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Screening for HIV Infection in Asymptomatic, Nonpregnant Adolescents and Adults: A Systematic Review for the U.S. Preventive Services Task Force

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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Suggested Citation

Structured Abstract

**Background:** A 2012 systematic review on HIV screening for the U.S. Preventive Services Task Force (USPSTF) found strong evidence that antiretroviral therapy (ART) is associated with improved clinical outcomes in persons with CD4+ T helper cell (CD4) counts less than 500 cells/mm³ and substantially decreases risk of HIV transmission, with certain antiretroviral agents potentially associated with long-term cardiovascular harms. The USPSTF previously found HIV screening tests to be highly accurate.

**Purpose:** To systematically update the 2012 USPSTF review on screening for HIV in adolescents and adults, focusing on research gaps identified in the prior review.

**Data Sources:** We searched the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and MEDLINE (2012 to June 2018) and manually reviewed reference lists, with surveillance through January 2019.

**Study Selection:** Randomized, controlled trials (RCTs) and controlled observational studies on benefits and harms of screening versus no screening and on the yield of screening at different intervals; the effects of earlier versus later initiation of ART; and long-term (≥2 years) harms of ART.

**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):** We did not identify any studies on benefits or harms of HIV screening versus no screening, or on the yield of repeat versus one-time screening or of screening at different intervals. Two new RCTs conducted completely or partially in low-resource settings found initiation of ART in persons with CD4 counts greater than 500 cells/mm³ associated with lower risk of composite clinical outcomes (mortality, AIDS-defining events, or serious non-AIDS events) (relative risk [RR], 0.44 [95% confidence interval (CI), 0.31 to 0.63] and RR, 0.57 [95% CI, 0.35 to 0.95]); early initiation of ART was not associated with increased risk of cardiovascular events. A large observational study also found initiation of ART in persons in high-resource settings with CD4 counts greater than 500 cells/mm³ to be associated with reduced risk of mortality or AIDS events, although the magnitude of effect was smaller. New evidence regarding the association between abacavir use and increased risk of cardiovascular events was inconsistent, and certain antiretroviral regimens were associated with increased risk of long-term neuropsychiatric, renal, hepatic, and bone adverse events.

**Limitations:** Only English-language articles were included. Observational studies were included. Studies conducted in resource-poor settings were included, which might limit applicability to general screening in the United States.

**Conclusions:** New evidence extends effectiveness of ART to asymptomatic persons with CD4 counts greater than 500 cells/mm³. Certain ART regimens may be associated with long-term cardiovascular, neuropsychiatric, hepatic, renal, or bone harms, but early initiation of ART is not
associated with increased risk of cardiovascular events. Research is needed to inform optimal screening intervals.
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Chapter 1. Introduction and Background

Purpose

The purpose of this report is to update a previous review\(^1\)\(^2\) commissioned by the U.S. Preventive Services Task Force (USPSTF) on benefits and harms of screening for HIV infection. This report will be used by the USPSTF to update its 2013 recommendation\(^3\) on screening for HIV in adolescents and adults, which was based on the prior review. Prenatal HIV screening is addressed in a separate report.\(^4\)

In 2013, the USPSTF recommended that clinicians screen all adolescents and adults ages 15 to 65 years for HIV infection, as well as younger adolescents and older adults at increased risk (“A” recommendation). This recommendation reaffirmed and expanded on the prior (2005) USPSTF recommendation,\(^5\) in which the USPSTF recommended that clinicians screen all adolescents and adults at higher risk of HIV infection (“A” recommendation). In 2005, the USPSTF did not recommend for or against screening for HIV in adolescents and adults not at increased risk of HIV infection.

The expanded 2013 USPSTF recommendation was based on evidence supporting greater benefits of screening. Studies found that earlier treatment of HIV infection (i.e., at CD4+ T helper [CD4] cell counts of 350 to 500 cells/mm\(^3\)) was associated with improved clinical outcomes compared with delayed treatment, that antiretroviral therapy (ART) was associated with decreased risk of transmission,\(^1,2\) and that undiagnosed HIV infection was present in a significant proportion of patients. The USPSTF previously found strong evidence that standard screening tests accurately detect HIV infection, and that interventions, particularly ART, are associated with improved health outcomes in patients with more advanced HIV infection. The USPSTF determined that the harms associated with HIV screening and treatment are small or manageable and are substantially outweighed by the benefits. The USPSTF also reviewed modeling studies that estimated cost-effectiveness ratios of less than $50,000 (2004 U.S. dollars) or less than $60,000 (2007 U.S. dollars) per quality-adjusted life-year for screening versus no screening in settings with an HIV prevalence as low as 0.10 to 0.20 percent.\(^6,7\)

Condition Background

Condition Definition

HIV is a retrovirus that infects human immune cells, in particular CD4 cells. Left untreated, HIV infection results in progressive immunodeficiency, AIDS, and death.\(^8\) AIDS is a life-threatening condition characterized by presence of HIV infection and severe immune dysfunction (CD4 count \(\leq\)200 cells/mm\(^3\)) or one or more AIDS-defining neoplastic conditions or opportunistic infections.\(^8\) HIV-1 infection is the most common variant in the United States. HIV-2 infection is rare in the United States, less clinically severe, and endemic in parts of West Africa.\(^9\)
Prevalence and Burden of Disease/Illness

Since the first cases of AIDS were reported in 1981, more than 700,000 persons diagnosed with AIDS in the United States have died. The Centers for Disease Control and Prevention (CDC) estimates that 1 million persons in the United States were living with HIV infection in 2016. In 2015, an estimated 15 percent of infected persons were unaware of their infection. This represents a decrease since 2008, when approximately 20 percent of infected persons were estimated to be unaware of their positive status, and from 2010, when 17.1 percent were estimated to be unaware of their status. The number of new HIV infections annually in the United States has decreased slightly in recent years, from about 42,000 in 2011 to 40,000 each year from 2013 to 2016. Approximately 530,000 persons were living with AIDS in 2016. The estimated delay in diagnosis of HIV infection declined from a median of 3.6 years in 2011 to 3.0 years in 2015.

Groups disproportionately affected by HIV infection in the United States include men who have sex with men and black and Hispanic/Latino persons. Between 2006 and 2009, there was a 21 percent increase in HIV incidence among persons ages 13 to 29 years, driven largely by a 34 percent increase among men who have sex with men, the only risk group to experience a statistically significant increase in incidence during this period. In 2017, 31,239 (81%) HIV diagnoses were among adult and adolescent males (age ≥13 years), 7,401 (19%) among adult and adolescent females, and 99 among children younger than age 13 years. Persons ages 20 to 34 years accounted for half of the new diagnoses and had the highest incidence of HIV infection (25.6 to 32.8 per 100,000 persons). Among adolescents, the annual incidence of HIV infection rises sharply from age 13 to 14 years (0.3 per 100,000 persons) to age 15 to 19 years (8.1 per 100,000 persons). When stratified by race/ethnicity, 43 percent of new diagnoses occurred in black, 26 percent in white, and 25 percent in Hispanic/Latino populations. Among males, men who have sex with men are the most common transmission method (82%), followed by heterosexual contact (7.3%), injection drug use (4.4%), and both men who have sex with men and injection drug use (4.0%). Among females, heterosexual contact is the most common transmission method (86%), followed by injection drug use (14%).

Etiology and Natural History

HIV infection is acquired through mucosal or intravenous exposure to infected bodily fluids such as blood, semen, and genital tract secretions. Factors facilitating sexual transmission include the presence of sexually transmitted infections (STIs), certain sexual practices (e.g., penile-anal or penile-vaginal intercourse without a condom, sex with multiple partners, sex with persons with or at high risk of HIV infection), and high viral load in the infected partner. In persons who inject drugs, factors associated with HIV infection include increased frequency of injection drug use, sharing needles, and certain injection practices (e.g., backloading, or injecting drugs from one syringe into the back of another opened syringe).

The primary HIV infection syndrome usually develops 2 to 4 weeks following initial exposure to HIV. Acute infection is associated with nonspecific symptoms such as fever and fatigue that may resemble infectious mononucleosis, but is often unrecognized. Very early after acute infection, there is rapid virus production that declines to a variable set point as the host immune
Although a small proportion of untreated persons infected with HIV remain asymptomatic and show little evidence of progressive immune suppression after 10 or more years of infection, nearly all eventually develop AIDS.\textsuperscript{8} Before the era of highly active antiretroviral therapy (HAART), 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.\textsuperscript{30,31}

The primary mechanism by which chronic HIV infection causes immune deficiency is through a decrease in the level and functioning of CD4 cells. In untreated HIV infection, the CD4 count declines an average of 50 to 75 cells/mm\textsuperscript{3} per year.\textsuperscript{32} Most patients with CD4 counts greater than 200 cells/mm\textsuperscript{3} are either asymptomatic or have mild disease,\textsuperscript{33} although research indicates an increased risk of AIDS or even death in patients with CD4 counts greater than 500 cells/mm\textsuperscript{3}.\textsuperscript{34} Patients with CD4 counts less than 200 cells/mm\textsuperscript{3} have advanced immune deficiency and are at markedly increased risk of AIDS-related opportunistic infections, other AIDS-related complications, and AIDS-associated mortality.\textsuperscript{35-37}

A higher HIV viral load is a strong independent predictor of more rapid progression to AIDS.\textsuperscript{35-40} Other predictors of more rapid progression include older age at the time of infection,\textsuperscript{30,31,35,36,39,41,42} more severe symptoms at the time of primary HIV infection,\textsuperscript{43} and other clinical and genetic factors. One factor associated with slow progression is the C-C chemokine receptor type 5 delta32 genotype.\textsuperscript{44-48}

**Risk Factors**

Persons at increased risk of HIV infection include men who have sex with men; men and women who have unprotected vaginal or anal intercourse with more than one partner; men and women who exchange sex for drugs or money; persons with a history of or current injection drug use; persons seeking treatment for other STIs or who have a sexual partner with STIs; persons with a history of blood transfusion from 1978 to 1985; persons whose past or present sex partners are infected with HIV, men who have sex with men, or persons who inject drugs; persons who are transgender; and persons who do not report one of these risk factors but who request HIV testing.\textsuperscript{49-51} Settings in which the prevalence of HIV infection is often greater than 1 percent include STI clinics, correctional facilities, homeless shelters, tuberculosis clinics, clinics specialized in the care of sexual and gender minorities, and clinics caring for an adolescent community with a high prevalence of STIs.\textsuperscript{52}

**Rationale for Screening/Screening Strategies**

Identification and treatment of asymptomatic persons who are infected with HIV may help identify patients at higher CD4 counts before they develop severe immune deficiency or present with an AIDS-defining event. It may also lead to earlier initiation of interventions (including ART and prophylaxis for opportunistic infections)\textsuperscript{52} that reduce the risk of progression to AIDS, AIDS-defining clinical events, and mortality.\textsuperscript{1,2} Identification of asymptomatic persons who are
infected with HIV may also help reduce the risk of transmission by reducing behaviors \(^{53}\) associated with transmission or through effects of ART on transmission risk. \(^{54-57}\) Identification through screening could also lead to additional benefits through partner notification and testing. Persons at high risk of HIV infection who test negative on screening could benefit from pre-exposure prophylaxis with ART to reduce risk of HIV acquisition; \(^{58}\) the USPSTF commissioned a separate report to address pre-exposure prophylaxis. \(^{59}\)

**Interventions/Treatment**

There remains no effective vaccine to prevent HIV infection. Interventions for patients with HIV infection include ART, prophylaxis for opportunistic infections, immunizations, Papanicolaou and human papillomavirus testing, \(^{60}\) 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. \(^{61}\) As all currently recommended antiretroviral regimens meet criteria for HAART, this report will simply use the term “ART,” in accordance with current treatment guidelines. Current guidelines recommend initial ART regimens containing an integrase strand transfer inhibitor plus two nucleoside reverse transcriptase inhibitors (NRTIs) in most persons with HIV infection; other regimens are recommended in certain clinical situations. \(^{61}\) Of the interventions used to treat chronic HIV infection, ART has the greatest effect on clinical outcomes, including survival. \(^{62}\) Clinical practice has evolved from initiation of ART in persons with more advanced HIV infection toward use in all infected persons. \(^{61}\) Detailed and regularly updated guidelines for the U.S. population regarding specifically recommended antiretroviral regimens and chemoprophylaxis for opportunistic infections are available. \(^{61,63}\)

**Current Clinical Practice/Recommendations of Other Groups**

The CDC introduced a new HIV testing algorithm in 2014 that begins with a combined assay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigens, with supplemental testing following a reactive assay to differentiate HIV-1 and HIV-2 antibodies. If supplemental testing is nonreactive or indeterminate, \(^{64}\) HIV-1 ribonucleic acid testing is performed to differentiate acute HIV infection from a false-positive test result. Advantages of the new algorithm are earlier diagnosis of acute HIV infection (median, 18 days from time of infection until detection with combined antigen-antibody assays), \(^{65}\) fewer indeterminate results, faster turnaround time, and more accurate diagnosis of HIV-2 infection. \(^{56,67}\) The use of repeatedly reactive enzyme immunoassay on an office-based venipuncture specimen followed by confirmatory Western blot or immunofluorescent assay for positive tests, the prior standard method for testing for HIV infection, was previously reviewed by the USPSTF and found to be associated with a sensitivity and specificity greater than 99 percent. \(^{68,69}\) Point-of-care rapid HIV tests (primarily antibody-based) that can be used in nonclinical settings are also highly accurate and have turnaround times that range from 15 to 20 minutes. \(^{70}\)

As of 2010, about 45 percent of U.S. adults had ever been tested for HIV infection. \(^{71}\) HIV screening rates vary by state, age, sex, race/ethnicity, and other factors. Among persons age 18 years or older, the proportion ever tested for HIV infection ranges from 35 percent among those
ages 18 to 24 years to 57 percent among those ages 25 to 44 years, and from 41 percent in white persons to 65 percent in black persons. Testing rates are lower in men (40%) than in women (50%). Among high school students who have had sexual intercourse, 22 percent reported ever have been tested. In 2015, 71 percent of men who have sex with men (76% in black and 70% in white men), 58 percent of persons who inject drugs, and 41 percent of persons at risk of HIV infection due to heterosexual contact reported testing in the past 12 months. The median interval from infection to diagnosis (known as diagnosis delay) was estimated at 3.0 years. Diagnosis delay varies by race/ethnicity, from about 2.2 years in white persons to 3.3 to 4.2 years in nonwhite races/ethnicities, and by transmission category, with the longest delay in males at risk due to heterosexual contact (4.9 years).

