 0.1% prevalence rate)	Study duration/ followup	Treatment groups (or comparision groups if observational study)	Demographics/ baseline disease	Eligibility criteria	Exclusion criteria	Number screened/eligible/ enrolled/withdrawals/ % analyzed
Reynolds et al, 2011[112]	Retrospective cohort	Multicenter; Rakai, Uganda; high prevalence	Median followup Before ART initiation: 1.57 years After ART initiation: 1.54 years	PreART transmission vs. postART transmission	Male index partner: 58% (142/250) Consistent condom use: 4% Polygamous husbands: 20%	HIV-1 discordant married couples	None	15,000 screened; 250 eligible; 250 enrolled
Sullivan et al, 2009[113]	Retrospective cohort	Rwanda and Zambia	Median followup, 512 days (1.4 years)	ART vs. no ART	Not reported	HIV-serodiscordant couples	Not reported	2993 enrolled
Wang et al, 2010[114]	Retrospective cohort	Multicenter, community-based in Henan Province, China; assumed high prevalence (high risk)	Median followup, 2.8 years	ART vs. no ART	Mean age, 44 years; 43% female; 84% regular sexual intercourse; 78% condom use; 99% monogamous	Serodiscordant couples; stable marriage with no separation or divorce; voluntary participation and provided informed consent	None	4348 screened; 4301 eligible; 1927 enrolled; no withdrawals; 100% analyzed

Author, Year	Virologic response	CD4 count response	Outcomes	Adverse events	Funding source and role	Quality rating
Cohen et al, 2011[109]	Virologic failure, treatment vs. comparison 45/886 (5%) vs. 5/184 (3%); p=0.23	Treatment: 0.442 x 10^9 cells/L at enrollment to 0.603 x 10^9 cells/L at 12 months Comparison: 0.428 x 10^9 cells/L at enrollment to 0.399 x 10^9 cells/L at 12 months	Transmission events, treatment vs. comparison 4 events (IR, 0.3 per 100 person-years [95% CI, 0.1–0.6]) vs. 35 events (IR, 2.2 per 100 person-years [95% CI, 1.6–3.1]); HR, 0.11 (95% CI, 0.04–0.32); p<0.001 Total clinical events, treatment vs. comparison HR, 0.59 (95% CI, 0.40–0.88) Linked transmission, treatment vs. comparison HR, 0.04 (95% CI, 0.01–0.28); p<0.001	Severe or life-threatening adverse events, treatment vs. comparison 127/886 (14%) vs. 119/877 (14%); NS Most frequent adverse events: infections, psychiatric and nervous system disorders, and gastrointestinal disorders Grade 3 or 4 laboratory abnormalities, treatment vs. comparison 242/886 (27%) vs. 161/877 (18%); p<0.001 Most frequent laboratory abnormalities: neutropenia, abnormal phosphate levels, bilirubin elevations	National Institute of Allergy and Infectious Diseases	Good
Del Romero et al, 2010[93]	Detectable viral load in 111/120 (93%) not taking ART vs. 30/145 (21%) on ART; p<0.001	Not reported	Proportion engaging in unprotected sexual intercourse, no ART vs. ART 273/476 (57%) vs. 69/149 (46%); p=0.019 Proportion of couples with previous pregnancies, no ART vs. ART 226/476 (47%) vs. 53/149 (36%); p=0.011 Transmission, no ART vs. ART 5 instances vs. 0 instances Rate per 100 couple-years, no ART vs. ART 0.4 (95% CI, 0.2–1.4) vs. 0 (95% CI, 0–1.1)	Not reported	Grant from FIPSE (foundation formed by Spanish Ministry of Health and Consumer Affairs and multiple pharmaceutical companies) and Spanish Network for Research on AIDS	Fair

Appendix B15. Key Question 4a: Evidence Table of Studies of Effects of Counseling or Antiretroviral Therapy Use on HIV Transmission

Author, Year	Virologic response	CD4 count response	Outcomes	Adverse events	Funding source and role	Quality rating
Donnell et al, 2010[110]	Not reported	Not reported	PreART vs. postART transmission Overall: 102/4558 person-years (IR, 2.24 [95% CI, 1.84–2.72]) vs. 1/273 person-years (IR, 0.37 [95% CI, 0.09–2.04]) Overall adjusted incidence RR: 0.08 (95% CI, 0.00–0.57); p=0.004	Not reported	Bill & Melinda Gates Foundation; University of Washington Center for AIDS Research; University of Washington AIDS Clinical Trials Group Virology Support Laboratory; US National Institutes of Health	Good
Goncalves Melo et al, 2008[111]	Not reported	Not reported	Transmissions, ART vs. no ART 0/41 vs. 6/52 Median viral load, transmitters vs. nontransmitters 24,082 (range, 1479–100,539) vs. 4583 (range, 78–47,974); p=0.042	Not reported	Not reported	Fair
Musicco et al, 1994[107]	Not reported	Not reported	Seroconversions, zidovudine vs. no zidovudine 6/64 (3.8/100 person-years) vs. 21/? (4.4/100 person-years); adjusted RR, 0.5 (95% CI, 0.1–0.9)	Not reported	Ministry of Health, Italy; National Research Council of Italy	Fair
Reynolds et al, 2011[112]	6 months: 71.4% (20/28) below detectable limit and remaining 28.6% (8/28) below 2000 copies/mL 12 months: 85.2% (23/27) below 400 copies/mL, 14.8% (4/27) ranging from 2293 to 672,513 copies/mlL 24 months: 100% (28/28) below 400 copies/mL	Not reported	Transmission PreART: 9.2/100 person-years (95% CI, 6.59–12.36) PostART: 0/53.6 person-years (95% CI, -1.91 to 16.38); p=0.0097	Not reported	Division of Intramural Research, National Instutute of Allergy and Infectious Diseases; Eunice Kennedy Shriver National Instutute of Child Health and Human Development	Fair
Sullivan et al, 2009[113]	Not reported	Not reported	Transmissions, ART vs. no ART 4/175 vs. 171/175 Incidence density, ART vs. no ART 0.7%/100 person-years vs. 3.4%/100 person-years (RR, 0.21 [95% CI, 0.08–0.59]) Hazard of infection, ART vs. no ART HR, 0.21 (95% CI, 0.09–0.52)	Not reported	Not reported	NA

Appendix B15. Key Question 4a: Evidence Table of Studies of Effects of Counseling or Antiretroviral Therapy Use on HIV Transmission

Author, Year	Virologic response	CD4 count response	Outcomes	Adverse events	Funding source and role	Quality rating
Wang et al, 2010[114]	Not reported	Not reported	Seroconversions, ART vs. no ART 66/1369 (4.8%) vs 18/558 (3.2%); univariate RR, 0.76 (95% CI, 0.45–1.28)	Not reported	China and Fogarty International Center; National Institutes of Health, Office of the Director, Office of AIDS Research; National Cancer Center; National Eye Institute; National Heart, Blood, and Lung Institute; National Institute of Dental and Craniofacial Research; National Institute on Drug Abuse; National Institute of Mental Health; National Institute of Allergy and Infectious Diseases Health	Fair

ART = antiretroviral therapy; CI = confidence interval; HR = hazard rate; HSV-2 = herpes simplex virus 2; IDU = injection drug user; IR = incidence rate; IQR = interquartile range; NA = not applicable; RCT = randomized, controlled trial; RR = relative risk; STD = sexually transmitted disease.

Appendix B16. Key Question 4a: Quality Assessment of a Randomized, Controlled Trial

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup differential or high?	Intention-to-treat analysis?	Quality rating	Funding
Cohen et al, 2011[109]	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Differential: no High: no	Yes	Good	National Institute of Allergy and Infectious Diseases

Appendix B17. Key Question 4a: Quality Assessment of Cohort Studies

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified, defined, and ascertained using accurate methods?	Quality rating
Del Romero et al, 2010[93]	Yes	No	Yes	Yes; questionnaire, blood draw	Unclear	No	No	No	Yes	Fair
Donnell et al, 2010[110]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Goncalves Melo et al, 2008[111]	Unclear	No	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Musicco et al, 1994[107]	Yes	No; zidovudine patients had more advanced disease	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
Reynolds et al, 2011[112]	Unclear	No; condom use	Not relevant; retrospective	Yes	Unclear	Not relevant; retrospective	Yes	Not relevant; retrospective	Yes	Fair
Wang et al, 2010[114]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	No	Yes	Fair

Note: Sullivan et al, 2009[113] is omitted from this table because it is only available as an abstract.

Appendix B18. Key Question 4b: Evidence Table of Studies of Effects of Counseling or Antiretroviral Therapy Use on HIV Transmission

Author,year, study name	Type of study	Location/setting/high or low prevalence population (based on 0.1% prevalence rate)	Study duration/ followup	Treatment groups (or comparision groups if observational study)	Demographics/ baseline disease	Eligibility criteria
El-Bassel et al, 2010[117]; NIMH Multisite HIV/STD Prevention Trial for African American Couples Group, 2008[116]	Cluster RCT	Not reported	8 week duration; 12 month followup	Treatment: 8 weekly 2-hour sessions of couple-focused counseling intervention incorporating traditional African concepts with social cognitive theory and other elements of interventions found to be efficacious Comparison: individual-focused health promotion intervention	Mean age, 43.4 years Mean CD4 count, 0.526 x 10^9 cells/L % viral load >50 copies/mL, 29%	Couples in which both partners were age 18 or older, in a relationship for 6 months, intended to remain together for at least 12 months, ≥1 instance of unprotected intercourse in previous 90 days, no plans to relocate from study site, ≥1 partner African American or black, not planning pregnancy within 18 months, aware of each other's serostatus, 1 partner is HIV+ and has known for at least 3 months
Hernando et al, 2009[118]	Prospective cohort of serodiscordant dyads	Multidisciplinary clinic providing HIV/STD counseling, diagnosis, and treatment in Madrid, Spain	1989–2007, 1279 couple-years; mean followup, 3.2 years, median followup, 2.1 years	Pre-post study of counseling intervention including comprehensive medical consultation, HIV and STD testing, free condoms, risk counseling	56.7% with CD4 count >0.350 x 10^9 cells/L Median viral load, 405 copies/mL 82.3% of index cases were male Mean age of index case, 29.4 years for women and 32.9 years for men 30.3% receiving antiretrovirals	Heterosexual couples in an uninterrupted relationship for at least 6 months, in which 1 member was diagnosed with HIV and the nonindex partner was HIV-negative, who returned for at least 1 followup visit

Author, year, study name	Exclusion criteria	Number screened/eligible/ enrolled/withdrawals/ % analyzed	Virologic response	CD4 count response	Outcomes	Adverse events	Funding source and role
El-Bassel et al, 2010[117]; NIMH Multisite HIV/STD Prevention Trial for African American Couples Group, 2008[116]	No mailing address; clinically significant psychiatric, physical, or neurological impairment; victim of severe intimate partner violence; unwilling to complete study; not fluent in English; or participated in a couples-based HIV/STD risk-reduction intervention in the past year	589 couples eligible; 535 couples randomized	Not reported	Not reported	<u>HIV risk behaviors, adjusted for baseline response, over entire followup</u> Proportion of condom-protected sex: RR, 1.24 (95% CI, 1.09–1.41; p=0.006) Consistent condom use: RR, 1.45 (95% CI, 1.24–1.7; p<0.001) Mean difference in number of (log) unprotected intercourse acts: -1.52 (95% CI, -2.07 to -0.98; p<0.001) <u>HIV transmissions</u> Treatment: 2 seroconversions Comparison: 3 seroconversions	Not reported	National Institute of Mental Health
Hernando et al, 2009[118]	Index partner with other sexual partners	564 eligible; 399 returned for followup	Not reported	Not reported	Total number of coital relations: IQR, 24–84 vs. 24–72 (p=0.001) Median sexual risk practices: 2.6 (IQR, 0–31.7) vs. 0 (IQR, 0–11.1) (p<0.001) Systematic condom use: 49.4% vs. 68.9% (p<0.0001) Transmission: 5/399 (1.3%), HIV seroconversion rate 3.9 per 1000 couple-years (95% CI, 1.4–9.7). None took place in couples where index case was on antiretroviral therapy	Not reported	Grant from FIPSE (foundation formed by Spanish Ministry of Health and Consumer Affairs and multiple pharmaceutical companies) and Spanish Network for Research on AIDS

RCT = randomized, controlled trial; STD = sexually transmitted disease.

Appendix B19. Key Question 4b: Quality Assessment of a Randomized Controlled Trial

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup differential or high?	Intention-to-treat analysis	Quality rating	Funding
El-Bassel et al, 2010[117]	Yes	Yes	Yes	Yes	Unclear	No (not possible)	No (not possible)	Yes	Differential: no High: no	Yes	Good	National Institute of Mental Health

Appendix B20. Key Question 4b: Quality Assessment of a Cohort Study

Author, Year	Did study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were groups comparable at baseline on key prognostic factors (by restriction or matching)?	Did study maintain comparable groups through the study period?	Did study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did article report attrition?	Did study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified, defined, and ascertained using accurate methods?	Quality rating
Hernando et al, 2009[118]	Yes	Yes	No; participants who didn't return for second visit older, in longer relationships, used condoms less, fewer noninjection drug users, more ART use	Yes	Unclear	Not relevant	Yes	Not relevant	Yes	Fair

Appendix B21. Key Question 4c: Evidence Table of Trials of Effect of Initiating Highly Active Antiretroviral Therapy at Different CD4 Counts or Viral Load Thresholds on Clinical Outcomes

Author, Year	Study name	Type of study	Location/setting	Duration of followup	Treatment groups	Population characteristics	Inclusion criteria
Cohen et al, 2011[109]	HIV Prevention Trials Network study 052	RCT	Botswana, Kenya, Malawi, South Africa, Zimbabwe, India, Brazil, Thailand, and United States	Median, 42 months	Delayed treatment: initiation after 2 consecutive measures of CD4 count of ≤0.250 x 10^9 cells/mL or at onset of AIDS-related illness (n=877) Early treatment: immediate initiation of ART at CD4 count of 0.350 to 0.550 x 10^9 cells/mL (n=886)	n=1763 serodiscordant couples (HIV+ participants: n=886 early treatment, 877 delayed treatment) Mean age not reported; 61% of participants ages 26 to 40 years Median CD4 count, 0.442 x 10^9 cells/L for early-therapy group, 0.428 x 10^9 cells/L for delayed therapy group	Couples in which 1 partner is HIV-1 positive and other is negative; CD4 counts of 0.350 to 0.550 x 10^9 cells/L; in a stable relationship for at least 3 months; reported 3 or more instances of vaginal or anal intercourse; willing to disclose serostatus to partner
Severe et al, 2010[130]	Study not named	Open-label RCT	Haiti; single specialty clinic (Haitian Group for the Study of Karposi's Sarcoma and Opportunistic Infections [GHESKIO])	Mean, 21 months (range, 1–44 months)	Early treatment (CD4 count 0.201–0.350 x 10^9 cells/L) (n=408): lamivudine 150 mg + zidovudine 300 mg bid, efavirenz 600 mg qd Standard treatment (n=408): same intervention as early treatment group, started when CD4 count ≤0.200 x 10^9 cells/L	n=816 Mean age not reported, median age 40 years 58% female Median CD4 count, 0.281 x 10^9 cells/L	Age >18 years, HIV-infected, confirmed CD4 count >0.200 x 10^9 cells/L and <0.350 x 10^9 cells/L within 45 days before enrollment
SMART Study Group, 2008[131] Other publication: SMART Study Group, 2006[138]	Strategies for Management of Antiretroviral Therapy Study Group (SMART Study)	RCT (subgroup analysis)	United States/Europe; multicenter	Mean, 18 months (median, 15 months)	Intermittent ART-drug conservation group: CD4 count <0.250 x 10^9 cells/L or CD4 percentage <15% or symptomatic (n=131 ART naive) Continuous ART-viral supression group: CD4 count >0.350 x 10^9 cells/L (n=118 ART naive)	n=477 (249 ART naive; 228 no ART) Median age, 41 years 26% female 49% white, 36% black, 15% other Median CD4 count, 0.447 x 10^9 cells/L (range, 0.385–0.536 x 10^9)	ART naive or no use of ART for a minimum of 6 months prior to study entry; at least 1 HIV RNA measure and level at least >10,000 copies/mL

Author, Year	Exclusion criteria	Number screened/ eligible/enrolled/ withdrawals/% analyzed	Clinical outcomes	Adverse events	Funding source and role	Quality rating
Cohen et al, 2011[109]	Previous ART (with the exception of short-term prevention of mother-to-child transmission)	10,838 screened; 1763 couples enrolled	Mortality Delayed treatment, 13/877 (2%) vs. early treatment, 10/886 (1%); HR, 1.3 (95% CI, 0.57 to 3.0) Clinical event (death, WHO Stage 4 event, severe bacterial infection, pulmonary infection) Delayed treatment, 65/877 (7%) vs. early treatment, 40/886 (5%); adjusted HR, 1.7 (95% CI, 1.1 to 2.5) Extrapulmonary tuberculosis Delayed treatment, 17/877 (2%) vs. early treatment, 3/886 (0.3%); RR, 5.6 (95% CI, 1.7 to 20) Pulmonary tuberculosis Delayed treatment, 15/877 (2%) vs. early treatment, 13/886 (2%); RR, 1.2 (95% CI, 0.56 to 2.4)	Severe or life-threatening adverse events Early treatment, 127/886 (14%) vs. delayed treatment, 119/877 (14%)	National Institute of Allergy and Infectious Diseases	Good

Appendix B21. Key Question 4c: Evidence Table of Trials of Effect of Initiating Highly Active Antiretroviral Therapy at Different CD4 Counts or Viral Load Thresholds on Clinical Outcomes