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 was documented to be less than 0.1 percent within the community. 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, to reduce barriers to testing. The CDC recommended that persons get tested at least once in their lifetimes and those with risk factors get tested more frequently (e.g., annually), and recently recommended that clinicians consider testing sexually active men who have sex with men more frequently (e.g., every 3 or 6 months), based on risk behaviors, HIV prevalence in the community, and other considerations.

In 2009, the American College of Physicians issued a guidance statement on HIV screening consistent with the CDC approach, and the Infectious Diseases Society of America recommended routine HIV screening for all sexually active adults. The American College of Obstetricians and Gynecologists recommends that all females ages 13 to 64 years be tested at least once in their lifetime and then annually thereafter if they have risk factors. The American Academy of Pediatrics recommends offering routine HIV testing to all adolescents at least once by age 16 to 18 years when prevalence of HIV is greater than 0.1 percent in the community, and testing of all sexually active adolescents and those with risk factors in low-prevalence settings. The American Academy of Family Physicians follows the 2013 USPSTF recommendation, except it recommends that routine screening not begin until age 18 years.
Chapter 2. Methods

Key Questions and Analytic Framework

Using the methods developed by the USPSTF, the USPSTF and the Agency for Healthcare Research and Quality 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 1). Key informants with expertise in HIV screening were surveyed for input, and the draft Research Plan was posted for public comment prior to finalization.

Key Questions

1. What are the benefits of screening for HIV infection in asymptomatic, nonpregnant adolescents and adults on mortality, AIDS and opportunistic infections, quality of life, function, and reduced transmission of HIV and other STIs?
2. What is the yield (number of new diagnoses per tests performed) of screening for HIV infection at different intervals in asymptomatic, nonpregnant adolescents and adults, and how does the screening yield vary in different risk groups?
3. What are the harms of screening for HIV infection in asymptomatic, nonpregnant adolescents and adults?
4. What are the effects of initiating ART in adolescents and adults with chronic HIV infection at a higher versus lower CD4 count on mortality, AIDS and opportunistic infections, quality of life, function, and reduced transmission of HIV and other STIs?
5. What are the longer-term harms (≥2 years) associated with currently recommended ART regimens?

Search Strategies

We searched the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Ovid MEDLINE (2012 through June 2018) for relevant studies and systematic reviews. Search strategies are available in Appendix A1. We also reviewed reference lists of relevant articles.

After June 2018, we conducted surveillance through article alerts and targeted searches of high-impact journals to identify major studies that may affect conclusions. The last surveillance was conducted on January 25, 2019, and identified no primary research that would meet inclusion criteria for this review.

Study Selection

All titles and abstracts identified through searches were independently reviewed by two members
of the research team for eligibility using predefined inclusion/exclusion criteria, as specified using the PICOTS (population, intervention, comparator, outcome, timing, study design) framework (Appendix A2). Studies marked for possible inclusion by either reviewer underwent full-text review. All results were tracked in an EndNote® database (Thomson Reuters, New York, NY).

Each full-text article was independently reviewed by two trained members of the research team for inclusion or exclusion on the basis of the eligibility criteria. If the reviewers disagreed, conflicts were resolved by discussion and consensus or by consulting another member of the review team. Results of the full-text review were also tracked in the EndNote® database, including the reason for exclusion. The selection of literature is summarized in the literature flow diagram (Appendix A3). Appendix A4 lists the included studies, and Appendix A5 lists the excluded studies with reasons for exclusion.

**Scope of Review**

This update is a focused review to inform an update of the prior USPSTF recommendation for screening for HIV infection in the general population (“A” recommendation). It targets gaps identified in the prior review, including direct evidence on benefits and harms of screening, the yield of screening at different intervals, and longer-term harms of ART, concentrating on regimens currently recommended by the U.S. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents (Appendix A6). This update also includes a Key Question on effects of earlier versus later initiation of ART, given evolution in clinical practice from reserving ART for patients with more advanced HIV infection to offering it to all patients. We focused on studies on initiation of ART in patients with baseline CD4 counts greater than 350 cells/mm³, as the effectiveness of ART in patients with more advanced immune deficiency is well established.

The USPSTF previously determined that ART and prophylaxis for immunologically advanced HIV infection are effective and that screening (with rapid or standard HIV tests) is highly accurate. Given recommendations for universal HIV screening from the USPSTF and other groups, the update does not address universal versus targeted screening, which the USPSTF determined was not relevant for current clinical practice.

The target population for Key Questions related to screening was nonpregnant adolescents (defined as persons ages 13 to <18 years) and adults without signs or symptoms of HIV infection, regardless of risk of HIV infection. Patient subgroups of interest included those defined by age and race/ethnicity. The screening intervention is combination antigen/antibody testing, according to the 2014 CDC testing algorithm, or point-of-care rapid testing (usually antibody-based). Outcomes were mortality, risk of AIDS and opportunistic infections, quality of life, function, risk of HIV transmission and STIs, harms of screening (e.g., harms due to false-positive results, anxiety, effects of labeling, and partner discord, abuse, or violence), and long-term harms of currently recommended ART (defined as harms occurring at least 2 years after initiation of therapy), with a focus on cardiovascular, renal, hepatic, and bone (fracture) harms. For screening at different intervals, we assessed the yield of screening, defined as the number of
new diagnoses per number of tests performed. For all Key Questions, we included RCTs, cohort studies, and case-control studies. This update focuses on studies conducted in the United States and other high-income countries with low prevalence of HIV infection and in which HIV management is similar to that in the United States, unless studies are not available in those settings.

Data Abstraction and Quality Rating

For studies meeting inclusion criteria, we created data abstraction forms to summarize characteristics of study populations, interventions, comparators, outcomes, study designs, settings, and methods. One investigator conducted data abstraction, which was reviewed for completeness and accuracy by another team member. Randomized trials of early versus delayed ART primarily reported outcomes using hazards ratios (HRs). To estimate absolute risk differences, we calculated relative risks (RRs) based on the event rates reported in the trials. Because the RRs and HRs were very similar, we reported results based on RRs. Both HRs and calculated RRs are presented in the evidence table.

Predefined criteria were used to assess the quality of individual controlled trials, systematic reviews, and observational studies by using criteria developed by the USPSTF; studies were rated as “good,” “fair,” or “poor” per USPSTF criteria, depending on the seriousness of the methodological shortcomings (Appendix A7). For each study, quality assessment was performed by two team members. Disagreements were resolved by consensus.

Data Synthesis

For all Key Questions, the overall quality of evidence was determined using the approach described in the USPSTF Procedure Manual. Evidence was rated “good,” “fair,” or “poor,” based on study quality, consistency of results between studies, precision of estimates, study limitations, risk of reporting bias, and applicability.

External Review

The draft report was reviewed by content experts (Appendix A8), USPSTF members, Agency for Healthcare Research and Quality Project Officers, and collaborative partners and was posted for public comment; it has been revised accordingly.

Response to Public Comments

The draft report was posted for public comment from November 20, 2018 to December 26, 2018, and few comments were received. In response to the comments, we updated the report with recently published 2017 HIV surveillance data, revised the section on “Risk Factors” to focus on sexual risk behaviors (specifically, men who have sex with men) rather than sexual
orientation, and added having a partner with an STI as a risk factor.
Chapter 3. Results

A total of 4,886 references from electronic database searches and manual searches of recently published studies were reviewed for this update, and 361 full-text papers were evaluated for inclusion. Eighteen new studies (in 29 articles) were included, and 11 studies were carried forward from the prior USPSTF report. Included studies and quality ratings are described in Appendix B Tables 1–14.

Key Question 1. What Are the Benefits of Screening for HIV Infection in Asymptomatic, Nonpregnant Adolescents and Adults on Mortality, AIDS and Opportunistic Infections, Quality of Life, Function, and Reduced Transmission of HIV and Other STIs?

As in the prior USPSTF review, no randomized trial or observational study compared clinical outcomes between adults and adolescents screened and not screened for HIV infection.

Key Question 2. What Is the Yield of Screening for HIV Infection at Different Intervals in Asymptomatic, Nonpregnant Adolescents and Adults, and How Does the Screening Yield Vary in Different Risk Groups?

As in the prior USPSTF review, no randomized trial or observational study evaluated the yield of repeated 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, or repeat screening at different intervals).

Key Question 3. What Are the Harms of Screening for HIV Infection in Asymptomatic, Nonpregnant Adolescents and Adults?

No randomized trial or observational study compared harms between adults and adolescents screened and not screened for HIV infection.
Key Question 4. What Are the Effects of Initiating ART in Adolescents and Adults With Chronic HIV Infection at a Higher Versus Lower CD4 Count on Mortality, AIDS and Opportunistic Infections, Quality of Life, Function, and Reduced Transmission of HIV and Other STIs?

Summary

Initiation of ART at CD4 counts greater than 500 cells/mm³:

- The prior USPSTF review found inconsistent effects of initiation of ART in persons infected with HIV with CD4 counts greater than 500 cells/mm³ versus delayed initiation on clinical outcomes, based on four observational studies.81-84
- Two subsequent RCTs found immediate initiation of ART in persons infected with HIV with CD4 counts greater than 500 cells/mm³ associated with decreased risk of composite clinical outcomes (mortality, AIDS-defining events, or serious non-AIDS events [e.g., bacterial infection, cancer]) compared with delayed initiation (RR, 0.44 [95% confidence interval (CI), 0.31 to 0.63] and RR, 0.57 [95% CI, 0.35 to 0.95]).85,86 Effects on all-cause mortality (RR, 0.58 [95% CI, 0.29 to 1.18] and RR, 0.79 [95% CI, 0.24 to 2.57]) and AIDS-related events/progression to AIDS also favored immediate initiation of ART (RR, 0.28 [95% CI, 0.16 to 0.51] and RR, 0.55 [95% CI, 0.29 to 1.05]).
- Two new observational studies of U.S. and European cohorts found initiation of ART in persons infected with HIV with CD4 counts greater than 500 cells/mm³ associated with lower risk of death and AIDS-related events than delayed initiation, although one study reported effects smaller than those observed in the randomized trials.87,88

Initiation of ART at CD4 counts of 350 cells/mm³ or greater:

- The prior USPSTF review found initiation of ART at CD4 counts greater than 350 cells/mm³ associated with decreased risk of death or AIDS events after approximately 1.5 years compared with initiation at CD4 counts less than 250 cells/mm³, based on two RCTs (including one post hoc subgroup analysis) (RR, 0.31 [95% CI, 0.11 to 0.83] and RR, 0.61 [95% CI, 0.42 to 0.89]).85,89 One of the trials (HIV Prevention Trials Network [HPTN] 052) also found early initiation of ART associated with decreased risk of HIV transmission to uninfected partners after a median of 1.7 years (RR, 0.11 [95% CI, 0.04 to 0.32] for any transmission and RR, 0.04 [95% CI, 0.005 to 0.27] for virologically-linked transmission).85
- Longer (mean, 2.1 years) followup from one of the randomized trials (HPTN 052) included in the prior USPSTF review found initiation of ART at CD4 counts of 350 cells/mm³ or greater to less than 550 cells/mm³ associated with decreased risk of AIDS-related events versus initiation at CD4 counts less than 250 cells/mm³ (RR, 0.65 [95% CI, 0.44 to 0.95]); much of the difference in risk of AIDS-related events was related to effects on tuberculosis.90 Effects on all-cause (RR, 0.72 [95% CI, 0.33 to 1.57]) and AIDS-related mortality (RR, 0.25 [95% CI, 0.03 to 2.20]) favored early initiation of...
ART, but differences were not statistically significant.

- Longer (5.5 years) followup from the HPTN 052 trial also found early ART initiation associated with continued reduction in risk of HIV transmission to uninfected partners (RR, 0.32 [95% CI, 0.19 to 0.53] for any transmission and RR, 0.07 [95% CI, 0.02 to 0.22] for virologically-linked transmission).

- One cohort study published subsequent to the prior USPSTF review found initiation of ART at CD4 counts of 350 to 500 cells/mm\(^3\) associated with decreased risk of 5-year mortality (RR, 0.87 [95% CI, 0.79 to 0.95]) and 10-year mortality (RR, 0.93 [95% CI, 0.86 to 1.00]) compared with delayed initiation.\(^{88}\)

- Two RCTs found no association between early initiation of ART and increased risk of cardiovascular events, with one trial showing a potential protective effect (RR, 0.07 [95% CI, 0.004 to 1.24])\(^{89}\) and RR, 0.87 [95% CI, 0.40 to 1.88]).\(^{85}\)

**Evidence**

Effects of ART in reducing risk of mortality and AIDS-associated events in persons with advanced immunodeficiency (e.g., CD4 count <200 cells/mm\(^3\)) are well established. The prior USPSTF review focused on effects of ART in persons with less advanced immunodeficiency.\(^1\) It included one randomized trial conducted in Haiti that found initiation of ART at CD4 counts greater than 200 to less than 350 cells/mm\(^3\) was associated with decreased risk of mortality versus initiation at CD4 counts of 200 cells/mm\(^3\) or less (RR, 0.26 [95% CI, 0.11 to 0.63]).\(^{91}\)

Two trials in the prior USPSTF review found initiation of ART at CD4 counts greater than 350 cells/mm\(^3\) associated with decreased risk of death or AIDS events compared with initiation at CD4 counts less than 250 cells/mm\(^3\).\(^{55,89}\) A post hoc subgroup analysis of patients infected with HIV (n=477) enrolled in the open-label Strategies for Management of Antiretroviral Therapy (SMART) randomized trial with CD4 counts greater than 350 cells/mm\(^3\) at baseline (median, 447 cells/mm\(^3\)) found immediate initiation of ART associated with decreased risk of death or AIDS events compared with delayed initiation after a mean of 18 months (RR, 0.31 [95% CI, 0.11 to 0.83]).\(^{89}\) The subgroup analysis focused on persons who were ART naïve or had not received ART recently (within 6 months). The SMART trial was conducted in 33 primarily high-income countries and enrolled patients from 2002 to 2006. The open-label HPTN 052 trial, which enrolled 1,763 persons infected with HIV between 2007 and 2010 from primarily low- and middle-income countries with baseline CD4 counts between 350 and 550 cells/mm\(^3\) (median, 428 to 442 cells/mm\(^3\)), also found immediate initiation of ART associated with decreased risk of the combined endpoint of death or AIDS events after a median of 1.7 years (RR, 0.61 [95% CI, 0.42 to 0.89]).\(^{55}\) Results were strongly driven by effects on extrapulmonary tuberculosis (RR, 0.17 [95% CI, 0.05 to 0.59]), with no statistically significant effect on mortality (RR, 0.76 [95% CI, 0.34 to 1.72]). The HPTN 052 trial also found early initiation of ART associated with decreased risk of HIV transmission to partners who were not infected at baseline (RR, 0.11 [95% CI, 0.04 to 0.32] for any transmission and RR, 0.04 [95% CI, 0.005 to 0.27] for virologically-linked transmission). Neither study reported industry funding, other than donation of study drugs in the HPTN 052 trial. The prior USPSTF review also included four observational studies that consistently found an association between initiation of ART at CD4 counts between 350 and 500 cells/mm\(^3\) and decreased risk of mortality, or a trend toward decreased risk, compared with deferred or no ART (Table 1).\(^{81,82,84,92}\) Evidence on initiation of ART at CD4 counts greater than 500 cells/mm\(^3\) was only available from observational studies and did not consistently
demonstrate beneficial effects on clinical outcomes (Table 1).81-84 Neither the prior report nor this update found evidence on the effect of early versus later ART initiation on quality of life or function.