Author, Year	Exclusion criteria	Number screened/ eligible/enrolled/ withdrawals/% analyzed	Clinical outcomes	Adverse events	Funding source and role	Quality rating
Severe et al, 2010[130]	History of AIDS-defining illness (WHO Stage 4) or previously used ART	816/816; unclear	Mortality Standard treatment, 23/408 (6%) vs. early treatment, 6/408 (2%); unadjusted HR, 4 (95% CI, 1.6 to 9.8) Incident tuberculosis Standard treatment, 36/408 (9%) vs. early treatment, 18/408 (4%); unadjusted HR, 2 (95% CI, 1.2 to 3.6)	Any severe or life-threatening drug reaction Standard treatment, 18/160* (11%) vs. early treatment, 32/408 (8%) Anemia Standard treatment, 13/160 (8%) vs. early treatment, 14/408 (3%) *160/408 standard treatment patients received ART once CD4 counts reached ≤200 x 10^9 cells/L	National Institute of Allergy and Infectious Disease; Fogarty International Center; Global Fund to Fight AIDS, Tuberculosis and Malaria; GlaxoSmithKline; Abbot Laboratory; Fondation Merieux	Good
SMART Study Group, 2008[131] Other publication: SMART Study Group, 2006[138]	No use of ART for <6 months before randomization	SMART subgroup analysis: 477 screened; 477 eligible; 477 enrolled	Opportunistic disease or death* DC, 4/131 (event rate, 2.7/100 person-years) vs. 1/118 (event rate, 0.5/100 person-years); HR, 5.3; p=0.13 Fatal or nonfatal opportunistic disease* DC, 3/131 (event rate, 2/100 person-years) vs. 1/118 (event rate, 0.5/100 person-years); HR, 4.1; p=0.22 Serious nonAIDS events, including death due to nonopportunistic disease* DC, 4/131 (event rate, 2.8/100 person-years) vs. VS, 1/118 (event rate, 0.5/100 person-years); HR, 5.1; p=0.15 Fatal or nonfatal opportunistic disease or serious nonAIDS event including death due to nonopportunistic disease* DC, 7/131 (event rate, 4.9/100 person-years) vs. VS, 2/118 (event rate, 1/100 person-years); HR, 4.6; p=0.06 *ART naive only	Not reported	National Institute of Allergy and Infectious Diseases	Good

ART = antiretroviral therapy; DC = drug conservative; HR = hazard rate; RCT = randomized, controlled trial; VS = viral suppression; WHO = World Health Organization.

Appendix B22. Key Question 4c: Quality Assessment of Randomized, Controlled Trials

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup differential or high overall?	Intention-to-treat analysis	Quality rating	Funding
Severe et al, 2010[130]	Yes	Unclear	Yes	Yes	Yes	No	No	Yes	Differential: no High overall: no	Yes	Good	National Institute of Allergy and Infectious Disease; Fogarty International Center; Global Fund to Fight AIDS, Tuberculosis and Malaria; Glaxo Smith Kline; Abbot Laboratory; Fondation Merieux
SMART Study Group, 2008[131] Other publication: SMART Study Group, 2006[138]	Yes	Unclear	Yes	Yes	Yes	No	No	No (post-hoc subgroup analysis)	Differential: no High overall: no	Yes	Good	National Institute of Allergy and Infectious Diseases

Appendix B23. Key Question 4c: Evidence Table of Cohort Studies of Effects of Initiating Highly Active Antiretroviral Therapy at Different CD4 Counts or Viral Load Thresholds on Clinical Outcomes

Author, Year	Study name	Study design	Setting/data source	Cohorts	Duration of followup
HIV-CAUSAL Collaboration, 2011[133] Other publication: HIV-CAUSAL Collaboration 2010[134]	HIV-CAUSAL Collaboration	Retrospective cohort	Pooled national health care data from 12 European cohorts	UK CHIC; ATHENA; French Hospital Database on HIV (FHDH ANRS CO4); Swiss HIV Cohort Study; PICIS Cohort Study; CoRIS; Veterans Aging Cohort Study Virtual Cohort (VACS-VC); UK Register of Seroconverters; ANRS PRIMO; ANRS SEROCO; Spanish Multicenter Study Group of Seroconverters	Median, 12 months (interquartile range, 5–26 months)
HIV-CAUSAL Collaboration, 2010[134] Other publication: HIV-CAUSAL Collaboration 2011[133]	HIV-CAUSAL Collaboration	Retrospective cohort	Pooled national health care data from 12 European cohorts	UK CHIC; ATHENA; French Hospital Database on HIV (FHDH ANRS CO4); Swiss HIV Cohort Study; PICIS Cohort Study; CoRIS; Veterans Aging Cohort Study Virtual Cohort (VACS-VC); UK Register of Seroconverters; ANRS PRIMO; ANRS SEROCO; Spanish Multicenter Study Group of Seroconverters	Mean duration, 3 years
Kitahata et al, 2009[135]	North American AIDS Cohort Collaboration (NA-ACCORD)	Retrospective cohort	Pooled data from 22 cohorts in North America	AIDS Link to the IntraVenous Experience; AACTG Longitudinal Linked Randomized Trials; Case Western Reserve University Immunology Unit Patient Care and Research Database; Fenway Community Health Center; HIV Research Network; ART Observational Medical Evaluation and Research; HIV Outpatient Study; Johns Hopkins HIV Clinical Cohort; Kaiser Permanente Northern California; Longitudinal Study of Ocular Complications of AIDS; Multicenter AIDS Cohort Study; Second Multicenter Hemophilia Cohort Study; Montreal Chest Institute Immunodeficiency Service Cohort; Ontario HIV Treatment Network Cohort Study; Retrovirus Research Center; Southern Alberta Clinic Cohort; SCOPE (Study of the Consequences of the Protease Inhibitor); EraSUN (Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy); University of Alabama at Birmingham 1917 Clinic Cohort; University of North Carolina, Chapel Hill HIV Clinic; University of Washington HIV Cohort; VACS (Veterans Aging Cohort Study and Virtual Cohort); Vanderbilt-Meharry CFAR Cohort; Women's Interagency HIV Study	Mean duration not reported; data for 23,977 person-years for CD4 counts 0.351–0.500 x 10^9 cells/L, 26,439 person-years for CD4 counts >0.500 x 10^9 cells/L
May et al, 2007[136] Other publications: Lanoy et al, 2009[139]; Moore et al, 2009[140]	Antiretroviral Therapy Cohort Collaboration (ART)	Retrospective cohort	Pooled data from 12 cohorts in Europe and North America	Italian Cohort of Antiretroviral-Naive Patients (ICONA); Swiss HIV Cohort Study (SHCS); AIDS Therapy Evaluation Project Netherlands (ATHENA); Multicenter Study Group on EuroSIDA; Collaborations in HIV Outcomes Research US (CHORUS); Frankfurt HIV Cohort; Aquitaine Cohort ANRS CO3; ART Observational Medical Evaluation and Research (HOMER), British Columbia Center for Excellence in HIV/AIDS; Royal Free Hospital Cohort; South Alberta Clinic; Koln/Bonn Cohort	Mean duration not reported; 34% had <2 years, 49% had 2–5 years, 17% had 5 years; 61,798 patient-years
When to Start Consortium, 2009[137]	When to Start Consortium	Retrospective cohort	Pooled data from 18 cohorts in Europe and North America	Multicenter AIDS Cohort Study (MACS); Swiss HIV Cohort Study (SHCS); ANRS CO4 French Hospital Database on HIV (FHDH); ANRS CO3 Aquitaine Cohort; Amsterdam Cohort Studies; South Alberta Clinic; Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE); ATHENA; ICONA; CHORUS; VACS; PISCIS; EuroSIDA	Mean duration, 3 years
Writing Committee for the CASCADE Collaboration, 2011[132]	CASCADE Collaboration	Retrospective cohort	Pooled data from 23 clinical cohorts in Europe, Australia, and Canada	Austrian HIV Cohort Study; PHAEDRA cohort; Southern Alberta Clinic Cohort; Aquitaine Cohort; French Hospital Database; Lyon Primary Infection Cohort; SEROCO Cohort; French PRIMO Cohort; German Cohort; AMACS; Greek Haemophilia Cohort; Italian Seroconversion Study; ICONA cohort; Amsterdam Cohort Studies in Homosexual Men and IDUs; Oslo and Ulleval Hospital Cohorts; Badalona IDU Hospital Cohort; Barcelona IDU Cohort; CoRIS-scv; Madrid Cohort; Valencia IDU Cohort; Swiss HIV Cohort Study; Early Infection Cohorts; Genital Shedding Study Cohort; Edinburgh Hospital Cohort; UK Register of HIV Seroconverters; Royal Free Haemophilia Cohort	Median, 4.7 years (range, 2–9 years; 52,268 person-years)

Appendix B23. Key Question 4c: Evidence Table of Cohort Studies of Effects of Initiating Highly Active Antiretroviral Therapy at Different CD4 Counts or Viral Load Thresholds on Clinical Outcomes