This update focuses on evidence on effects of initiation of ART in persons with CD4 counts greater than 350 cells/mm³. We identified longer-term (up to 5.5 years) followup data from the HPTN 052 trial,80,83 two new RCTs,85,86,94 and three large (n ≥1,000) fair-quality cohort studies (reported in four publications) conducted in the United States, Europe, and Canada87,88,95,96 on effects of initiating ART at higher versus lower CD4 counts (Table 2; Appendix B Tables 1-6).

The new International Network for Strategic Initiatives in Global HIV Trials Strategic Timing of Antiretroviral Treatment (INSIGHT START, or START) trial (n=4,685) randomized ART-naïve, HIV-positive participants with CD4 counts greater than 500 cells/mm³ (median, 651 cells/mm³) at baseline to immediate initiation of ART versus deferred initiation at CD4 counts less than 350 cells/mm³.85 Randomization occurred between 2009 and 2013. Mean age was 36 years and 26 percent of participants were female. START was an international study, with about half of participants enrolled from high-income geographic regions (United States, Europe, and Australia). Mean duration of followup was 3 years. The other new RCT, the African TEMPRANO ANRS 12136 trial (n=2,056), enrolled persons between 2008 and 2012 with baseline CD4 counts less than 800 cells/mm³ without an indication for ART, based on then-current World Health Organization (WHO) guidelines.86 Followup was 2.5 years. A prespecified subgroup analysis was conducted in persons with a CD4 count of 500 cells/mm³ or greater at baseline (~40% of trial population). About three-quarters of participants were women.

TEMPRANO ANRS 12136 utilized a 2×2 factorial design in which patients were randomized to isoniazid versus no isoniazid and to immediate or delayed initiation of ART; in addition, the treatment initiation thresholds for delayed ART varied over the course of the study, based on changing WHO guidance. At the beginning of the trial, criteria for delayed initiation of ART were a CD4 count less than 200 cells/mm³, WHO clinical stage 4, or a CD4 count of 200 to 350 cells/mm³ and WHO clinical stage 2 or 3. At the end of the trial, the criteria were a CD4 count less than 350 cells/mm³ regardless of WHO clinical stage, WHO clinical stage 2 or 3, or any CD4 count in patients with a seronegative partner (Table 2). Both the START and TEMPRANO ANRS 12136 trials evaluated a composite primary outcome consisting of mortality, AIDS-defining events, and serious non-AIDS events (e.g., bacterial infection, cancer); neither trial evaluated effects on quality of life, function, risk of HIV transmission, or other STIs. Neither of the new trials reported industry funding, other than donation of study drugs in the START trial. The START trial was rated good quality and TEMPRANO ANRS 12136 was rated fair quality due to open-label design and changing criteria for delayed initiation of ART. The HPTN 052 trial was previously rated good-quality (Appendix B Table 1).1

In the three new fair-quality cohort studies, sample sizes ranged from 3,532 to 55,826 (total n=63,478) (Table 2; Appendix B Tables 4–6).87,88,95,96 Two publications were based on data from the large HIV Cohorts Analyzed Using Structural Approaches to Longitudinal (HIV CAUSAL) Collaboration (n=55,826).87,95 HIV CAUSAL is a collaboration of 12 cohort studies in the United States and Europe with more than 70,000 participants (mean age, 35 years). Three-year data from the HIV CAUSAL Collaboration were included in the prior USPSTF report.82 New publications from the HIV CAUSAL Collaboration report 7-year outcomes87 and subgroup
analyses for adults older than age 50 years. The other two studies evaluated cohorts from Canada (n=4,120; mean age, 42 years) and the United States (n=3,532; approximately half of subjects ages 18 to 34 years). All studies reported analyses adjusted for confounders, most commonly age, sex, and HIV viral load at baseline, and focused on effects of ART on mortality and AIDS-associated events.

**Immediate Versus Delayed Initiation of ART in Persons With Baseline CD4 Counts Greater Than 500 cells/mm³**

In the prior review, evidence on effects of initiating ART at CD4 counts greater than 500 cells/mm³ versus delayed initiation was limited to observational studies and inconsistent in showing beneficial effects. Two new RCTs found early initiation of ART associated with beneficial effects on clinical outcomes in this population (Table 3; Appendix B Table 2). In the START trial, immediate initiation of ART in persons with CD4 counts greater than 500 cells/mm³ at baseline was associated with decreased risk of the primary composite outcome of all-cause mortality, serious AIDS-related events, and serious non–AIDS-related events after a mean of 3 years (1.8% vs. 4.1%; RR, 0.44 [95% CI, 0.31 to 0.63]; adjusted risk difference [ARD], -2.3% [95% CI, -3.2 to -1.3]), compared with delayed initiation at CD4 counts less than 350 cells/mm³. When outcomes were disaggregated, immediate initiation of ART was associated with reduced risk of serious AIDS-related events (0.6% vs. 2.1%; RR, 0.28 [95% CI, 0.16 to 0.51]; ARD, -1.52% [95% CI, -2.18 to -0.86]), tuberculosis (0.3% vs. 0.8%; RR, 0.30 [95% CI, 0.12 to 0.76]; ARD, -0.59% [95% CI, -1.01 to -0.17]), and serious bacterial infection (0.6% vs. 1.5%; RR, 0.39 [95% CI, 0.21 to 0.73]; ARD, -0.92% [95% CI, -1.51 to -0.34]). Effects on all-cause mortality (0.5% vs. 0.9%; RR, 0.58 [95% CI, 0.29 to 1.18]) and AIDS-related mortality (0.04% vs. 0.2%; RR, 0.25 [95% CI, 0.03 to 2.27]) favored immediate initiation of ART, but effects were not statistically significant and there were only 5 cases of AIDS-related mortality (Table 3). Results for the primary outcome were similar when patients were stratified according to whether they were from a high- or low-income geographic region (HR, 0.39 vs. 0.48; p=0.55 for interaction), and in subgroup analyses based on age (older or younger than age 35 years), sex, race/ethnicity, baseline HIV viral load, smoking status, and Framingham 10-year cardiovascular risk. In the TEMPRANO ANRS 12136 trial, in a prespecified subgroup analysis of patients with CD4 counts of 500 cells/mm³ or greater at baseline, immediate initiation of ART was associated with decreased risk of the primary composite outcome of all-cause mortality, progression to AIDS, AIDS-defining cancer, or non–AIDS-defining invasive bacterial disease after 2.5 years (5.3% vs. 9.2%; RR, 0.57 [95% CI, 0.35 to 0.95]; ARD, -3.9% [95% CI, -7.4 to -0.4]). Effects on all-cause mortality (1.1% vs. 1.5%; RR, 0.79 [95% CI, 0.24 to 2.57]), progression to AIDS (3.2% vs. 5.8%; RR, 0.55 [95% CI, 0.29 to 1.05]), tuberculosis (2.8% vs. 5.1%; RR, 0.54 [95% CI, 0.27 to 1.09]) and invasive bacterial disease (1.1% vs. 1.9%; RR, 0.59 [95% CI, 0.20 to 1.80]) also favored immediate initiation of ART, but effects were not statistically significant (Table 3). Results were similar when adjusted for study center and concomitant isoniazid use (Appendix B Table 2).

Results from cohort studies published subsequent to the prior USPSTF report were consistent with the RCTs in showing effectiveness of initiating ART at CD4 counts greater than 500 cells/mm³. An analysis of the HIV CAUSAL Collaboration (n=55,826; median baseline CD4 count, 376 cells/mm³) found ART initiation at CD4 counts less than 350 cells/mm³ associated
with increased risk of all-cause mortality (4.2% vs. 4.0%; RR, 1.06 [95% CI, 1.03 to 1.10]) or the composite endpoint of progression to AIDS or death (8.5% vs. 7.1%; RR, 1.20 [95% CI, 1.17 to 1.23]) after 7 years, compared with initiation of ART at CD4 counts greater than 500 cells/mm\(^3\) (Table 1; Appendix B Table 5), although effects were smaller than those observed in the START and TEMPRANO ANRS 12136 trials.\(^8\) Effects of immediate initiation of ART were stronger in the subgroup of patients with baseline CD4 counts greater than 500 cells/mm\(^3\) (7.1% vs. 4.9%; RR, 1.52 [95% CI, 1.34 to 1.77]). Analyses were adjusted for CD4 count, HIV-ribonucleic acid viral load, AIDS diagnosis, age, HIV risk group, sex, geographical origin, and racial/ethnic origin. Results were similar in a subgroup analysis from HIV CAUSAL of patients older than age 50 years.\(^9\) Another cohort study (n=4,120) reported the probability of death or AIDS-related illness with use of early versus delayed ART, according to CD4 count and period of ART initiation (2000–2006 or 2007–2012) (Table 1; Appendix B Table 5).\(^9\) From 2007 to 2012, initiation of ART at CD4 counts of 500 cells/mm\(^3\) or greater was associated with lower probability of mortality (0.01; interquartile range [IQR], 0.01 to 0.02) and AIDS-related morbidity (0.01; IQR, 0.00 to 0.01) than initiation at CD4 counts less than 500 cells/mm\(^3\) (probability, 0.05; IQR, 0.03 to 0.08 and 0.03, IQR, 0.01 to 0.04, for mortality and AIDS-related mortality, respectively) or less than 350 cells/mm\(^3\) (probability, 0.05, 0.03 to 0.08 and 0.05, IQR, 0.03 to 0.08, for mortality and AIDS-related mortality, respectively). From 2000 to 2006, patients with ART initiation at CD4 counts of 500 cells/mm\(^3\) or greater had a slightly higher probability of mortality than those with CD4 counts less than 500 cells/mm\(^3\) (0.16 vs. 0.13), although the probability of AIDS-related illness remained lower (0.02 vs. 0.04). Analyses were based on a small number of patients (n=50) with CD4 counts of 500 cells/mm\(^3\) or greater.

**Immediate Versus Delayed Initiation of ART in Persons With Baseline CD4 Counts of 350 or Greater to 500 or 550 cells/mm\(^3\)**

The prior USPSTF review included two randomized trials (HPTN 052 and a subgroup analysis from SMART) that found initiation of ART in patients infected with HIV with CD4 counts greater than 350 cells/mm\(^3\) associated with decreased risk of mortality or AIDS events compared with delayed initiation at CD4 counts less than 250 cells/mm\(^3\) after 18 to 19 months; the HPTN 052 trial also found early initiation of ART associated with decreased risk of HIV transmission to an uninfected partner (Table 3).\(^5\)\(^,\)\(^6\)\(^,\)\(^8\)\(^9\) There was also consistent evidence from four observational studies of an association between initiation of ART at CD4 counts between 350 and 500 cells/mm\(^3\) and decreased risk of mortality, or trend toward decreased risk, compared with deferred initiation or no ART (Table 1).\(^8\)\(^1\)\(^2\)\(^8\)\(^4\)\(^2\)\(^9\)

Longer-term followup from the HPTN 052 trial (n=1,763) is now available (Table 3; Appendix B Table 2).\(^9\)\(^0\)\(^9\) At mean followup of 2.1 years, initiation of ART at CD4 counts of 350 cells/mm\(^3\) or greater to less than 550 cells/mm\(^3\) was associated with decreased risk of AIDS-related events (4.5% vs. 7.0%; RR, 0.65 [95% CI, 0.44 to 0.95]); much of the difference in risk of AIDS-related events was due to effects on tuberculosis (1.9% vs. 3.9%; RR, 0.49 [95% CI, 0.28 to 0.88]). Effects on the primary composite outcome (death, serious AIDS events, and serious non-AIDS events) (6.4% vs. 8.8%; RR, 0.73 [95% CI, 0.53 to 1.02]), all-cause mortality (1.2% vs. 1.7%; RR, 0.72 [95% CI, 0.33 to 1.57]), and AIDS-related mortality (0.1% vs 0.5%; RR, 0.25 [95% CI, 0.03 to 2.20]) favored early initiation of ART, but effects were not statistically significant. After 5.5 years, the HPTN 052 trial found early initiation of ART
remained associated with decreased risk of any HIV transmission to uninfected partners (2.1% vs. 6.6%; RR, 0.32 [95% CI, 0.19 to 0.53]) as well as virologically-linked transmission (0.3% vs. 4.9%; RR, 0.07 [95% CI, 0.02 to 0.22]); almost all of the reduction in transmission risk was due to fewer virologically-linked cases (Table 3; Appendix B Table 2).93

A new U.S.-based cohort study (n=3,532) found that compared with initiation of ART at CD4 counts less than 500 cells/mm³, initiation at less than 200 cells/mm³ was associated with greater risk of 10-year all-cause mortality (RR, 1.25 [95% CI, 1.08 to 1.44]) than initiation at less than 350 cells/mm³ (RR, 1.08 [95% CI, 1.00 to 1.16]) (Table 1; Appendix B Table 5).88 However, the CIs for the risk estimates overlapped and there was no test for statistical significance for the difference. Risk estimates were generally similar for 5-year mortality and consistent across age groups.

**Harms of Immediate Versus Delayed Initiation of ART**

Two RCTs found no evidence of an increased risk of cardiovascular events with early versus delayed initiation of ART, although data were limited by small numbers of events. In the SMART trial subgroup of patients who were ART-naïve or not recently on ART, there was no statistically significant difference in risk of cardiovascular events between initiation at a CD4 count greater than 350 cells/mm³ versus initiation at less than 250 cells/mm³, but there were few events and the estimate was imprecise (0% vs. 2.4%; RR, 0.07 [95% CI, 0.004 to 1.24]).89 However, an analysis of the entire SMART cohort (including persons currently or recently on ART) found continuous use of ART associated with decreased risk of fatal or nonfatal cardiovascular disease compared with episodic use (initiate at CD4 count <250 cells/mm³ and discontinue when CD4 count >350 cells/mm³) (1.1% vs. 1.8%; RR, 0.64 [95% CI, 0.41 to 1.0]).85 In the START trial, there was also no clear difference between early and delayed initiation of ART in risk of cardiovascular disease (0.5% vs. 0.6%; RR, 0.87 [95% CI, 0.40 to 1.88]).85 The START, HPTN 052, and TEMPRANO ANRS 12136 trials also found no clear differences between early versus delayed initiation of ART and risk of other harms, such as liver disease, renal disease, and new-onset diabetes (Appendix B Table 2).85,86,90 However, few adverse events were reported and some risk estimates were imprecise.

**Key Question 5. What Are the Longer-Term Harms (2 Years or More) Associated With Currently Recommended ART Regimens?**

**Summary**

- The prior USPSTF report found mixed evidence on the risk of long-term cardiovascular events with abacavir use based on four studies97-100 and no evidence of increased risk of cardiovascular events with efavirenz use.97
- A meta-analysis of 26 trials (total n=9,868) published since the prior report found no association between ART containing abacavir versus ART without abacavir and risk of myocardial infarction (risk difference, 0.008% [95% CI, -0.26 to 0.27]).101 This conflicts
with longer-term (median, 7.0 years) followup from the large (n=49,717) D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) observational study, which found abacavir use associated with increased risk of myocardial infarction (RR, 1.98 [95% CI, 1.72 to 2.29]).102 and another cohort study, which found abacavir use associated with increased risk of cardiovascular events (odds ratio [OR], 1.50 [95% CI, 1.26 to 1.79]).103

- The D:A:D study found no association between long-term (>3 years) exposure to the protease inhibitor atazanavir and risk of myocardial infarction (RR, 0.95 [95% CI, 0.87 to 1.05]) or stroke (RR, 0.95 [95% CI, 0.87 to 1.05]).104 Another cohort study found efavirenz, lamivudine, and zidovudine associated with increased risk of cardiovascular events (OR range, 1.40 to 1.53).103

- A systematic review of 42 randomized and quasirandomized trials (n=8466 exposed to efavirenz; mean duration, 78 weeks) found efavirenz associated with an increased risk of severe neuropsychiatric adverse events versus ritonavir-boosted atazanavir (RR, 2.4 [95% CI, 1.5 to 3.8]), dolutegravir (RR, 16.7 [95% CI, 2.0 to 137.8]), and maraviroc (RR, 5.3 [95% CI, 1.6 to 18.1]).105

- Three observational studies, including D:A:D, found no association between use of efavirenz and death from suicide or suicidal ideation.106-108

- A D:A:D analysis found longer exposure to ART associated with lower risk of AIDS-defining cancer (rate ratio, 0.88/year [95% CI, 0.85 to 0.92]).109 Protease inhibitor use but not non-NRTI use was associated with higher risk of non–AIDS-defining cancer (rate ratio, 1.03/year [95% CI, 1.01 to 1.05]).

- A D:A:D analysis found long-term tenofovir disoproxil fumarate (TDF) (relative rate, 1.46 [95% CI, 1.11 to 1.93]) use associated with increased risk of end-stage liver disease or hepatocellular carcinoma, and emtricitabine associated with decreased risk (relative rate, 0.51 [95% CI, 0.32 to 0.83]).110

- A D:A:D analysis found an association between use of TDF (rate ratio, 1.14 per year of exposure [95% CI, 1.10 to 1.19]) or ritonavir-boosted atazanavir (rate ratio, 1.20 per year of exposure [95% CI, 1.13 to 1.26]) and increased risk of chronic kidney disease;111 other observational studies also found TDF and protease inhibitors associated with increased risk of renal adverse events.

- A cohort study found ever use of TDF associated with increased risk of fracture (incidence rate ratio [IRR], 1.40 [95% CI, 1.15 to 1.70]), but no association between cumulative exposure to TDF and risk of fracture (IRR per 5 years of exposure, 1.08 [95% CI, 0.94 to 1.25]).112

**Evidence**

The prior USPSTF review included analyses from the D:A:D study (a large [n >49,000] ongoing international study of 11 prospective cohorts from Europe, Australia, and the United States that began enrolling patients in 1999)97,113,114 and three other cohort studies on cardiovascular harms associated with ART after 4 to 6 years of followup.98-100 In the D:A:D study, longer exposure to the protease inhibitors indinavir alone, ritonavir-boosted indinavir, and ritonavir-boosted lopinavir were each associated with increased risk of myocardial infarction compared with nonuse (adjusted RR per year of exposure, 1.1 to 1.2).97 However, these protease inhibitors are no longer recommended for use in ART regimens, and no other protease inhibitor was associated with increased myocardial infarction risk. The prior USPSTF review found mixed evidence on the
association between NRTI use and risk of myocardial infarction. Two studies, including the D:A:D study, found abacavir exposure associated with increased risk of myocardial infarction (adjusted RR, 1.7 and 2.0),97,99 but two other studies found no association (adjusted HR, 0.6 and 1.2).98,100 There was no association between use of other NRTIs or the non-NRTI efavirenz and increased risk of cardiovascular events.97

Since the prior USPSTF review, we identified two new RCTs on longer-term harms of TDF,115 raltegravir, and efavirenz.116 There is also new evidence on cardiovascular risks from a meta-analysis of randomized trials of abacavir,101 longer-term followup data from the D:A:D study,102,104 and an analysis of Veterans Health Administration (VHA) data103 (Table 4). Other new evidence on longer-term harms include a systematic review,105 a D:A:D analysis,107 and two cohort studies106,108 on the association between efavirenz and neuropsychiatric adverse events, as well as analyses from D:A:D and other large cohort studies on risk of cancer,109 liver disease,110,117 renal adverse events,110,111,118,119 fracture,112,120 and non–AIDS-related deaths121 (Appendix B Tables 7-14).

Both new RCTs were rated as good quality. We previously rated the D:A:D study as good quality; other studies of harms had methodological shortcomings, including not reporting whether outcome assessors, data analysts, or both were blinded to the exposure being studied and high attrition rates, and were rated as fair quality (Appendix B Tables 9 and 12-14).

Cardiovascular Events

Two good-quality RCTs published since the prior USPSTF review evaluated serious cardiovascular or cerebrovascular events with tenofovir alafenamide versus TDF, each coformulated with elvitegravir, cobicistat, and emtricitabine (duration, 144 weeks),115 or raltegravir versus efavirenz, each in combination with TDF/emtricitabine (duration, 5 years) (Appendix B Tables 10 and 11).116 Neither trial found any difference between ART regimens in risk of cardiovascular events.

As in the prior USPSTF review, new evidence on the association between abacavir use and risk of cardiovascular events was somewhat inconsistent (Table 4). A meta-analysis conducted by the U.S. Food and Drug Administration of 26 randomized trials (total n=9,868) found no association between ART versus without abacavir and risk of myocardial infarction (0.48% vs. 0.46%; risk difference, 0.008% [95% CI, -0.26 to 0.27]) after a mean of approximately 1.5 years.101 However, longer-term (median, 7.0 years) followup from the D:A:D study (n=49,717) was consistent with prior (5 to 6 year) analyses from D:A:D in finding an association between abacavir use and increased risk of myocardial infarction after adjustment for demographic factors, cardiovascular risk factors, and other potential confounders (RR, 1.98 [95% CI, 1.72 to 2.29]).102 The association remained present whether abacavir was initiated before or after March 2008, despite data indicating a trend over time toward decreased use of abacavir in persons at higher cardiovascular risk. A cohort study (n=24,510) of VHA data also found abacavir use increased the risk of combined cardiovascular events (myocardial infarction, stroke, or cardiovascular procedure) after 2.2 years (OR, 1.50 [95% CI, 1.26 to 1.79]).103

An analysis of the D:A:D cohort (n=49,734) published subsequent to the prior USPSTF review
found no association between exposure to the protease inhibitor atazanavir for more than 3 years and risk of myocardial infarction (RR, 0.95 [95% CI, 0.87 to 1.05]) or stroke (RR, 0.95 [95% CI, 0.87 to 1.05]).\textsuperscript{104} In a VHA cohort, efavirenz (2.2 years followup; OR, 1.40 [95% CI, 1.19 to 1.66]), lamivudine (3.4 years followup; OR, 1.53 [95% CI, 1.34 to 1.75]), and zidovudine (2.6 years followup; OR, 1.41 [95% CI, 1.22 to 1.63]) were each associated with increased risk of a composite cardiovascular outcome (myocardial infarction, stroke, or cardiovascular procedure).\textsuperscript{103} For other antiretrovirals, there was no association with risk of cardiovascular events or duration of followup was less than 2 years.

**Neuropsychiatric Adverse Events**

The non-NRTI efavirenz has recently been linked to neuropsychiatric adverse events, including depression and suicidal ideation.\textsuperscript{122} A systematic review of 42 randomized and quasirandomized trials (n=8,466 exposed to efavirenz; mean duration, 78 weeks) reported neuropsychiatric adverse events of any grade in 29.6% (95% CI, 21.9 to 37.3) of patients prescribed efavirenz.\textsuperscript{105} The most frequent neuropsychiatric adverse events were dizziness (12.8% [95% CI, 9.1 to 16.5]) and abnormal dreams (8.4% [95% CI, 4.3% to 12.5%]). The rate of severe neuropsychiatric adverse events was 6.1% (95% CI, 4.3% to 7.9%), and efavirenz was associated with an increased risk of severe neuropsychiatric adverse events compared with ritonavir-boosted atazanavir (RR, 2.4 [95% CI, 1.5 to 3.8]), dolutegravir (RR, 16.7 [95% CI, 2.0 to 137.8]) and maraviroc (RR, 5.3 [95% CI, 1.6 to 18.1]); there were no data on severe neuropsychiatric adverse events with the integrase inhibitor raltegravir. The rate of depression was 3.3 percent (95% CI, 2.2 to 4.3) and the rate of suicidal ideation was 0.60 percent (95% CI, 0.20 to 1.10). However, an analysis of the D:A:D cohorts found no association between use of efavirenz and death from suicide,\textsuperscript{107} and an analysis on a large (n=19,983) U.S. administrative cohort found no association between initiation of efavirenz and increased risk of suicidal ideation.\textsuperscript{106} Another cohort study (n=694) also found no increased risk of suicidal ideation with efavirenz versus nevirapine (adjusted HR, 0.47 [95% CI, 0.21 to 1.07]).\textsuperscript{108} Rather, efavirenz was associated with lower risk of depression than nevirapine (adjusted HR, 0.56 [95% CI, 0.35 to 0.89]).

**Cancer**

An analysis of the D:A:D cohort found longer exposure to ART associated with lower risk of AIDS-defining cancer (rate ratio, 0.88/year [95% CI, 0.85 to 0.92]).\textsuperscript{109} However, protease inhibitor use was associated with higher risk of non–AIDS-defining cancer (rate ratio, 1.03/year [95% CI, 1.01 to 1.05]), largely due to an increased risk of anal cancer (rate ratio, 1.08/year [95% CI, 1.04 to 1.13]). There was no association between non-NRTI use and risk of non–AIDS-defining cancer. The overall incidence of non–AIDS-defining cancer in the D:A:D cohort was 0.46 per 100 person-years.

**Hepatic and Renal Adverse Events**

Two D:A:D analyses and three other studies reported increased risk of hepatic or renal adverse events with ART (Appendix B Tables 10 and 11). An analysis of the D:A:D cohorts found TDF (relative rate, 1.46 [95% CI, 1.11 to 1.93]) associated with increased risk of end-stage liver disease or hepatocellular carcinoma, independent of viral hepatitis status, and emtricitabine...
associated with decreased risk (relative rate, 0.51 [95% CI, 0.32 to 0.83]). However, the risk of ART-related liver deaths in the D:A:D cohorts was low (0.04/1,000 person-years). Another D:A:D analysis found an association between use of TDF (rate ratio, 1.14 per year of exposure [95% CI, 1.10 to 1.19]) or ritonavir-boosted atazanavir (rate ratio, 1.20 per year of exposure [95% CI, 1.13 to 1.26]) and increased risk of chronic kidney disease. After discontinuation, the incidence of renal impairment decreased, suggesting that effects depend on ongoing exposure. A cohort study of VHA data (n=10,841; 5.5 years followup) also found TDF associated with increased risk of chronic kidney disease (adjusted HR for any exposure, 1.88 [95% CI, 1.50 to 2.36] and for cumulative exposure, 1.36 [95% CI, 1.22 to 1.51]). Both TDF (adjusted HR, 1.63 [95% CI, 1.26 to 2.10]) and protease inhibitors (adjusted HR, 1.46 [95% CI, 1.07 to 2.01]) were associated with increased likelihood of decreased kidney function (estimated glomerular filtration rate <90 mL/min/1.73m²) in another (n=1,043) observational study with up to 10 years of followup (HR, 1.63 [95% CI, 1.26 to 2.10]). Finally, another cohort study (n=9,876) with 2.5 years followup found efavirenz associated with lower risk of renal adverse events (based on International Classification of Diseases, Ninth Revision, Clinical Modification codes for renal disease) compared with elvitegravir/cobicistat, when each was combined with emtricitabine and TDF (adjusted incidence rate difference, -1.78 [95% CI, -2.19 to -1.50]).

Fracture

An analysis of the EuroSIDA cohort (n=11,820) found ever use of TDF associated with increased risk of fracture compared with nonuse (adjusted IRR, 1.40 [95% CI, 1.15 to 1.70]) after more than 86,000 person-years followup. However, there was no difference in risk of fracture based on cumulative duration of TDF use (adjusted IRR per 5 years of exposure, 1.08 [95% CI, 0.94 to 1.25]). Another large study (n=10,383) found efavirenz associated with lower risk of fracture compared with elvitegravir/cobicistat, when each was combined with emtricitabine and TDF (adjusted incidence rate difference, -3.85 [95% CI, -5.02 to -2.78]).

Non-AIDS Mortality

An analysis of a European cohort (EuroSIDA; n=12,069) found no association between longer-term (>2 years) exposure to ART and risk of non-AIDS-related death after a median of 5.4 years.
Summary of Review Findings

This report updates a 2012 USPSTF review\(^2\) on screening for HIV infection in nonpregnant adolescents and adults. As in previous USPSTF reviews,\(^2,52\) we found no direct evidence on clinical benefits and harms of screening for HIV infection versus no screening, or on the yield of repeat screening. Other evidence reviewed for this update is summarized in Table 5.