Author, year	Population characteristics	Inclusion criteria	Exclusion criteria	Number eligible/ enrolled/analyzed	Comparison groups
HIV-CAUSAL Collaboration, 2011[133] Other publication: HIV-CAUSAL Collaboration 2010[134]	N=20,971 Mean age not reported; 48% <35 years, 44% 35–49 years, 8% ≥50 years Race not reported 44% homosexual or bisexual 30% heterosexual 11% injection drug users 15% other/unknown Median CD4 count, 0.660 x 10^9 cells/L	Age >18 years; HIV-1 infection; ART naive; no history of CD4 count <0.500 x 10^9 cells/L; CD4 count and HIV RNA measurements within 6 months of each other	Pregnancy; history of AIDS-defining illness	Not reported; not reported; 20,971	CD4 count: 0.200 x 10^9 (n=8066*) 0.250 x 10^9 (n=8078) 0.300 x 10^9 (n=8101) 0.350 x 10^9 (n=8144) 0.400 x 10^9 (n=8201) 0.450 x 10^9 (n=8281) 0.500 x 10^9 (n=8392) *Patient-level data may cross CD4 thresholds
HIV-CAUSAL Collaboration, 2010[134] Other publication: HIV-CAUSAL Collaboration 2011[133]	N=62,760 Mean age not reported 26% female Race not reported 13% injection drug users Median CD4 count, 0.390 x 10^9 cells/L Median HIV RNA, 29,700/mL	Age >18 years; HIV-1 infection; ART naive; HIV RNA >500 copies/mL; CD4 count and HIV RNA measurements within 6 months of each other	Pregnancy; history of category C AIDS-defining illness	Not reported; not reported; 62,760	CD4 count: <0.100 x 10^9 (n=5319) 0.100 to <0.200 x 10^9 (n=6521) 0.200 to <0.350 x 10^9 (n=14,886) 0.350 to <0.500 x 10^9 (n=15,360) ≥0.500 x 10^9 (n=20,674)
Kitahata et al, 2009[135]	N=17,517 Mean age not reported; median, 38 years 24% female 43% white 42% black 15% other Median CD4 count Total cohort: 0.401 x 10^9 cells/L Among patients 0.351–0.500 x 10^9: 0.422 x 10^9 (early-therapy group) and 0.286 x 10^9 (deferred therapy group) Among patients >0.500 x 10^9 cells/L: 0.679 x 10^9 (early-therapy group) and 0.410 x 10^9 (deferred therapy group)	Patients receiving medical care between January 1996 and December 2005, no previous AIDS-defining illness or ART, stratified between baseline CD4 counts of 0.351–0.500 x 10^9 and >0.500 x 10^9 cells/L	None reported	Not reported; not reported; 17,517	CD4 count 0.351–0.500 x 10^9: Early therapy (n=2084) Deferred therapy (n=6278) CD4 count >0.500 x 10^9: Early therapy (n=2220) Deferred therapy (n=6936)
May et al, 2007[136] Other publications: Lanoy et al, 2009[139]; Moore et al, 2009[140]	N=20,379 Median age, 36 years 24% female Race not reported 40% MSM 35% heterosexual 16% injection drug users 9% other CD4 count 10% <0.025 x 10^9 6% 0.025–0.049 x 10^9 10% 0.050–0.099 x 10^9 18% 0.100–0.199 x 10^9 27% 0.200–0.349 x 10^9 28% ≥0.350 x 10^9	Age ≥16 years, no previous ART and started ART with a combination of at least 3 drugs, median duration of followup at least 1 year	Baseline HIV-1 RNA <1000 copies/mL (possibly not treatment-naive)	20,379; 20,379; 20,379	CD4 count: <0.025 x 10^9 (n=2034) 0.025–0.049 x 10^9 (n=1295) 0.050–0.099 x 10^9 (n=2059) 0.100–0.199 x 10^9 (n=3782) 0.200–0.349 x 10^9 (n=5550) ≥0.350 x 10^9 (n=5659) HIV-RNA: ≥5 log copies/mL (n=9734) 4.99 log copies/ml (n=8391) 3–3.99 log copies/mL (n=2254)

Appendix B23. Key Question 4c: Evidence Table of Cohort Studies of Effects of Initiating Highly Active Antiretroviral Therapy at Different CD4 Counts or Viral Load Thresholds on Clinical Outcomes

Author, year	Population characteristics	Inclusion criteria	Exclusion criteria	Number eligible/ enrolled/analyzed	Comparison groups
When to Start Consortium, 2009[137]	N=45,691 (24,444 received ART) Mean age, 36 years 26% female Race not reported 47% MSM 42% heterosexual 11% other/unknown Mean CD4 count, 0.288 x 10^9 cells/L (range, 0.130–0.448 x 10^9)	For cohorts: age >16 years with no previous ART, started treatment with at least 3 drugs, and median duration of followup of at least 1 year	Commencement of combination therapy prior to January 1, 1996; presumed HIV transmission due to injecting drug use	Not reported; not reported; 24,444	CD4 count: <0.051 x 10^9 (n=2594) 0.051–0.150 x 10^9 (n=4638) 0.151–0.250 x 10^9 (n=6406) 0.251–0.350 x 10^9 (n=5753) 0.351–0.400 x 10^9 (n=3260) 0.451–0.500 x 10^9 (n=1793)
Writing Committee for the CASCADE Collaboration, 2011[132]	N=9455 Median age at seroconversion, 30 years 22% female 57% MSM	Age ≥13 years; ART-naive as of first month of trial; no end point of interest (AIDS or death) as of end of the month; no more than 21 days of cumulative monotherapy or dual therapy; CD4 count <0.800 x 10^9 cells/L; ≥180 after seroconversion and in previous 365 days	Not reported	18,347; 9455; 9455	CD4 count, unique individuals (numbers overlap): 0–0.049 x 10^9 (n=183) 0.050–0.199 x 10^9 (n=1521) 0.200–0.349 x 10^9 (n=4459) 0.350–0.499 x 10^9 (n=5527) 0.500–0.799 x 10^9 (n=5162)

Author, year	Adjusted variables for statistical analysis	Clinical outcomes	Quality rating	Funding source
HIV-CAUSAL Collaboration, 2011[133] Other publication: HIV-CAUSAL Collaboration 2010[134]	Sex, age, race, geographic origin, method of transmission, CD4 count, HIV-1 RNA level, calendar year, cohort, months from baseline to first CD4 count <0.500 x 10^9 cells/L	<u>Mortality, initiation of ART at CD4 count 0.500 x 10^9 (n=65/8392) vs:</u> 0.200 x 10^9 (n=99/8066): HR, 0.83 (CI, 0.68 to 1.03) 0.250 x 10^9 (n=95/8078): HR, 0.92 (CI, 0.78 to 1.09) 0.300 x 10^9 (n=97/8101): HR, 0.99 (CI, 0.84 to 1.18) 0.350 x 10^9 (n=94/8144): HR, 0.99 (CI, 0.82 to 1.19) 0.400 x 10^9 (n=89/8201): HR, 0.95 (CI, 0.79 to 1.16) 0.450 x 10^9 (n=81/8281): HR, 0.97 (CI, 0.88 to 1.09) <u>Mortality, initiation of ART at CD4 count 0.350 x 10^9 (n=94/8144) vs:</u> 0.200 x 10^9 (n=99/8066): HR, 0.85 (CI, 0.68 to 1.05) 0.250 x 10^9 (n=95/8078): HR, 0.93 (CI, 0.75 to 1.16) 0.300 x 10^9 (n=97/8101): HR, 1.01 (CI, 0.79 to 1.28) 0.400 x 10^9: (n=89/8201): HR, 0.97 (CI, 0.85 to 1.10) 0.450 x 10^9 (n=81/8281): HR, 0.99 (CI, 0.79 to 1.22) 0.500 x 10^9 (n=65/8392): HR, 1.01 (CI, 0.74 to 1.41) <u>AIDS-defining illness or death, initiation of ART at CD4 count 0.500 x 10^9 (n=158/8392) vs:</u> 0.200 x 10^9 (n=330/8066):HR, 0.53 (CI, 0.47 to 0.60) 0.250 x 10^9 (n=329/8078): HR, 0.60 (CI, 0.54 to 0.67) 0.300 x 10^9 (n=317/8101): HR, 0.68 (CI, 0.61 to 0.75) 0.350 x 10^9 (n=296/8144): HR, 0.72 (CI, 0.64 to 0.81) 0.400 x 10^9 (n=256/8201): HR, 0.78 (CI, 0.68 to 0.87) 0.450 x 10^9 (n=209/8281): HR, 0.88 (CI, 0.82 to 0.93) <u>AIDS-defining illness or death, initiation of ART at CD4 count 0.350 x 10^9 (n=296/8144) vs:</u> 0.200 x 10^9 (n=330/8066): HR, 0.73 (CI, 0.64 to 0.83) 0.250 x 10^9 (n=329/8078): HR, 0.83 (CI, 0.72 to 0.95) 0.300 x 10^9 (n=317/8101): HR, 0.93 (CI, 0.81 to 1.09) 0.400 x 10^9 (n=256/8201): HR, 1.06 (CI, 0.99 to 1.16) 0.450 x 10^9 (n=209/8281): HR, 1.20 (CI, 1.05 to 1.39) 0.500 x 10^9 (n=158/8392): HR, 1.39 (CI, 1.14 to 1.69)	Fair	Not reported

Appendix B23. Key Question 4c: Evidence Table of Cohort Studies of Effects of Initiating Highly Active Antiretroviral Therapy at Different CD4 Counts or Viral Load Thresholds on Clinical Outcomes