New data extends evidence on effectiveness of ART to persons with CD4 counts greater than 500 cells/mm\(^3\), further expanding upon previous findings regarding estimated benefits of interventions as a result of HIV screening. In 2005, the 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 <200 cells/mm\(^3\)) are associated with substantial clinical benefits.\(^{52}\) The 2012 USPSTF review found strong evidence of an association between initiation of ART at CD4 counts of 350 to 500 cells/mm\(^3\) and reduced risk of death or AIDS-related illness and substantially reduced risk of sexual transmission of HIV infection compared with initiation at lower CD4 counts; evidence on effectiveness of initiation of ART in patients with CD4 counts greater than 500 cells/mm\(^3\) was limited to observational studies and inconsistent.\(^2\) New evidence from the START and TEMPRANO ANRS 12136 randomized trials and the large observational HIV CAUSAL study found initiation of ART at CD4 counts greater than 500 cells/mm\(^3\) associated with decreased risk of death, AIDS events, and other clinical outcomes compared with delayed initiation or no ART.\(^{85-87}\) Effects were relatively modest in HIV CAUSAL (reduction in risk of death or AIDS events, 17%) compared with the randomized trials (reduction in risk, 43% to 53%). A factor that could explain the difference in magnitude of effects is that HIV CAUSAL was conducted in cohorts from the United States and Europe, whereas the RCTs were conducted entirely (TEMPRANO ANRS 12136) or partially (START) in low-income settings, where patients may benefit more from early initiation of ART due to higher incidence of certain infections (e.g., tuberculosis), reduced access to opportunistic infection prophylaxis, or other factors. However, estimates on effectiveness of ART in START were similar when analyses were stratified according to high- versus low-/moderate-income setting (HR for the primary outcome, 0.39 for high-income setting and 0.48 for low-income setting [95% CIs not reported]; p=0.55 for interaction). Residual confounding could explain the observed differences if HIV CAUSAL patients with favorable prognosis were less likely to start early ART than those with less favorable prognosis, and confounders associated with prognosis were not completely captured in the analysis. Our findings regarding the effectiveness of ART in patients with CD4 counts greater than 500 cells/mm\(^3\) differed from previously published systematic reviews on timing of ART, which found insufficient evidence in this population but were conducted prior to the publication of the TEMPRANO ANRS 12135 and START trials.\(^{124,125}\) Longer-term followup from the HPTN 052 trial was consistent in showing sustained effects of ART initiated at CD4 counts greater than 350 cells/mm\(^3\) on reduced risk of HIV transmission in heterosexual couples and AIDS-related clinical outcomes.\(^{90,93}\)

Understanding long-term harms of ART is important because patients are started on ART earlier and typically continue it indefinitely. The 2012 USPSTF report found some evidence indicating
increased risk of long-term cardiovascular harms with the NRTI abacavir, though data were somewhat inconsistent. New evidence regarding cardiovascular harms of abacavir remains mixed. A large meta-analysis of randomized trials found no association between abacavir use and increased risk, but longer-term followup from the large, ongoing D:A:D observational study and other observational studies continued to find an association between abacavir exposure and increased risk of myocardial infarction (risk approximately doubled). One explanation for the difference between randomized and observational data on abacavir cardiovascular risk is that patients in randomized trials might have been at lower baseline risk of cardiovascular events. However, estimates in D:A:D did not change when patients were stratified according to whether abacavir was started before or after March 2008, despite a decreased propensity to prescribe abacavir in persons at higher cardiovascular risk after 2008. The randomized trials were also shorter in duration (~1.5 years) compared with D:A:D (7 years). Our findings regarding the association between abacavir use and risk of cardiovascular events are consistent with a recent systematic review that also noted a discrepancy between randomized trials and observational studies. A new analysis from D:A:D found no association between the currently used protease inhibitor atazanavir and risk of cardiovascular events. Despite a potential association between certain antiretrovirals and increased risk of cardiovascular events, data from randomized trials found no association between early initiation of ART and increased risk of cardiovascular events. The SMART trial, in which ART was initiated at CD4 counts greater than 350 cells/mm, found a potential protective effect on risk of cardiovascular events (RR, 0.07 [95% CI, 0.004 to 1.24]), but the START trial, in which ART was initiated at CD4 counts greater than 500 cells/mm, found no protective effect (RR, 0.87 [95% CI, 0.40 to 1.88]). As HIV infection itself is associated with increased cardiovascular risk, effects of ART on mitigating cardiovascular risk may be greater in persons with more advanced disease.

Data are also available on other long-term harms, including neuropsychiatric adverse events and hepatic and renal adverse events. Although a systematic review found efavirenz associated with an increased risk of severe neuropsychiatric adverse events compared with other antiretroviral medications, other studies found no clear association between efavirenz use and death from suicide or suicidal ideation. Long-term data on neuropsychiatric adverse events associated with integrase inhibitors are limited. Some new evidence also indicates long-term hepatic, renal, and bone (fracture) adverse events associated with certain antiretroviral medications. The clinical effects of neuropsychiatric, renal, hepatic, and bone adverse events will depend on the degree to which they are reversible, the severity of the event, and the availability and use of effective alternative ART regimens. Abacavir and efavirenz are not recommended as part of initial ART in most persons with HIV, but are recommended in certain clinical situations.

Although no study directly evaluated effects of screening versus no screening on clinical outcomes, epidemiological and observational data indicate recent trends toward less delayed diagnosis, fewer patients with undiagnosed HIV infection, and lower incidence of HIV infection. The degree to which these trends are attributable to adoption of universal HIV screening or other factors, and the effects of such trends on clinical outcomes such as mortality, AIDS events, and quality of life, are uncertain.

No clinical study evaluated the yield of repeat versus one-time screening, or compared the yield
of screening at different intervals. Modeling studies suggest that repeat screening as frequently as once every 3 months may be cost effective in high-risk persons, depending on the frequency of testing, incidence of new HIV infections, HIV risk category, assay used for testing, and other factors.\textsuperscript{130-132} A recent CDC systematic review found insufficient evidence to support general recommendations on screening more frequently than annually in men who have sex with men, but noted suggestive findings from mathematical models that screening more frequently than annually could prevent some new HIV infections and be cost effective.\textsuperscript{74}

**Limitations**

We excluded non–English-language articles, which could result in language bias, though we identified no non–English-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, although 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-limited and high-prevalence settings, which could reduce applicability to U.S. practice. However, as noted above, a subgroup analysis from the START trial found similar effects of initiation of ART at CD4 counts greater than 500 cells/mm\(^3\) when results were stratified according to enrollment from a high- or low-/middle-income setting.\textsuperscript{85} Studies of long-term harms of ART often did not specify the regimen used or analyzed effects of specific antiretroviral drugs rather than the regimen as a whole, making it difficult to determine applicability of results to current recommended ART regimens. In addition, analyzing long-term harms of ART regimens is a challenge due to potential interactions between ART drugs and difficulty in accounting for drug regimen switches.

**Emerging Issues/Next Steps**

ART regimens and indications for initiating long-term ART continue to evolve and treatment guidelines are regularly updated.\textsuperscript{61} Since 2012, new antiretroviral agents approved by the U.S. Food and Drug Administration for treatment of HIV infection include the integrase inhibitors dolutegravir and elvitegravir, the pharmacokinetic enhancer cobicistat, and several ART combinations.\textsuperscript{133} Some short-term studies have reported potential neuropsychiatric effects of the integrase inhibitor dolutegravir, but longer-term studies are lacking.\textsuperscript{134-136}

**Relevance for Priority Populations, Particularly Racial/Ethnic Minorities**

HIV infection disproportionately affects racial/ethnic minorities. Evidence on benefits of early versus delayed initiation of ART was primarily limited to the START trial, which found similar
effects in subgroups stratified according to age and race/ethnicity. Although testing rates of men who have sex with men, persons who inject drugs, and persons at increased risk of HIV infection due to heterosexual contact are similar or slightly higher in racial/ethnic minorities compared with white persons, diagnosis delays are greater in racial/ethnic minorities (median, 3.3 years in black persons vs. 3.3 years in Hispanic/Latino persons vs. 4.2 years in Asian persons) than in white persons (median, 2.2 years), and linkage to care is lower in black versus white persons (76% vs. 85%). However, rates of ART use and viral suppression appear similar across racial/ethnic groups. Diagnosis delay also increases with age (median, 4.5 years in persons age ≥55 years vs. 2.4 years in persons ages 13 to 24 years). Evidence on benefits of early initiation of ART in adolescents remains very sparse; limited data indicate that benefits of early initiation of ART are maintained in older (age >50 years) patients.

**Future Research**

Research is needed on the yield of repeat versus one-time screening and annual versus more frequent screening, to help inform optimal screening intervals. Continued followup of patients taking ART is needed to further understand effects of long-term exposure to ART, as the duration of exposure to ART continues to lengthen. Ideally, studies should report effects of currently recommended ART regimens, including newly approved agents, in addition to analyses based on individual components of ART regimens, to better inform considerations regarding applicability to current practice. Additional research is needed on the neuropsychiatric effects of integrase inhibitors, given their status as first-line agents for ART and potential associated clinical consequences (e.g., suicide attempts and decreased quality of life), as well as the extent to which these and other effects (e.g., hepatic, renal) are reversible with discontinuation of therapy. Evidence on effects of ART on risk of HIV transmission in men who have sex with men and persons who inject drugs is limited, but an observational study of serodiscordant male homosexual couples published as a conference abstract found no cases of virologically-linked transmission from men with undetectable viral loads, and few cases of transmission overall.

**Conclusions**

The USPSTF previously determined that HIV screening is accurate, ART is effective at reducing risk of mortality and AIDS-defining events in asymptomatic patients with CD4 counts less than 500 cells/mm³, and ART reduces risk of sexual transmission of HIV infection. New evidence extends effectiveness of ART to persons with CD4 counts greater than 500 cells/mm³. Certain ART regimens may be associated with long-term cardiovascular, neuropsychiatric, hepatic, bone, or renal harms, but early initiation of ART is not associated with increased risk of cardiovascular events. Research is needed to inform optimal screening intervals.
References


46. Lathey JL, Tierney C, Chang SY, et al. Associations of CCR5, CCR2, and stromal cell-derived factor 1 genotypes with human immunodeficiency virus disease progression in


96. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug


Figure 1. Analytic Framework and Key Questions

Abbreviations: CD4=cluster of differentiation 4; STI=sexually transmitted infection.

Key Questions

1. What are the benefits of screening for HIV infection in asymptomatic, nonpregnant adolescents and adults on mortality, AIDS and opportunistic infections, quality of life, function, and reduced transmission of HIV and other sexually transmitted infections?
2. What is the yield (number of new diagnoses per tests performed) of screening for HIV infection at different intervals in asymptomatic, nonpregnant adolescents and adults, and how does the screening yield vary in different risk groups?
3. What are the harms of screening for HIV infection in asymptomatic, nonpregnant adolescents and adults?
4. What are the effects of initiating antiretroviral therapy in adolescents and adults with chronic HIV infection at a higher versus lower CD4 count on mortality, AIDS and opportunistic infections, quality of life, function, and reduced transmission of HIV and other sexually transmitted infections, and harms?
5. What are the longer-term harms (≥2 years) associated with currently recommended antiretroviral therapy regimens?
### Table 1. Cohort Studies of Early vs. Delayed Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Mortality</th>
<th>AIDS-related events</th>
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<tbody>
<tr>
<td><strong>CASCADE Collaboration</strong></td>
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<tr>
<td>2011*4</td>
<td>≥350 to &lt;500 cells/mm³ vs. no treatment initiation&lt;br&gt; All-cause mortality: HR, 0.51 (95% CI, 0.33 to 0.80)</td>
<td>≥350 to &lt;500 cells/mm³ vs. no treatment initiation&lt;br&gt; Progression to AIDS or death: HR, 0.75 (95% CI, 0.49 to 1.14)</td>
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<td>≥500 cells/mm³ vs. no treatment initiation&lt;br&gt; All-cause mortality: HR, 1.02 (95% CI, 0.49 to 2.12)</td>
<td>≥500 cells/mm³ vs. no treatment initiation&lt;br&gt; Progression to AIDS or death: HR, 1.10 (95% CI, 0.67 to 1.79)</td>
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<td><strong>Kitahata 2009</strong></td>
<td>≥350 to 500 vs. &lt;350 cells/mm³&lt;br&gt; All-cause mortality: RR, 0.61 (95% CI, 0.46 to 0.83)</td>
<td>NR</td>
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<tr>
<td><strong>May 2007</strong></td>
<td>≥350 vs. &lt;250 cells/mm³&lt;br&gt; All-cause mortality: HR, 0.34 (95% CI, 0.27 to 0.44)</td>
<td>≥350 vs. &lt;250 cells/mm³&lt;br&gt; Progression to AIDS or death: HR, 0.23 (95% CI, 0.19 to 0.27)</td>
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<td><strong>Ray 2010</strong></td>
<td>500 vs. 350 cells/mm³&lt;br&gt; All-cause mortality: HR, 0.99 (95% CI, 0.82 to 1.19)</td>
<td>500 vs. 350 cells/mm³&lt;br&gt; Progression to AIDS or death: HR, 0.72 (95% CI, 0.64 to 0.81)</td>
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<td><strong>Stere 2009</strong></td>
<td>&gt;450 to 550 vs. ≥350 to 450 cells/mm³&lt;br&gt; All-cause mortality: HR, 0.93 (95% CI, 0.6 to 1.40)</td>
<td>&gt;450 to 550 vs. ≥350 to 450 cells/mm³&lt;br&gt; Progression to AIDS or death: HR, 0.90 (95% CI, 0.76 to 1.29)</td>
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<tr>
<td><strong>Lodi 2015</strong></td>
<td>≥500 vs. &lt;500 cells/mm³&lt;br&gt; All-cause mortality: RR, 0.98 (95% CI, 0.97 to 0.99)</td>
<td>≥500 vs. &lt;500 cells/mm³&lt;br&gt; Progression to AIDS or death: RR, 0.94 (95% CI, 0.93 to 0.94)</td>
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<td>≥500 vs. &lt;350 cells/mm³&lt;br&gt; All-cause mortality: RR, 0.94 (95% CI, 0.91 to 0.97)</td>
<td>≥500 vs. &lt;350 cells/mm³&lt;br&gt; Progression to AIDS or death: RR, 0.83 (95% CI, 0.81 to 0.85)</td>
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<td>Subgroup of patients with baseline CD4 count &gt;500 cells/mm³ vs. entire sample&lt;br&gt; Progression to AIDS or death: 7.1% vs. 4.9%; RR, 1.52 (95% CI, 1.34 to 1.77)</td>
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<td><strong>Lodi 2017</strong></td>
<td>≥500 vs. &lt;500 cells/mm³&lt;br&gt; All-cause mortality, general HIV population: RR, 0.97 (95% CI, 0.94 to 0.99)</td>
<td>NR</td>
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<td></td>
<td>≥500 vs. &lt;350 cells/mm³&lt;br&gt; All-cause mortality, general HIV population: RR, 0.93 (95% CI, 0.87 to 0.98)</td>
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<td><strong>Lima 2015</strong></td>
<td>All-cause mortality, probability (IQR):&lt;br&gt; CD4 &lt;350 cells/mm³, 2007–2012: 0.05 (0.03 to 0.08)&lt;br&gt; CD4 ≥350 cells/mm³, 2007–2012: 0.02 (0.01 to 0.04)</td>
<td>AIDS-defining illness, probability (IQR):&lt;br&gt; CD4 &lt;350 cells/mm³, 2007–2012: 0.05 (0.03 to 0.08)&lt;br&gt; CD4 ≥350 cells/mm³, 2007–2012: 0.03 (0.01 to 0.05)</td>
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<td>CD4 &lt;500 cells/mm³, 2007–2012: 0.05 (0.03 to 0.02)&lt;br&gt; CD4 ≥500 cells/mm³, 2007–2012: 0.01 (0.01 to 0.02)</td>
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Table 1. Cohort Studies of Early vs. Delayed Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Mortality</th>
<th>AIDS-related events</th>
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| Edwards 2015<sup>88</sup> | <500 vs. <350 cells/mm<sup>3</sup>  
All-cause mortality, 5 years: RR, 0.87 (95% CI, 0.79 to 0.95)  
• Ages 18 to 34 years: RR, 0.95 (95% CI, 0.79 to 1.15)  
• Ages 35 to 44 years: RR, 0.93 (95% CI, 0.82 to 1.05)  
• Ages 45 to 65 years: RR, 0.81 (95% CI, 0.71 to 0.93)  
All-cause mortality, 10 years: RR, 0.93 (95% CI, 0.86 to 1.00)  
• Ages 18 to 34 years: RR, 1.00 (95% CI, 0.87 to 1.15)  
• Ages 35 to 44 years: RR, 0.92 (95% CI, 0.83 to 1.01)  
• Ages 45 to 65 years: RR, 0.89 (95% CI, 0.80 to 0.99) | NR                  |