Author, year	Adjusted variables for statistical analysis	Clinical outcomes	Quality rating	Funding source
HIV-CAUSAL Collaboration, 2010[134] Other publication: HIV-CAUSAL Collaboration 2011[133]	Ever use of ART, month of followup, CD4 count, HIV RNA level, gender, transmission group, calendar year, age, geographic origin, race, years since HIV diagnosis, cohort	Mortality, initiation of ART vs. no initiation of ART, by CD4 count: <0.100 x 10^9: HR, 0.29 (CI, 0.22 to 0.37) 0.100 to <0.200 x 10^9: HR, 0.33 (CI, 0.25 to 0.44) 0.200 to <0.350 x 10^9: HR, 0.38 (CI, 0.28 to 0.52) 0.350 to <0.500 x 10^9: HR, 0.55 (CI, 0.41 to 0.74) ≥0.500 x 10^9: HR, 0.77 (CI, 0.58 to 1.01) Mortality, initiation of ART vs. no initiation of ART, by HIV RNA: <10,000: HR, 0.82 (CI, 0.64 to 1.05) 10,000–100,000: HR, 0.46 (CI, 0.36 to 0.60) >100,000: HR, 0.36 (CI, 0.28 to 0.45)	Fair	National Institutes of Health
Kitahata et al, 2009[135]	Sex, age, CD4 count at baseline and HIV RNA level, history of injection drug use, HCV infection when known (unknown status analyzed separately)	Mortality, initiation of ART at CD4 count 0.351–0.500 x 10^9 vs. ≤0.350 x 10^9 Early therapy vs. deferred therapy, adjusted for age, sex, and HIV RNA level: RR, 0.61 (CI, 0.46 to 0.83) Early therapy vs. deferred therapy, adjusted for history of injection drug use: RR, 0.78 (CI, 0.52 to 1.18) Early therapy vs. deferred therapy, adjusted for presence of HCV infection: RR, 0.58 (CI, 0.41 to 0.83) Mortality, CD4 count >0.500 x 10^9 vs. ≤500 x 10^9 Early therapy vs. deferred therapy, adjusted for age, sex, and HIV RNA level: RR, 0.54 (CI, 0.35 to 0.83) Early therapy vs. deferred therapy, excluding patients with history of injection drug use: RR, 0.5 (CI, 0.29 to 0.87) Early therapy vs. deferred therapy, excluding patients with HCV infection: RR, 0.52 (CI, 0.31 to 0.88)	Fair	National Institutes of Health; AHRQ
May et al, 2007[136] Other publications: Lanoy et al, 2009[139]; Moore et al, 2009[140]	HIV-1 RNA level, age, assumed transmission group, clinical AIDs	Mortality, initiation of ART at varying CD4 counts vs. CD4 count <0.025 x 10^9 0.025–0.049 x 10^9: 111/1295 vs. 222/2034; HR, 0.82 (CI, 0.66 to 1.04) 0.050–0.099 x 10^9: 162/2059 vs. 222/2034; HR, 0.77 (CI, 0.63 to 0.95) 0.100–0.199 x 10^9: 202/3782 vs. 222/2034; HR, 0.67 (CI, 0.55 to 0.82) 0.200–0.349 x 10^9: 178/5550 vs. 222/2034; HR, 0.48 (CI, 0.39 to 0.60) ≥0.350 x 10^9: 130/5659 vs. 222/2034; HR, 0.34 (CI, 0.27 to 0.44) AIDS or death from start of ART, initiation of ART at varying CD4 counts vs. CD4 count <0.025 x 10^9 0.025–0.049 x 10^9: 277/1295 vs. 519/2034; HR, 0.85 (CI, 0.73 to 0.98) 0.050–0.099 x 10^9: 408/2059 vs. 519/2034; HR, 0.76 (CI, 0.66 to 0.87) 0.100–0.199 x 10^9: 445/3782 vs. 519/2034; HR, 0.49 (CI, 0.43 to 0.56) 0.200–0.349 x 10^9: 361/5550 vs. 519/2034; HR, 0.29 (CI, 0.25 to 0.33) ≥0.350 x 10^9: 298/5659 vs. 519/2034; HR, 0.23 (CI, 0.19 to 0.27) Mortality, initiation of ART at varying HIV-1 RNA viral loads vs. HIV-1 RNA ≥100,000 copies/mL 10,000 to <100,000: 305/8391 vs. 607/9734; HR, 0.89 (CI, 0.77 to 1.02) 1000 to <10,000: 93/2254 vs. 607/9734; HR, 1.11 (CI, 0.89 to 1.39) AIDS or death, initiation of ART at varying HIV-1 RNA viral loads vs. HIV-1 RNA ≥100,000 copies/mL 10,000 to <100,000: 701/8391 vs. 1449/9734; HR, 0.80 (CI, 0.73 to 0.88) 1000 to <10,000: 158/2254 vs. 1449/9734; HR, 0.80 (CI, 0.68 to 0.95)	Fair	UK Medical Research Grant; Glaxo Smith Kline
When to Start Consortium, 2009[137]	Age, gender, CD4 count, method of transmission, year of enrollment, lead time, unseen events	Mortality, initiation of ART at varying CD4 counts vs. 0.351–0.450 x 10^9 0.451–0.550 x 10^9: HR, 0.93 (CI, 0.6 to 1.4) 0.251–0.350 x 10^9: HR, 0.83 (CI, 0.59 to 1.25) 0.151–0.250 x 10^9: HR, 0.67 (CI, 0.51 to 0.99) Progression to AIDS or death, initiation of ART at varying CD4 counts vs. 0.351–0.450 x 10^9 0.451–550 x 10^9: HR, 0.90 (CI, 0.76 to 1.29) 0.251–0.350 x 10^9: HR, 0.74 (CI, 0.59 to 0.95) 0.151–0.250 x 10^9: HR, 0.45 (CI, 0.37 to 0.53)	Fair	United Kingdom Medical Research Council

Appendix B23. Key Question 4c: Evidence Table of Cohort Studies of Effects of Initiating Highly Active Antiretroviral Therapy at Different CD4 Counts or Viral Load Thresholds on Clinical Outcomes

Author, year	Adjusted variables for statistical analysis	Clinical outcomes	Quality rating	Funding source
Writing Committee for the CASCADE Collaboration, 2011[132]	Injection drug use, HIV test interval <30 days, gender, time since seroconversion, age, calendar year, HCV, HBV, CD4 count, days between last CD4 count and start of followup, number of previous CD4 measures, most recent viral load, days between last viral load and start of followup, peak viral load, number of previous viral load measures	<u>Mortality, treatment vs. no treatment initiation during index month, by CD4 count</u> 0–0.049 x 10^9: HR, 0.37 (CI, 0.14 to 0.95); RD, -18.2 (CI, -32 to -4.4); NNT, 6 (CI, 3 to 23) 0.050–0.199 x 10^9: HR, 0.55 (CI, 0.28 to 1.07); RD, -7.2 (CI, -10.1 to -4.4); NNT, 14 (CI, 10. to 23) 0.200–0.349 x 10^9: HR, 0.71 (CI, 0.44 to 1.15); RD, -1.4 (CI, 03 to 0.3); NNT, 74 (CI, 33 to ∞) 0.350–0.499 x 10^9: HR, 0.51 (CI, 0.33 to 0.80); RD, -1.4 (CI, -2.2 to -0.6); NNT, 71 (45 to 165) 0.500–0.799 x 10^9: HR, 1.02 (CI, 0.49 to 2.12); RD, -0.4 (CI, -2 to 1.2); NNT, 239 (49 to ∞) <u>Progression to AIDS or death, treatment vs. no treatment initiation during index month, by CD4 count</u> 0–0.049 x 10^9: HR, 0.32 (CI, 0.17 to 0.59); RD, -30 (CI, -45.1 to -15); NNT, 2 (CI, 2 to 7) 0.050–0.199 x 10^9: HR, 0.48 (CI, 0.31 to 0.74); RD, -15 (CI, -19.7 to -10.3); NNT, 7 (CI, 5 to 10) 0.200–0.349 x 10^9: HR, 0.59 (CI, 0.43 to 0.81); RD, -4.8 (CI, -7 to -2.6); NNT, 21 (CI, 14 to 38) 0.350–0.499 x 10^9: HR, 0.75 (CI, 0.49 to 1.14); RD, -2.9 (CI, -5 to -0.9); NNT, 34 (CI, 20 to 115) 0.500–0.799 x 10^9: HR, 1.10 (CI, 0.67 to 1.79); RD, 0.3 (CI, -3.7 to 4.2); NNT, ∞	Fair	National Institute of Allergy and Infections Diseases, National Institutes of Health

AHRQ = Agency for Healthcare Research and Quality; ART = antiretroviral therapy; CI = confidence interval; HBV = hepatitis B virus; HCV = hepatitis C virus; HR = hazard rate; MSM = men who have sex with men; NR = not reported; RR = relative risk.