Abbreviations: CASCADE=Concerted Action on Seroconversion to AIDS and Death in Europe; CD4=cluster of differentiation 4; CI=confidence interval; HR=hazard ratio; IQR=interquartile range; NR=not reported; RR=relative risk; VA=U.S. Department of Veterans Affairs.
<table>
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<tr>
<th>Study design</th>
<th>Study name</th>
<th>Author, year</th>
<th>Duration</th>
<th>Geographic setting</th>
<th>Intervention groups</th>
<th>Population</th>
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</table>
| RCT          | START      | Lundgren 2015<sup>85</sup> | 3 years | Africa, Europe, Israel, North America, South America, Mexico, Australia | A. Immediate ART (n=2,326): CD4 >500 cells/mm<sup>3</sup>  
B. Deferred ART (n=2,359): CD4 <350 cells/mm<sup>3</sup> | A vs. B  
Mean age 36 vs. 36 years  
27% vs. 27% female  
9% vs. 8% Asian; 30% vs. 30% black; 14% vs. 14% Latino/Hispanic; 44% vs. 45% white; 4% vs. 3% other  
CD4 count (median): 651 vs. 651 cells/mm<sup>3</sup> |
| RCT          | HPTN 052   | Grinsztejn 2014<sup>90</sup> | 2-5.5 years* | Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, United States, Zimbabwe | A. Immediate ART (n=886): CD4 ≥350 to <550 cells/mm<sup>3</sup>  
B. Delayed ART (n=877): CD4 ≤250 cells/mm<sup>3</sup> | A vs. B  
Mean age <25 years 13% vs. 13%; 25 to 39 years, 64% vs. 64%; ≥40 years, 24% vs. 23%  
49% vs. 50% female  
Race NR; 16% vs. 15% South America; 30% vs. 30% Africa; 54% vs. 55% Asia  
CD4 count: 442 vs. 428 cells/mm<sup>3</sup> |
| RCT          | TEMPRANO ANRS 12136 Study | TEMPRANO ANRS Study Group 2015<sup>91</sup> | 30 months | Ivory Coast | A. Early ART (n=1,033): Immediate ART initiation upon study enrollment  
B. Delayed ART (n=1,023): ART initiation according to the following criteria:  
- From March 1, 2008 to November 30, 2009, the criteria for ART initiation were: one CD4 count <200 cells/mm<sup>3</sup> or WHO clinical stage 4; or one CD4 count 200 to 350 cells/mm<sup>3</sup> and WHO clinical stage 2 or 3.  
- From December 1, 2009 to July 31, 2013, the criteria for ART initiation were: two consecutive CD4 counts <350 cells/mm<sup>3</sup> regardless of WHO clinical stage; or WHO clinical stage 3 or 4.  
- From August 1, 2013 to study cessation, two consecutive CD4 counts <350 cells/mm<sup>3</sup>, regardless of WHO clinical stage; or WHO clinical stage 3 or 4; or ART may be proposed to persons who have not yet reached the WHO criteria, if their partner is known to be HIV seronegative | A vs. B  
Median age 35 vs. 35 years  
80% vs. 77% female  
Race NR; study conducted in Africa  
CD4 count 459 (IQR, 359 to 575) vs. 466 cells/mm<sup>3</sup> (IQR, 369 to 584) |
<table>
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<tr>
<th>Study design</th>
<th>Study name</th>
<th>Author, year</th>
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<th>Geographic setting</th>
<th>N</th>
<th>Intervention groups</th>
<th>Population</th>
</tr>
</thead>
</table>
| Cohort       | HIV CAUSAL Collaboration          | Lodi 2015    | 7 years  | France, Greece, The Netherlands, Spain, Switzerland, United Kingdom, United States | 55,826 | A. Initiation of ART at ≥500 cells/mm³  
B. Initiation of ART at <500 cells/mm³  
C. Initiation of ART at <350 cells/mm³ | Mean age 35 (IQR, 28 to 44) vs. 38 years (IQR, 31 to 46)  
22% vs. 24% female  
30% vs. 40% heterosexual; 56% vs. 44% homosexual or bisexual; 2% vs. 3% PWID; 11% vs 14% other/unknown  
78% vs. 67% Western country; 11% vs. 20% sub-Saharan Africa; 8% vs. 9% rest of the world; 4% vs. 5% unknown |
| Cohort       | HIV CAUSAL Collaboration          | Lodi 2017    | 5 years  | Brazil, Canada, France, Greece, The Netherlands, Spain, Switzerland, United Kingdom, United States | 9,599  | A. Initiation of ART at ≥500 cells/mm³  
B. Initiation of ART at <500 cells/mm³  
C. Initiation of ART at <350 cells/mm³ | Data not stratified according to intervention group  
General HIV population  
Age 55 years (IQR, 52 to 59)  
21% female  
45% heterosexual; 43% homosexual; 2% PWID; 9% unknown  
63% Western country; 6% sub-Saharan Africa; 9% rest of the world; 22% unknown  
CD4 count (cells/mm³): 12% <100; 13% 100 to 200; 25% 200 to 349; 22% 350 to 499; 29% ≥500  
HIV RNA: 23% <10,000; 41% 10,000 to 100,000; 36% >100,000 log₁₀ copies/mL  
VA population  
Age 56 years (IQR, 53 to 60)  
2% female  
CD4 count (cells/mm³): 20% <100; 16% 100 to 200; 23% 200 to 349; 19% 350 to 499; 22% ≥500  
HIV RNA: 26% <10,000; 47% 10,000 to 100,000; 27% >100,000 log₁₀ copies/mL |
| Cohort       | Lima 2015                         | Canada       | 5 years  |        | 4,120 | A. Initiation of ART at ≥500 cells/mm³  
B. Initiation of ART at <500 cells/mm³  
C. Initiation of ART at ≥350 cells/mm³  
D. Initiation of ART at <350 cells/mm³ | Data not stratified according to intervention group  
Mean age 42 years (IQR, 35 to 49)  
20% female  
Race/ethnicity NR  
36% history of PWID  
CD4 count (cells/mm³): 44% <200; 32% 200 to 349; 14% 350 to 499; 10% ≥500 |
Table 2. Characteristics of Studies Published Since the Prior USPSTF Review of Immediate vs. Delayed Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Study design</th>
<th>Study name Author, year Duration Geographic setting N</th>
<th>Intervention groups</th>
<th>Population</th>
</tr>
</thead>
</table>
| Cohort       | Edwards 2015<sup>th</sup> United States 10 years n=3,532 | A. Initiation of ART at <500 cells/mm<sup>3</sup>  
B. Initiation of ART at <350 cells/mm<sup>3</sup> | Data not stratified according to intervention group  
Mean age NR; 49% 18 to 34 years; 32% 35 to 44 years; 19% 45 to 65 years  
18% female  
9% Hispanic; other race/ethnicity NR  
MSM: 67%; PWID: 17%  
Median CD4 count 646 cells/mm<sup>3</sup> |

*Duration varied according to outcome; 1.7-year results from HPTN 052 trial included in prior report.

**Abbreviations:** ANRS=Agence Nationale de Recherche sur le SIDA; ART=antiretroviral therapy; CD4=cluster of differentiation 4; HTPN=HIV Prevention Trials Network; NR=not reported; IQR=interquartile range; MSM=men who have sex with men; PWID=persons who inject drugs; RCT=randomized, controlled trial; RNA=ribonucleic acid; START=Strategic Timing of Antiretroviral Treatment; USPSTF=U.S. Preventive Services Task Force; VA=U.S. Department of Veterans Affairs; WHO=World Health Organization.
Table 3. Randomized, Controlled Trials of Immediate vs. Delayed Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Baseline CD4 count</th>
<th>Study name</th>
<th>Primary composite outcome</th>
<th>Mortality</th>
<th>AIDS-related events</th>
<th>Tuberculosis or bacterial infection</th>
<th>HIV transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;500 cells/mm³</td>
<td>START⁵⁵</td>
<td>All-cause mortality, serious AIDS-related events, and serious non–AIDS-related events: RR, 0.44 (95% CI, 0.31 to 0.63)</td>
<td>All-cause mortality: RR, 0.58 (95% CI, 0.29 to 1.18)</td>
<td>Serious AIDS-related event: RR, 0.28 (95% CI, 0.16 to 0.51)</td>
<td>Tuberculosis: RR, 0.30 (95% CI, 0.12 to 0.76)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mortality due to AIDS-related event: RR, 0.25 (95% CI, 0.03 to 2.27)</td>
<td></td>
<td>Grade 4 bacterial infection: RR, 0.39 (95% CI, 0.21 to 0.73)</td>
<td></td>
</tr>
<tr>
<td>&gt;500 cells/mm³</td>
<td>TEMPRANO ANRS⁶⁶</td>
<td>All-cause mortality, progression to AIDS, AIDS-defining cancer, or non–AIDS-defining invasive bacterial disease: RR, 0.57 (95% CI, 0.35 to 0.95)</td>
<td>All-cause mortality: RR, 0.79 (95% CI, 0.24 to 2.57)</td>
<td>Progression to AIDS: RR, 0.55 (95% CI, 0.29 to 1.05)</td>
<td>Tuberculosis: RR, 0.54 (95% CI, 0.27 to 1.09)</td>
<td>NR</td>
</tr>
<tr>
<td>≥350 to 550 cells/mm³</td>
<td>HPTN 052, 2011*⁵⁵,⁹⁰</td>
<td>All-cause mortality, serious AIDS-related events, and serious non–AIDS-related events: RR, 0.73 (95% CI, 0.53 to 1.02)</td>
<td>All-cause mortality, 1.7-year followup: RR, 0.76 (95% CI, 0.34 to 1.73)</td>
<td>Any AIDS-related event: RR, 0.65 (95% CI, 0.4 to 0.95)</td>
<td>Tuberculosis: RR, 0.49 (95% CI, 0.28 to 0.88)</td>
<td>Any HIV transmission, 1.7-year followup: RR, 0.11 (95% CI, 0.04 to 0.32); 5.5-year followup: RR, 0.32 (95% CI, 0.19 to 0.53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All-cause mortality, 2.1-year followup: RR, 0.72 (95% CI, 0.33 to 1.57)</td>
<td></td>
<td>Serious bacterial infection: RR, 1.52 (95% CI, 0.76 to 3.04)</td>
<td>Linked HIV transmission, 1.7-year followup: RR, 0.04 (95% CI, 0.005 to 0.27); 5.5-year followup: RR, 0.07 (95% CI, 0.02 to 0.22)</td>
</tr>
<tr>
<td>≥350 to 500 cells/mm³</td>
<td>SMART⁸⁹</td>
<td>All-cause mortality or opportunistic disease: RR, 0.31 (95% CI, 0.11 to 0.83)</td>
<td>All-cause mortality: RR, 0.26 (95% CI, 0.05 to 1.25)</td>
<td>Any opportunistic disease: RR, 0.33 (95% CI, 0.11 to 1.03)</td>
<td>Tuberculosis: RR, 0.46 (95% CI, 0.04 to 5.02)</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Included in prior USPSTF report.