Appendix B24. Key Question 4c: Quality Assessment of Cohort Studies

Author, Year	Did study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were groups comparable at baseline on key prognostic factors (by restriction or matching)?	Did study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did article report attrition?	Did study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified, defined, and ascertained using accurate methods?	Quality rating
HIV-CAUSAL Collaboration, 2010[134] Other publication: HIV-CAUSAL Collaboration 2011[133]	Yes	No	Yes	Unclear	No	Yes	Differential: unclear High overall: unclear	Yes	Fair
Kitahata et al, 2009[135]	Yes	Unclear	Yes	Unclear	No	Yes	Differential: unclear High overall: unclear	Yes	Fair
May et al, 2007[136] Other publications: Lanoy et al, 2009[139]; Moore et al, 2009[140]	Yes	Unclear	Yes	Unclear	Yes	Yes	Differential: unclear High overall: yes (19%)	Yes	Fair
When to Start Consortium, 2009[137]	Yes	Unclear	Yes	Unclear	No	Yes	Differential: unclear High overall: unclear	Yes	Fair
Writing Committee for the CASCADE Collaboration, 2011[132]	Yes	Unclear	Yes	Unclear	Yes	Yes	Differential: unclear High overall: no	Yes	Fair

Appendix B25. Key Question 5: Evidence Table of Studies of Longer-Term Harms of Highly Active Antiretroviral Therapy Use

Author, Year	Study design	Setting/data source	Duration of followup	Population characteristics	Inclusion criteria	Exclusion criteria	Number eligible/ enrolled/analyzed
Bedimo et al, 2011[145]	Retrospective observational study	Veteran's Health Administration (VHA) Clinical Case Registry (CCR)	Median, 4 years	n=19,424 Median age, 46 years 2% female 29% smokers 13% diabetes 38% hypertension 26% hypercholesterolemia 8% chronic kidney disease 32% HCV infection	HIV infected; enrolled in VHA facility between 1996 and 2004 and entered into CCR	Not reported	Not reported; 19,424; 19,424
DAD Study Group, 2010[144]	Prospective observational study	11 North American, European, and Australian cohorts	Median, 6 years	n=33,308 Median age, 44 years 26% female Race not reported Framingham risk, total population: -53% low risk; -15% moderate risk; -4% high risk Framingham risk, patients with MI: -26% low risk; -30% moderate risk; -18% high risk Framingham risk, patients without MI: -54% low risk; -15% moderate risk; -4% high risk	HIV infected; enrolled in 1 of 11 cohorts	Not reported	33,308; 33,308; 33,308
DAD Study Group, 2008[143]	Prospective observational study	11 North American, European, and Australian cohorts	Median, 5 years	n=33,347 Mean age, 43 years 26% female Race not reported Framingham risk, patients with MI: -22% (113/517) low risk; -26% (134/517) moderate risk; -23% (120/517) high risk; -29% (150/517) unknown risk	HIV infected; enrolled in 1 of 11 cohorts	Not reported	33,347; 33,347; 33,347
DAD Study Group, 2007[142] Other publication: Friis-Moller et al, 2003[141]	Prospective observational study	11 North American, European, and Australian cohorts	Median, 5 years (range, <1 to >7 years)	n=23,437 Median age, 39 years 24% female 78% white* 17% black 3% Hispanic 2% Asian 27% AIDS 61% current/former smokers 14% hypertension 42% dyslipidemia (*61% of patients had data on race)	HIV infected; enrolled in 1 of 11 cohorts	Not reported	23,437; 23,437; 23,437
Danish HIV Cohort Study, Obel et al, 2010[146] Other publications: Obel et al, 2008[148]; Lohse et al, 2006[149]	Prospective observational study	Danish National Hospital Registry	Mean, 6 years (19,124 person-years)	n=2952 Median age, 39 years 76% male 82% white (other races not reported) Median CD4 count not reported CVD risk factors not reported	Age >15 years; HIV-infected with diagnosis prior to January 1, 2005; treated with HAART; treated in 1 of 8 specialized treatment centers	MI prior to HAART initiation	2952; 2952; 2952

Appendix B25. Key Question 5: Evidence Table of Studies of Longer-Term Harms of Highly Active Antiretroviral Therapy Use

Author, Year	Study design	Setting/data source	Duration of followup	Population characteristics	Inclusion criteria	Exclusion criteria	Number eligible/ enrolled/analyzed
Ribaudo et al, 2011[147]	Retrospective observational analyses of clinical trial data	AIDS Clinical Trials Group (ACTG) Logitudinal linked randomized trials	Median, 3 years	n=5056 (1122 with 6-year data) Median age, 37 years 18% female 40% white 36% black 21% Hispanic 10% prior IV drug user 15% 2 or more CVD risk factors 5% CVD 10-year risk score ≥10	HIV-infected; prospectively randomized to receive ART within ACTG trials between June 1998 and November 2007; ART naive	Not reported	5056; 5056; 4640 (1-year data); 1122 (6-year data)

Author, Year	Interventions	Adjusted variables for statistical analysis	Clinical outcomes	Quality rating	Funding source
Bedimo et al, 2011[145]	Any HAART (n=14,063)	Age, diabetes, hypertension, hypercholesterolemia, smoking	MI, cumulative exposure Abacavir: adjusted HR, 1.18 (95% CI, 0.92 to 1.5); p=0.19 Other NRTIs: adjusted HR, 0.99 (CI, 0.87 to 1.11); p=0.87 Mono- or dual-therapy ART: adjusted HR, 1.29 (CI, 1.10 to 1.52); p=0.002 Cerebrovascular event, cumulative exposure Abacavir: adjusted HR, 1.15 (CI, 0.97 to 1.37); p=0.1 Other NRTIs: adjusted HR, 0.93 (CI, 0.86 to 1.0); p=0.48 Mono- or dual-therapy ART: adjusted HR, 1.11 (CI, 0.98 to 1.25); p=0.1	Fair	Not reported
DAD Study Group, 2010[144]	Protease inhibitors: Nelfinavir (n=10,370) Indinavir (n=11,985) Lopinavir-ritonavir (n=9,995) Saquinavir (n=8070) NRTIs: Zidovudine (n=25,754) Didanosine (n=13,851) Zalcitabine (n=4951) Stavudine (n=16,840) Lamivudine (n=28,835) Abacavir (n=12,511) Tenofovir (n=13,100) NNRTIs: Nevirapine (n=12,194) Efavirenz (n=13,522)	Age, sex, HIV transmission group, race, calendar year, cohort, smoking, family history of CVD, previous CV event, BMI, exposure to other ART	MI, all patients Incidence: 3.2/1000 person-years Absolute rate, any MI: 1.7% (580/33,308) Absolute rate, fatal MI: 0.4% (148/33,308) MI, with cumulative PI use (relative rate) Nelfinavir: 1.04 (CI, 0.98 to 1.11) Indinavir: 1.12 (CI, 1.07 to 1.18) Lopinavir-ritonavir: 1.13 (CI, 1.05 to 1.21) Saquinavir: 1.04 (CI, 0.98 to 1.11) MI, per year of PI exposure (relative rate) Indinavir: 1.11 (CI, 1.05 to 1.18) Indinavir + ritonavir: 1.18 (CI, 1.07 to 1.30) Saquinavir: 1.07 (CI, 0.97 to 1.20) Saquniavir + ritonavir: 1.06 (CI, 0.97 to 1.14) MI, with cumulative NRTI use (relative rate) Zidovudine: not significant (data not reported) Didanosine: 1.41 (CI, 1.09 to 1.82) Zalcitabine: not significant (data not reported) Stavudine: not significant (data not reported) Lamivudine: not significant (data not reported) Abacavir: 1.07 (CI, 1.00 to 1.14) Tenofovir: 1.04 (CI, 0.91 to 1.18) MI, recent NRTI use (relative rate) Abacavir: 1.7 (CI, 1.17 to 2.47) Tenofovir: 1.14 (CI, 0.85 to 1.53) MI, with cumulative NNRTI use (relative rate) Nevirapine: 0.97 (CI, 0.92 to 1.03) Efavirenz: 1.02 (CI, 0.96 to 1.08)	Good	HAART Oversight Committee; Health Insurance Fund Council; Agence Nationale de Recherches sur le SIDA; Australian Department of Health and Ageing; National Institutes of Health; Fondo de Investigación Sanitaria; Fundación para la Investigación y la Prevención del SIDA en Espanã; European Commission BIOMED 1, BIOMED 2, the 5th and 6th Framework; Bristol-Myers Squibb; GlaxoSmithKline; Roche; Gilead; Pfizer; Merck; Tibotec; Boehringer-Ingelheim

Appendix B25. Key Question 5: Evidence Table of Studies of Longer-Term Harms of Highly Active Antiretroviral Therapy Use