**Abbreviations:** ANRS=Agence Nationale de Recherche sur le SIDA; CD4=cluster of differentiation 4; CI=confidence interval; HPTN=HIV Prevention Trials Network; NR=not reported; RR=relative risk; SMART=Strategies for Management of Antiretroviral Therapy; START=Strategic Timing of Antiretroviral Treatment.
**Table 4. New Studies on the Association Between Antiretroviral Therapy and Long-Term Cardiovascular Harms**

<table>
<thead>
<tr>
<th>Author, Year Study Quality</th>
<th>Study details</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D:A:D Study Monforte, 2013</strong>&lt;sup&gt;104&lt;/sup&gt; Good</td>
<td>Prospective analysis of 11 cohorts&lt;br&gt;Europe, Australia, and United States&lt;br&gt;N=49,734</td>
<td>ATV, boosted or unboosted by RTV</td>
<td>MI: Overall events: 844/49,734; incidence, 0.28/100 person-years followup (95% CI, 0.26 to 0.30)&lt;br&gt; &gt;3 years exposure to ATV: 0.20 (95% CI, 0.12 to 0.32)/100 person-years followup&lt;br&gt; No exposure to ATV: 0.28 (95% CI, 0.26 to 0.30)/100 person-years followup&lt;br&gt; No association between cumulative exposure to ATV and MI risk: univariate relative rate/year, 0.96 (95% CI, 0.88 to 1.04); multivariable relative rate/year, 0.95 (95% CI, 0.87 to 1.05)</td>
</tr>
<tr>
<td><strong>D:A:D Study Sabin, 2016</strong>&lt;sup&gt;102&lt;/sup&gt; Good</td>
<td>Prospective analysis of 11 cohorts&lt;br&gt;Europe, Australia, United States&lt;br&gt;N=49,717</td>
<td>ABC vs. non-ABC</td>
<td>MI: Overall events: 844/49,734; incidence, 0.28/100 person-years followup (95% CI, 0.26 to 0.30)&lt;br&gt; &gt;3 years exposure to ATV: 0.20 (95% CI, 0.12 to 0.32)/100 person-years followup&lt;br&gt; No exposure to ATV: 0.28 (95% CI, 0.26 to 0.30)/100 person-years followup&lt;br&gt; No association between cumulative exposure to ATV and MI risk: univariate relative rate/year, 0.96 (95% CI, 0.88 to 1.04); multivariable relative rate/year, 0.95 (95% CI, 0.87 to 1.05)</td>
</tr>
</tbody>
</table>
Table 4. New Studies on the Association Between Antiretroviral Therapy and Long-Term Cardiovascular Harms

<table>
<thead>
<tr>
<th>Author, Year Study Quality</th>
<th>Study details</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desai 2015&lt;sup&gt;103&lt;/sup&gt;</td>
<td>Retrospective analysis of VA data</td>
<td>Current ART exposure vs. nonexposure</td>
<td>Cardiovascular event (MI, stroke, or cardiovascular procedure)</td>
</tr>
<tr>
<td>N=24,510</td>
<td></td>
<td></td>
<td>ABC: OR, 1.50 (95% CI, 1.26 to 1.79)</td>
</tr>
<tr>
<td>Mean duration of followup varied according to study drug (results for interventions with &lt;2 years followup not shown)</td>
<td></td>
<td></td>
<td>EFV: OR, 1.40 (95% CI, 1.19 to 1.66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3TC: OR, 1.53 (95% CI, 1.34 to 1.75)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>NVP: OR, 0.91 (95% CI, 0.70 to 1.18)</td>
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<tr>
<td></td>
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<td></td>
<td>D4T: OR, 1.14 (95% CI, 0.95 to 1.37)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Tenofovir: OR, 1.10 (95% CI, 0.93 to 1.30)</td>
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<td></td>
<td></td>
<td></td>
<td>ZDV: OR, 1.41 (95% CI, 1.22 to 1.63)</td>
</tr>
<tr>
<td>Ding, 2012&lt;sup&gt;101&lt;/sup&gt;</td>
<td>Systematic review of 26 RCTs included in meta-analysis</td>
<td>ABC vs. non-ABC</td>
<td>MI events:</td>
</tr>
<tr>
<td>U.S. Food and Drug Administration Fair</td>
<td>N=9,868</td>
<td></td>
<td>Overall: 0.48% (24/5,028) vs. 0.46% (22/4,840); RD, 0.008% (95% CI, -0.26% to 0.27%); OR, 1.02 (95% CI, 0.56 to 1.84)</td>
</tr>
<tr>
<td>Mean followup (ABC vs. non-ABC): 1.43 vs. 1.49 person-years</td>
<td></td>
<td></td>
<td>Glaxo-Smith Kline trials: 0.26% (6/2,341) vs. 0.38% (9/2,367); RD, -0.11% (95% CI, 0.43% to 0.21%); OR, 0.70 (95% CI, 0.25 to 2.00)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>AIDS Clinical Trials Group trials: 0.60% (12/1,985) vs. 0.89% (9/1,016); RD, 0.03% (95% CI, -0.45% to 0.51%); OR, 1.06 (95% CI, 0.43 to 2.61)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other trials: 0.85% (6/702) vs. 0.46% (4/863); RD, 0.31% (95% CI, -0.53% to 1.16%); OR, 1.60 (95% CI, 0.46 to 5.62)</td>
</tr>
</tbody>
</table>

Abbreviations: 3TC=lamivudine; ABC=abacavir; aRR=adjusted rate ratio; ART=antiretroviral therapy; ATV=atazanavir; CI=confidence interval; D4T=stavudine; D:A:D=Data Collection on Adverse Events of Anti-HIV Drugs; EFV=efavirenz; MI=myocardial infarction; NVP=nevirapine; OR=odds ratio; RCT=randomized, controlled trial; RD=risk difference; RTV=ritonavir; VA=U.S. Department of Veterans Affairs; ZDV=zidovudine.
<table>
<thead>
<tr>
<th>KQ</th>
<th>No. of studies (k) Number of participants (n) Study design</th>
<th>Summary of findings by outcome</th>
<th>Consistency/ precision/reporting bias</th>
<th>Overall risk of bias/quality</th>
<th>Body of evidence limitations</th>
<th>EPC Assessment of strength of evidence for KQ</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ 1. Benefits of HIV screening vs. no screening</td>
<td>No studies</td>
<td>--</td>
<td>--</td>
<td>--</td>
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</tr>
<tr>
<td>KQ 2. Yield of repeat vs. one-time HIV screening, or HIV screening at different intervals</td>
<td>No studies</td>
<td>--</td>
<td>--</td>
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<td>--</td>
</tr>
<tr>
<td>KQ 3. Harms of HIV screening vs. no screening</td>
<td>No studies</td>
<td>--</td>
<td>--</td>
<td>--</td>
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<td>--</td>
</tr>
<tr>
<td>KQ 4. Benefits of immediate vs. delayed ART • CD4 count &gt;500 cells/mm³</td>
<td>2012 USPSTF review: k=4 observational studies (n=74,563) New evidence: k=4 (2 RCTs [n=6,761] and 2 observational studies [n=59,946])</td>
<td>Four observational studies in the prior USPSTF review found inconsistent evidence on effects of initiation of ART in patients with CD4 counts &gt;500 cells/mm³ vs. delayed initiation. Two new RCTs found initiation of ART in patients with CD4 counts &gt;500 cells/mm³ associated with decreased risk of death, AIDS events, and serious non-AIDS events (RR, 0.44 [95% CI, 0.31 to 0.63] and RR, 0.57 [95% CI, 0.35 to 0.95]). Two new observational studies also found initiation of ART at CD4 counts &gt;500 cells/mm³ associated with lower risk of death and AIDS-related events than delayed initiation, although one study reported effects smaller than those observed in the randomized trials. In one RCT, there was no association between early initiation of ART and increased risk of cardiovascular events (RR, 0.87 [95% CI, 0.40 to 1.88]).</td>
<td>Some inconsistency between RCTs and observational studies. Estimates in the RCTs precise for the primary composite outcome but some imprecision for some individual outcomes. No reporting bias detected.</td>
<td>Fair</td>
<td>One new RCT reported that ART drugs were provided by industry. One new RCT was open label, changed criteria for initiation of ART in the delayed therapy group over the course of the trial to match revisions to WHO recommendations, and conducted a prespecified subgroup analysis of patients with baseline CD4 counts &gt;500 cells/mm³ (41% of study population).</td>
<td>Moderate</td>
<td>One trial was conducted in a low-income setting and the other trial was international and partially conducted in low-middle-income settings. Median CD4 count was 651 cells/mm³ in one trial and in the other trial baseline CD4 count ranged from 500 to 800 mm/cells³ (average CD4 count not reported in the subgroup of patients with a CD4 count &gt;500 cells/mm³ at baseline). Patients were randomized between 2008 and 2013 in the trials. The observational studies were conducted in U.S. and European cohorts.</td>
</tr>
</tbody>
</table>
Table 5. Summary of Evidence

| KQ 4. Benefits of immediate vs. delayed ART • CD4 count >350 to <500 or 550 cells/mm³ | No. of studies (k) Study design | Summary of findings by outcome | Consistency/precision/reporting bias | Overall risk of bias/quality | Body of evidence limitations | EPC Assessment of strength of evidence for KQ | Applicability |
|---|---|---|---|---|---|---|---|---|
| 2012 USPSTF review: k=6 (2 RCTs [n=2,012] and 4 observational studies [n=71,460]) | Two RCTs in the prior USPSTF review found initiation of ART at CD4 counts >350 cells/mm³ associated with decreased risk of death or AIDS events after ~1.5 years compared with initiation at CD4 counts <250 cells/mm³ (RR, 0.30 [95% CI, 0.11 to 0.81] and RR, 0.61 [95% CI, 0.42 to 0.89]) and one of the RCTs found early initiation of ART associated with decreased risk of HIV transmission (RR, 0.04 [95% CI, 0.005 to 0.27] for virologically-linked transmission). Four observational studies reported consistent findings on clinical outcomes. One RCT found a potential protective effect of early initiation of ART on risk of cardiovascular events (RR, 0.07 [95% CI, 0.004 to 1.24]). | Consistent. Some imprecision in study estimates for certain outcomes. No reporting bias detected. | Good | Study drugs were donated in one RCT. One RCT included in the prior USPSTF review conducted a post hoc subgroup analysis of patients with CD4 counts >350 cells/mm³ at baseline. | High | One trial was primarily conducted in high-income settings and one trial was primarily conducted in low-income settings. Median CD4 counts at baseline in the RCTs were 430 to 440 cells/mm³. Patients were randomized between the years 2002 to 2006 in one trial and from 2007 to 2010 in the other trial. |
## Table 5. Summary of Evidence

<table>
<thead>
<tr>
<th>KQ</th>
<th>No. of studies (k)</th>
<th>Number of participants (n)</th>
<th>Study design</th>
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<th>Body of evidence limitations</th>
<th>EPC Assessment of strength of evidence for KQ</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ 5. Long-term harms of ART</td>
<td>2012 USPSTF review: k=4 observational studies (n&gt;60,500*)</td>
<td>New evidence: k=11 (2 systematic reviews [n=18,334], 2 trials [n=2,296], and 8 observational studies in 16 publications [n=134,225*], including longer-term followup from a large observational study included in the prior review)</td>
<td>Cardiovascular harms: A meta-analysis of 26 trials found no association between ABC use and risk of myocardial infarction, but two observational studies found ABC associated with increased risk (RR, 1.98 [95% CI, 1.72 to 2.29] and OR, 1.50 [95% CI, 1.26 to 1.79]). Neuropsychiatric harms: A systematic review of randomized and quasirandomized trials found EFV associated with increased risk of neuropsychiatric adverse events vs. other antiretroviral agents. Three observational studies found no association between use of EFV and death from suicide or suicidal ideation. Hepatic harms: An observational study found tenofovir associated with increased risk of end-stage liver disease or hepatocellular carcinoma, and emtricitabine associated with decreased risk. Renal harms: Two observational studies found tenofovir associated with increased risk of chronic kidney disease and two observational studies found ATV/r and protease inhibitors associated with renal adverse events. Fracture: A cohort study found ever use of tenofovir associated with increased risk of fracture (IRR, 1.40 [95% CI, 1.15 to 1.70]), but no association between cumulative exposure to tenofovir and risk of fracture (IRR per 5 years of exposure, 1.08 [95% CI, 0.94 to 1.25]).</td>
<td>Some inconsistency between RCT and observational data regarding cardiovascular risks of ABC. Findings reasonably precise. No reporting bias detected.</td>
<td>Fair</td>
<td>All studies were observational.</td>
<td>Low to moderate</td>
<td>Studies evaluated components of ART regimens rather than complete regimens, potentially limiting applicability to current regimens, and difficult to account for potential interactions between ART drugs and patients switching ART regimens in analyses. The largest study was conducted in the United States and Europe and began enrollment in 1999. Clinical importance of neuropsychiatric, renal, and hepatic harms likely to vary depending on reversibility following antiretroviral agent discontinuation and availability of alternative ART regimens.</td>
<td></td>
</tr>
</tbody>
</table>

*The number of participants in D:A:D cohort publications ranged from 23,905 to 49,717 depending on year of followup and outcome.

**Abbreviations:** ABC=abacavir; ART=antiretroviral therapy; ATV/r=ritonavir-boosted atazanavir; CD4=cluster of differentiation 4; CI=confidence interval; EFV=efavirenz; EPC=Evidence-based Practice Center; KQ=key question; OR=odds ratio; RCT=randomized, controlled trial; RR=relative risk; U.S.=United States; USPSTF=U.S. Preventive Services Task Force; WHO=World Health Organization.
Appendix A1. Search Strategies

Screening

Database: Ovid MEDLINE(R) without Revisions
1 exp HIV/
2 HIV Antibodies/
3 HIV Antigens/
4 HIV Seroprevalence/
5 HIV Seropositivity/
6 HIV Seronegativity/
7 AIDS Serodiagnosis/
8 human immunodeficiency virus.ti.
9 hiv.ti.
10 Mass Screening/
11 screen$.ti.
12 or/1-9
13 10 or 11
14 12 and 13
15 limit 14 to (english language and humans)
16 limit 15 to yr="2012 - 2018"
17 limit 16 to (clinical trial, all or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews)
18 (random* or control* or cohort).ti,ab.
19 16 and 18
20 17 or 19
21 20 not pregnan*.ti.

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 exp HIV/
2 HIV Antibodies/
3 HIV Antigens/
4 HIV Seroprevalence/
5 HIV Seropositivity/
6 HIV Seronegativity/
7 AIDS Serodiagnosis/
8 human immunodeficiency virus.ti.
9 hiv.ti.
10 Mass Screening/
11 screen$.ti.
12 or/1-9
13 10 or 11
14 12 and 13
15 limit 14 to yr="2012 - 2018"
16 15 not pregnan*.ti.

Treatment

Database: Ovid MEDLINE(R) without Revisions
1 exp HIV Infections/dt, pc, th
2 exp Anti-Retroviral Agents/ad, tu
3 Antiretroviral Therapy, Highly Active/
4 or/1-3
5 Viral Load/
6 exp CD4 Lymphocyte Count/
7 CD4.ti,ab.
8 or/5-7
9 4 and 8
Appendix A1. Search Strategies

10 (timing or initiat*).mp.
11 9 and 10
12 limit 11 to (english language and humans)
13 limit 12 to (clinical trial, all or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews)
14 12 and (random* or control* or cohort).ti,ab.
15 13 or 14
16 limit 15 to yr="2012 - 2018"
17 16 not pregnan*.ti.