Author, Year	Interventions	Adjusted variables for statistical analysis	Clinical outcomes	Quality rating	Funding source
DAD Study Group, 2008[143]	NRTIs (n not reported): Zidovudine Didanosine Stavudine Lamivudine Abacavir	Age, sex, risk group, race, cohort, BMI, family history of CVD, smoking, previous CV event, year, cumulative exposure to other ART	MI, cumulative exposure (relative rate) Zidovudine: 1.04 (CI, 0.99 to 1.09); p=0.15 Didanosine: 1.00 (CI, 0.93 to 1.07); p=0.91 Stavudine: 1.02 (CI, 0.95 to 1.09); p=0.6 Lamivudine: 0.99 (CI, 0.93 to 1.06); p=0.8 Abacavir: 1.00 (CI, 0.92 to 1.08); p=0.91 MI, recent exposure (relative rate) Zidovudine: 1.22 (CI, 0.82 to 1.81) Didanosine: 1.53 (CI, 1.10 to 2.13) Stavudine: 1.22 (CI, 0.84 to 1.77) Lamivudine: 1.69 (CI, 1.02 to 2.8) Abacavir: 1.94 (CI, 1.48 to 2.55) MI, past exposure (relative rate) Zidovudine: 1.29 (CI, 0.89 to 1.85) Didanosine: 1.08 (CI, 0.84 to 1.39) Stavudine: 1.24 (CI, 0.93 to 1.66) Lamivudine: 1.45 (CI, 0.88 to 2.4) Abacavir: 1.29 (CI, 0.94 to 1.77) MI, CV death, or invasive CV procedure, cumulative exposure (relative rate) Zidovudine: 1.04 (CI, 1.00 to 1.08); p=0.06 Didanosine: 0.99 (CI, 0.94 to 1.05); p=0.84 Stavudine: 1.04 (CI, 0.99 to 1.10); p=0.13 Lamivudine: 1.01 (CI, 0.96 to 1.06); p=0.74 Abacavir: 1.03 (CI, 0.96 to 1.10); p=0.38 MI, CV death, or invasive CV procedure, any recent exposure (relative rate) Zidovudine: 0.98 (CI, 0.79 to 1.21); p=0.83 Didanosine: 1.40 (1.11 to 1.77); p=0.005 Stavudine: 0.99 (CI, 0.78 to 1.25); p=0.9 Lamivudine: 1.15 (CI, 0.91 to 1.44); p=0.23 Abacavir: 1.63 (CI, 1.3 to 2.04); p=0.0001 Possible or definite stroke, cumulative exposure (relative rate) Zidovudine: 1.07 (CI, 0.99 to 1.19); p=0.1 Didanosine: 0.9 (CI, 0.8 to 1.02); p=0.09 Stavudine: 1.04 (CI, 0.94 to 1.16); p=0.47 Lamivudine: 0.99 (CI, 0.89 to 1.10); p=0.89 Abacavir: 1.06 (CI, 0.93 to 1.21); p=0.40 Possible or definite stroke, any recent exposure (relative rate) Zidovudine: 0.85 (CI, 0.55 to 1.29); p=0.44 Didanosine: 1.09 (CI, 0.67 to 1.77); p=0.74 Stavudine: 0.91 (CI, 0.56 to 1.46); p=0.69 Lamivudine: 1.04 (CI, 0.67 to 1.62); p=0.86 Abacavir: 1.05 (CI, 0.66 to 1.67); p=0.84	Good	See above

Appendix B25. Key Question 5: Evidence Table of Studies of Longer-Term Harms of Highly Active Antiretroviral Therapy Use

Author, Year	Interventions	Adjusted variables for statistical analysis	Clinical outcomes	Quality rating	Funding source
DAD Study Group, 2007[142] Other publication: Friis-Moller et al, 2003[141]	Any HAART (n=21,921) Protease inhibitors (n=18,919) NNRTI (n=15,142)	Model 1: age, sex, cohort, HIV transmission group, race, age, BMI, family history of CVD, smoking, previous CV event, calendar year Model 2: all from Model 1 plus total cholesterol, HDL, hypertension, diabetes	MI, all patients Incidence: 3.65/1000 person-years Absolute rate: 1.5% (345/23,347) MI with HAART use (relative rate) Incidence: 97/16,805 person-years; 5.77/1000 person-years Model 1: 1.16 (CI, 1.09 to 1.23) MI with PI use (relative rate) Model 1: 1.16 (CI, 1.10 to 1.23); p<0.001 Model 2: 1.10 (CI, 1.04 to 1.18); p=0.002 Excluding patients exposed to NRTIs: 1.15 (CI, 1.06 to 1.25) MI with NRTI use (relative rate) Model 1: 1.05 (CI, 0.98 to 1.13); p=0.17 Model 2: 1.00 (CI, 0.93 to 1.09); p=0.92 Excluding patients exposed to PIs: 0.94 (CI, 0.74 to 1.19)	Good	See above
Danish HIV Cohort Study, Obel et al, 2010[146] Other publications: Obel et al, 2008[148]; Lohse et al, 2006[149]	Triple NRTI regimen including abacavir NNRTI or PI regimen including abacavir Specific drugs: Abacavir (n=1761) Zidovudine (n=2711) Lamivudine (n=2867) Stavudine (n=1031) Didanosine (n=813)	Age, gender, year of diagnosis, year of HAART initiation, CD4 count, viral load, race, injecting drug use, use of other antiretrovirals, comorbiditites	MI, abacavir use vs. nonuse Any abacavir exposure: incidence 2.4/1000 (CI, 1.7 to 3.4) vs. 5.7/1000 (CI, 4.1 to 7.9); adjusted RR, 2.0 (CI, 1.1 to 3.6) Actual abacavir use: RR, 1.95 (CI, 1.05 to 3.6) Early abacavir use: RR, 2.37 (CI, 0.88 to 6.36) Abacavir as part of triple NRTI: RR, 1.91 (CI, 0.88 to 4.17) Abacavir with NNTRI or PI: RR, 2.06 (CI, 1.06 to 4.01) Abacavir intiated within 2 years of HAART: RR, 1.77 (CI, 0.82 to 3.82) Abacavir initiated >2 years of HAART: RR, 2.66 (CI, 1.31 to 5.39)	Good	No outside funding
Ribaudo et al, 2011[147]	Abacavir (n=1704) No abacavir (n=3352)	Age, sex, race, CVD risk factors, smoking, family history of CVD	MI, abacavir use vs. nonuse 1 year: adjusted HR, 0.7 (CI, 0.2 to 2.6) 6 years: adjusted HR, 0.6 (CI, 0.3 to 1.4) Serious CVD events, abacavir use vs. nonuse 1 year: adjusted HR, 1.1 (CI, 0.5 to 2.1) 6 years: adjusted HR, 0.9 (CI, 0.5 to 1.3)	Good	National Institute of Allergy and Infectious Diseases

ART = antiretroviral therapy; BMI = body mass index; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; HAART = highly active antiretroviral therapy; HDL = high-density lipoprotein; MI = myocardial infarction; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RR = relative risk.

Appendix B26. Key Question 5: Quality Assessment of Cohort Studies

Author, Year	Did study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were groups comparable at baseline on key prognostic factors?	Did study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did article report attrition?	Did study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified, defined, and ascertained using accurate methods?	Quality rating
Bedimo et al, 2011[145]	Yes	No	Yes	Unclear	Yes	Yes	Differential: unclear High overall: no	Yes	Fair
DAD Study Group, 2010[144]	Yes	Yes	Yes	Yes	Yes	Yes	Differential: unclear High overall: no	Yes	Good
DAD Study Group, 2008[143]	Yes	Yes. A slightly higher proportion of patients with recent use of abacavir had a moderate to high CHD risk profile compared with recent use of other NRTIs (20% vs. 16–18%)	Yes	Yes	Yes	Yes	Differential: unclear High overall: no	Yes	Good
DAD Study Group, 2007[142] Other publication: Friis-Moller et al, 2003[141]	Yes	Yes	Yes	Yes	Yes	Yes	Differential: unclear High overall: no	Yes	Good
Danish HIV Cohort Study, Obel et al, 2010[146] Other publications: Obel et al, 2008[148]; Lohse et al, 2006[149]	Yes	Yes	Yes	Unclear	Yes	Yes	Differential: unclear High overall: no	Yes	Good
Ribaudo et al, 2011[147]	Yes	Unclear	Yes	Yes	Yes	Yes	Differential: unclear High overall: no	Yes	Good

Appendix B27. Key Question 6a: Evidence Table of Studies of Effect of Viremia on HIV Transmission Rates

Author, Year	Type of study	Location/setting/high or low prevalence population (based on 0.1% prevalence rate)	Study duration/ followup	Comparision groups	Demographics/ baseline disease	Eligibility criteria
Studies examining individual patients						
Donnell et al, 2010[105]	Pre-post analysis of prospective cohort data	14 sites in 7 African countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia)	Median study duration at ART initiation: 13 months	Pre-ART transmission vs. post-ART transmission	HIV-infected partner vs. HIV-susceptible partner Mean age: 32 vs. 33 years Female sex: 68% vs. 32% HSV-2 positive: 100% vs. 68%	HIV-1 and HSV-2 serodiscordant couples reporting ≥3 episodes of vaginal intercourse during previous 3 months, with seropositive partner age ≥18 years, CD4 count ≥0.250 x 10^9 cells/L
Fideli et al, 2001[155]	Case-control	HIV testing and counseling center; Lusaka, Zambia; assumed high prevalence	Mean followup: 22 months	Transmitters vs. nontransmitters	Mean age, years Male transmitters: 33 Female transmitters: 26 Male nontransmitters: 36 Female nontransmitters: 27 Viral load, copies/mL <10,000: 5/63 male transmitters, 3/41 female transmitters, 16/114 male nontransmitters, 32/93 female nontransmitters 10,001–99,999: 22/63 male transmitters, 16/41 female transmitters, 46/114 male nontransmitters, 38/93 female nontransmitters >100,000: 36/63 male transmitters, 22/41 female transmitters, 52/114 male nontransmitters, 23/93 female nontransmitters	Discordant HIV status, cohabitating for at least 6 months, women younger than age 48 years and men younger than age 65 years
Fisher et al, 2010[156]	Retrospective and prospective cohort	HIV treatment clinic, Brighton and Sussex University Hospital, United Kingdom	2000–2006	1 cohort, stratified by viral load	Not reported	HIV-infected men who have sex with men attending an HIV treatment clinic
Community viral load studies						
Das et al, 2010[157]	Retrospective cohort (using cross-sectional community viral load data)	San Francisco, CA	2004–2008	None (analyzes association between community viral load and demographics or treatments)	Mean community viral load: 23,348 copies/mL Female sex: 6% (786/12,512)	Reported HIV-positive diagnosis
Montaner et al, 2010[158]	Retrospective cohort	British Columbia, Canada	1996–2009	None	Not reported	Reported HIV-positive diagnosis
Wood et al, 2009[159]	Prospective cohort	Inner city Vancouver, Canada	1996–2007	HIV-positive vs. HIV-negative	HIV-positive vs. HIV-negative Median age: 36.6 vs. 36.1 years Female sex: 40.2% vs. 32.5% White: 43.4% vs. 37.1%	Injection drug users

Appendix B27. Key Question 6a: Evidence Table of Studies of Effect of Viremia on HIV Transmission Rates

Author, Year	Exclusion criteria	Number screened/eligible/ enrolled/withdrawals/% analyzed	Outcomes	Adverse events	Funding source and role	Quality rating
Studies examining individual patients						
Donnell et al, 2010[105]	History of AIDS-defining condition, receiving ART	3408 enrolled; 3381 analyzed Note: 27 couples' baseline serology did not confirm HIV-1 and HSV-2	Pre-ART vs. post-ART transmission Overall: 102/4558 person-years (incidence rate, 2.24 [95% CI, 1.84–2.72]) vs. 1/273 person-years (incidence rate, 0.37 [95% CI, 0.09–2.04]) Overall adjusted incidence rate ratio: 0.08 (95% CI, 0.00–0.57); p=0.004	Not reported	Bill & Melinda Gates Foundation; University of Washington Center for AIDS Research; UW AIDS Clinical Trials Group Virology Support Laboratory; United States National Institutes of Health	Good
Fideli et al, 2001[155]	None	1022 enrolled; 129 linked transmission pairs; 109 (84.5%) analyzed compared with 208 consecutive controls	Median viral load, transmitters vs. nontransmitters 123,507 vs. 51,310 (p<0.001)	Not reported	National Institutes of Health	Fair
Fisher et al, 2010[156]	None	1144 eligible; 859 enrolled	Adjusted rate ratio of tranmission risk per log_{10} higher viral load: RR, 1.61 (95% CI, 1.15–2.25); p=0.005	Not reported	University College London Hospitals/ University College London National Institute for Health Research Comprehensive Biomedical Research Center; European Community's Seventh Framework Programme	Fair
Community viral load studies						
Das et al, 2010[157]	None	12,512 seroconversions	Asssociation between decreasing community viral load and decreasing new HIV diagnoses Mean community viral load: p=0.003 Total community viral load: p=0.002	Not reported	California HIV/AIDS Research Program	Fair
Montaner et al, 2010[158]	None	Active ART users: 5413	Association between number of individuals on ART and number of new HIV diagnoses: 0.89 (p<0.0001) Estimated number of new HIV cases per log_{10} decrease in viral load: 0.86 (95% CI, 0.75–0.98)	Not reported	US National Institutes of Health; Canadian Institutes of Health Research; Michael Smith Foundation for Health Research; Merck; Gilead; ViiV Healthcare	Fair
Wood et al, 2009[159]	Not reported	Not reported; not reported; 2051 Of 1796 eligible HIV-negative individuals, 20.4% (367/1796) were lost to followup	Time to seroconversion according to plasma HIV RNA (per log_{10} increase): HR, 3.32 (95% CI, 1.82–6.08); p<0.001	Not reported	US National Institutes of Health, Canadian Institutes of Health Research	Fair

ART = antiretroviral therapy; HSV-2 = herpes simplex virus 2.

Appendix B28. Key Question 6a: Quality Assessment of Cohort Studies

Author, Year	Did study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were groups comparable at baseline on key prognostic factors (by restriction or matching)?	Did study maintain comparable groups through the study period?	Did study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified, defined, and ascertained using accurate methods?	Quality rating
Das et al, 2010[157]	Yes; all attempted	NR	NR	Yes	Unclear	No	Yes	NR	Yes	Fair
Donnell et al, 2010[105]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Fideli et al, 2001[155]	No	Yes; not age and STDs	Yes	Yes	Unclear	Yes	Yes	No	Yes	Fair
Fisher et al, 2010[156]	Unclear	NR	NR	Yes	Unclear	Yes	Yes	Yes; 25% loss	Yes	Fair
Montaner et al, 2010[158]	Yes; all attempted	NR	NR	Yes	Unclear	No	Yes	NR	Yes	Fair
Wood et al, 2009[159]	No; chain-referral (snowball) sampling	Yes; not sex and ethnicity	Yes	Yes	Unclear	Yes	Yes	Yes; 20.4% loss in HIV-negative group	Yes	Fair

NR = not reported; STD = sexually transmitted disease.

Appendix B29. Key Question 6b: Evidence Table of Studies of Effects of Risky Behaviors on HIV Transmission Rates

Author, Year	Type of study	Location/setting/high or low prevalence population (based on 0.1% prevalence rate)	Study duration/ followup	Treatment groups (or comparision groups if observational study)	Demographics/ baseline disease	Eligibility criteria	Exclusion criteria
Del Romero et al, 2010[93]	Prospective cohort	Madrid, Spain; HIV clinic; high prevalence (no ART: 9.2%, ART: 8.7%)	1355 couple-years	ART vs. no ART	Index cases 83% male Female median age, 29 years Male median age, 32 years Median CD4 count, 0.500 x 10^9 cells/L (IQR, 0.295–0.700 x 10^9) Median plasma HIV RNA, 200 copies/mL (IQR, not detectable–8876) 54% detectable viral load	All heterosexual couples who had an ongoing sexual relationship over preceding 6 months, were serodiscordant for HIV, and returned for ≥1 followup visit	Nonindex partner with previous HIV diagnosis or known risk exposures other than relationship with index partner
Wang et al, 2010[114]	Prospective cohort	County hospitals, community health centers, and home residences in Zhumadian City, Henan Province, China	Median followup: 2.84 years	Converters vs. nonconverters	Sex: 43.3% (835/1927) female Mean age: 44.2 years Race/ethnitic: 99.6% Han, 0.4% Hui	HIV-negative persons living with HIV-positive partner, in a stable marriage, and providing informed consent	None

Author, Year	Number screened/eligible/ enrolled/withdrawals/ % analyzed	Outcomes	Adverse events	Funding source and role	Quality rating
Del Romero et al, 2010[93]	648 eligible; 602 serodiscordant at first visit; 424 with followup	Proportion engaging in unprotected sexual intercourse, no ART vs. ART: 273/476 (57%) vs. 69/149 (46%); p=0.019 Proportion of couples with previous pregnancies, no ART vs. ART: 226/476 (47%) vs. 53/149 (36%); p=0.011 Transmission, no ART vs. ART: 5 instances vs. 0 instances Rate per 100 couple-years, no ART vs. ART: 0.4 (95% CI, 0.2–1.4) vs. 0 (95% CI, 0–1.1)	Not reported	Grant from FIPSE (foundation formed by Spanish Ministry of Health and Consumer Affairs and multiple pharmaceutical companies), and by Spanish Network for Research on AIDS	Fair
Wang et al, 2010[114]	4301 eligible; 1927 enrolled	Transmission rate: 1.71/100 person-years ART vs. no ART: 4.8% vs. 3.2%; p=0.12 Never switched ART regimen vs. switched ART regimen: RR, 2.66 (95% CI, 1.15–6.15); p=0.11 with multivariate analysis	<u>Reasons for switching ART regimens</u> Severe gastrointestinal symptoms: 31.8% (74/233) Skin rash: 8.6% (20/233) Anemia: 5.6% (13/233) Abnormal liver function test: 4.7% (11/233) Bone marrow suppression: 3.9% (9/233)	11th 5-year plan of China; International Clinical Research Fellows Program at Vanderbilt	Fair

ART = antiretroviral therapy; IQR = interquartile range.

Appendix B30. Key Question 6b: Quality Assessment of Cohort Studies

Author, Year	Did study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were groups comparable at baseline on key prognostic factors (by restriction or matching)?	Did study maintain comparable groups through the study period?	Did study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did article report attrition?	Did study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified, defined, and ascertained using accurate methods?	Quality rating
Del Romero et al, 2010[93]	Yes	No; differ on many factors	Yes	Yes; questionnaire, blood draw	Unclear	No	No	No	Yes	Fair
Wang et al, 2010[114]	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes; only 44.8% of sample completed surveys	Yes	Fair