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 exp HIV Infections/dt, pc, th
2 exp Anti-Retroviral Agents/ad, tu
4 or/1-3
5 Viral Load/
6 exp CD4 Lymphocyte Count/
7 CD4.ti,ab.
8 or/5-7
9 4 and 8
10 (timing or initiat*).mp.
11 9 and 10
12 limit 11 to yr="2012 - 2018"
13 12 not pregnan*.ti.

Treatment Harms

Database: Ovid MEDLINE(R) without Revisions
1 exp HIV Infections/dt, pc, th
2 exp Anti-Retroviral Agents/ad, tu
3 Antiretroviral Therapy, Highly Active/
4 or/1-3
5 4 and (harm* or safety or adverse).ti,ab.
6 limit 5 to yr="2012 - 2018"
7 6 not (pregnan* or mother*).ti.

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 exp HIV Infections/dt, pc, th
2 exp Anti-Retroviral Agents/ad, tu
3 Antiretroviral Therapy, Highly Active/
4 or/1-3
5 4 and (harm* or safety or adverse).ti,ab.
6 limit 5 to yr="2012 - 2018"
7 6 not (pregnan* or mother*).ti.

Screening and Treatment

Database: EBM Reviews - Cochrane Database of Systematic Reviews
1 (hiv or "human immunodeficiency virus").ti.
2 1 and screen*.ti.
3 1 and (treatment or antiretroviral or therapy).ti.
4 2 or 3
Appendix A2. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Include</th>
<th>Exclude</th>
</tr>
</thead>
</table>
| 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., sexually transmitted infection clinics, emergency room or urgent care)  
• Will focus on studies conducted in the United States and other high-income countries with low prevalence of HIV infection and in which HIV management is similar to that in the United States, unless studies are not available in those settings | Studies conducted in low- and middle-income countries, unless fair- or good-quality studies from the United States are not available |
| Populations*   | **KQs 1–3:** Asymptomatic adolescents and adults age 15 years and older  
**KQs 4, 5:** Adolescents and adults living with HIV | **KQs 1–3:** Persons who have known HIV infection, are on dialysis, are posttransplant, have occupational exposure (due to risk of needle stick or other parenteral exposure), or have known infection with hepatitis C virus, hepatitis B virus, or tuberculosis  
**KQ 4:** Persons who have acute HIV infection, are on dialysis, or are posttransplant; studies limiting enrollment to persons with hepatitis C virus, hepatitis B virus, or tuberculosis coinfection  
**KQ 5:** Same as for KQ 4, plus persons who are already or were previously taking antiretroviral therapy |
| Interventions  | **KQs 1–3:** Rapid or standard HIV testing  
**KQs 4, 5:** Currently recommended antiretroviral therapy regimens |                                                                                              |
| Outcomes       | **KQs 1, 4:** Mortality; AIDS and opportunistic infections; quality of life; function; reduced transmission of HIV and other sexually transmitted infections  
**KQ 2:** Number of new diagnoses per number of tests performed  
**KQ 3:** False-positive results, anxiety and effects of labeling, and partner discord, abuse, or violence  
**KQ 5:** Adverse outcomes associated with antiretroviral therapy, including cardiometabolic outcomes |                                                                                              |
| Comparisons    | **KQs 1, 3:** HIV screening vs. no screening  
**KQ 2:** Repeat HIV screening vs. one-time screening; screening at one interval vs. another  
**KQ 4:** Initiation of antiretroviral therapy at higher vs. lower CD4 counts |                                                                                              |
| Study designs  | **KQs 1–3:** Randomized, controlled trials and controlled observational studies  
**KQ 4:** Randomized, controlled trials and large (n >1,000) controlled observational studies  
**KQ 5:** Randomized, controlled trials and controlled observational studies; will consider treatment series if these study designs are not available | **KQ 1:** Uncontrolled observational studies |
| Timing         | **KQ 5:** Long-term followup, defined as ≥2 years |                                                                                              |

*For all KQs, subgroups of interest include those defined by sex, age (including adolescents), race/ethnicity, and risk group.

**Abbreviation:** KQ=key question.
Appendix A3. Literature Flow Diagram

4905 Citations identified through literature database searches

142 Citations identified through other sources*

11 Citations identified from previous reviews

4886 Citations screened after duplicates removed

4525 Citations excluded based on review of title and abstract

361 Full-text articles reviewed for eligibility for all Key Questions

29 new articles (18 studies) included†

0 studies included for Key Question 1

0 studies included for Key Question 2

0 studies included for Key Question 3

3 trials (5 articles) and 3 cohort studies (4 articles) included for Key Question 4

2 systematic reviews, 2 trials, and 8 cohort studies (16 publications) included for Key Question 5

*Other sources include reference lists of relevant articles, studies, systematic reviews, and suggestions from reviewers; includes background articles.

†In addition, 11 studies were carried forward from the prior U.S. Preventive Services Task Force reports.
Appendix A4. Included Studies List


Appendix A4. Included Studies List


Appendix A5. Excluded Studies List


Appendix A5. Excluded Studies List


Appendix A5. Excluded Studies List


Appendix A5. Excluded Studies List


Appendix A5. Excluded Studies List


Appendix A5. Excluded Studies List


Appendix A5. Excluded Studies List


Greig JR, Batchelor D, Wallis M. Positive predictive value is poor in low risk populations seen in universal screening for HIV infection [Comment on Sugarman "Implications of universal screening for HIV infection"]. BMJ. 2013;346:f3575. PMID: 23737279. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).


Appendix A5. Excluded Studies List


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Appendix A5. Excluded Studies List


Appendix A6. Currently Recommended Antiretroviral Therapy Regimens

**Preferred Regimens**

Integrase strand transfer inhibitor + two nucleoside reverse transcriptase inhibitors:
- Bictegravir/tenofovir alafenamide/emtricitabine
- Dolutegravir/abacavir/lamivudine*
- Dolutegravir + tenofovir\(^\d\)/emtricitabine*
- Raltegravir + tenofovir\(^\d\)/emtricitabine*

Secondary Regimens (Based on Clinical Considerations)

Integrase strand transfer inhibitor + two nucleoside reverse transcriptase inhibitors:
- Elvitegravir/tenofovir\(^\d\)/emtricitabine
- Raltegravir + abacavir/lamivudine*

Boosted protease inhibitor + two nucleoside reverse transcriptase inhibitors:
- Darunavir/cobicistat or darunavir/ritonavir + tenofovir\(^\d\)/emtricitabine*
- Atazanavir/cobicistat or atazanavir/ritonavir + tenofovir\(^\d\)/emtricitabine*
- Darunavir/cobicistat or darunavir/ritonavir + abacavir/lamivudine*

Nonnucleoside reverse transcriptase inhibitor + two nucleoside reverse transcriptase inhibitors:
- Doravirine/tenofovir disoproxil fumarate\(^\d\)/lamivudine or doravirine + tenofovir alafenamide\(^\d\)/emtricitabine
- Efvirenz + tenofovir disoproxil fumarate\(^\d\)/emtricitabine*
- Rilpivirine/tenofovir\(^\d\)/emtricitabine*

Regimens to consider when abacavir, tenofovir alafenamide, and tenofovir disoproxil fumarate cannot be used or are not optimal:
- Dolutegravir + lamivudine
- Darunavir/ritonavir + raltegravir twice daily
- Darunavir/ritonavir once daily + lamivudine*

*Lamivudine may be substituted for emtricitabine, or vice versa.
\(^\d\)Tenofovir alafenamide and tenofovir disoproxil fumarate are two forms of tenofovir approved by the U.S. Food and Drug Administration.

Appendix A7. Criteria for Assessing Internal Validity of Individual Studies

Systematic Reviews

Criteria:
- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance (especially important for systematic reviews)

Definition of ratings based on above criteria:
**Good:** Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions
**Fair:** Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies
**Poor:** Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies

Case-Control Studies

Criteria:
- Accurate ascertainment of cases
- Nonbiased selection of cases/controls, with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variables

Definition of ratings based on above criteria:
**Good:** Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; accurate diagnostic procedures and measurements applied equally to cases and controls; and appropriate attention to confounding variables
**Fair:** Recent, relevant, and without major apparent selection or diagnostic workup bias, but response rate less than 80 percent or attention to some but not all important confounding variables
**Poor:** Major selection or diagnostic workup bias, response rate less than 50 percent, or inattention to confounding variables

RCTs and Cohort Studies

Criteria:
- Initial assembly of comparable groups:
  - For RCTs: Adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - For cohort studies: Consideration of potential confounders, with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
Appendix A7. Criteria for Assessing Internal Validity of Individual Studies

- 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
- All important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs

Definition of ratings based on above criteria:
**Good:** Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

**Fair:** Studies are graded “fair” if any or all of the following problems occur, without the fatal flaws noted in the “poor” category below: Generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with 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. Intention-to-treat analysis is used for RCTs.

**Poor:** Studies are graded “poor” if any of the following fatal flaws 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 equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Diagnostic Accuracy Studies

Criteria:
- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of ratings based on above criteria:
**Good:** Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (>100) of broad-spectrum patients with and without disease

**Fair:** Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a “medium” spectrum of patients
Appendix A7. Criteria for Assessing Internal Validity of Individual Studies

**Poor:** Has a fatal flaw, such as: Uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients


- Maggie Czarnogorski, MD, MPH, Deputy Director, Comprehensive Women’s Health, U.S. Department of Veterans Affairs
- Lisa Metsch, PhD, Chair of Social Medicine, Columbia University
- Zelalem Temesgen, MD, Professor of Medicine, Mayo Clinic Director, Mayo Clinic Global HIV Education Initiative, Mayo Center for Tuberculosis
- Brandy Peaker, MD, MPH, Centers for Disease Control and Prevention
- Philip Peters, MD, DTM&H, Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention

Note: Reviewers provided comments on a prior version of the draft report and may or may not agree with the report findings.
## Appendix B Table 1. Key Question 4: Evidence Table of Trials of Initiating Antiretroviral Therapy at Different CD4 Counts on Clinical Outcomes—Study Characteristics

<table>
<thead>
<tr>
<th>Study name Author, Year</th>
<th>Study design</th>
<th>Setting</th>
<th>Duration of followup</th>
<th>Treatment groups</th>
<th>Inclusion criteria</th>
<th>Population characteristics</th>
<th>Screened Eligible Enrolled Analyzed Lost to followup</th>
<th>Funding source</th>
<th>Quality rating</th>
</tr>
</thead>
</table>
| START Lundgren, 2015    | RCT          | Africa, Europe, Israel, North America, South America, Mexico, Australia | 3 years (mean) | A. Immediate ART: CD4 >500 cells/mm³ (n=2,326)  
B. Deferred ART: CD4 <350 cells/mm³ (n=2,359) | HIV-positive patients age ≥18 years, not yet initiated ART, had no history of AIDS, and were in generally good health, two CD4 counts >500 cells/mm³ at least 2 weeks apart at least 60 days before enrollment. Excluded: Pregnant or breastfeeding | A vs. B  
Mean age 36 vs. 36 years  
27% vs. 27% female  
Race/ethnicity: 9% vs. 8% Asian; 30% vs. 30% black; 14% vs. 14% Latino/Hispanic; 44% vs. 45% white; 4% vs. 3% other Geographic region:  
22% vs. 21% Africa; 8% vs. 8% Asia; 2% vs. 2% Australia; 33% vs. 33% Europe/Israel; 11% vs. 11% North America; 25% vs. 25% South America/Mexico  
Mode of HIV infection: MSM: 56% vs. 55%; heterosexual: 38% vs. 39%; PWID: 2% vs. 1%; blood products/other/unknown: 5% vs. 6%  
Time since HIV infection (median): 1 vs. 1 year  
CD4 count (median): 651 (IQR, 585 to 765) vs. 651 (IQR, 582 to 764)  
HIV RNA (median): 13,000 vs. 12,550 copies/mL | Screened: NR  
Eligible: NR  
Enrolled: 4,685  
Analysed: 4,473  
Lost to followup: 212 | National Institute of Allergy and Infectious Diseases; National Institutes of Health Clinical Center; National Cancer Institute; National Heart, Lung, and Blood Institute; Eunice Kennedy Shriver National Institute of Child Health and Human Development; National Institute of Mental Health; National Institute of Neurological Disorders and Stroke; National Institute of Arthritis and Musculoskeletal and Skin Diseases; Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (France); National Health and Medical Research Council (Australia); National Research Foundation (Denmark); Bundesministerium für Bildung und Forschung (Germany); European AIDS Treatment Network; Medical Research Council (United Kingdom); National Institute for Health Research, National Health Service (United Kingdom); and University of Minnesota. Antiretroviral drugs were donated by: AbbVie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline /ViiV Healthcare, Janssen Scientific Affairs, Merck. | Good |
### Appendix B Table 1. Key Question 4: Evidence Table of Trials of Initiating Antiretroviral Therapy at Different CD4 Counts on Clinical Outcomes—Study Characteristics

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<th>Enrolled Analyzed</th>
<th>Lost to followup</th>
<th>Funding source</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>START</strong> O'Connor, 2017</td>
<td>Same as Lundgren, 2015</td>
<td>Same as Lundgren, 2015</td>
<td>Same as Lundgren, 2015</td>
<td>Same as Lundgren, 2015</td>
<td>Same as Lundgren, 2015</td>
<td>Same as Lundgren, 2015</td>
<td>Same as Lundgren, 2015</td>
<td>Same as Lundgren, 2015</td>
<td>Same as Lundgren, 2015</td>
<td>National Institute of Allergy and Infectious Diseases; study drug donations from Abbott Laboratories, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline/ViiV Healthcare, and Merck.</td>
<td>Good</td>
</tr>
<tr>
<td><strong>HPTN 052</strong> Grinsztejn, 2014</td>
<td>RCT</td>
<td>Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, U.S., Zimbabwe</td>
<td>Median 2.1 years</td>
<td>A. Immediate ART: CD4 ≥350 to &lt;550 cells/mm³ (n=886) B. Delayed ART: CD4 ≤250 cells/mm³ (n=877)</td>
<td>HIV-positive member of serodiscordant couple with CD4 ≥350 to &lt;550 cells/mm³ and no previous long-term ART</td>
<td>A vs. B</td>
<td>Median age 33 years (IQR, 27 to 39 years) Mean age &lt;25 years 13% vs. 13%; 25 to 39 years 64% vs. 64%; ≥40 years 24% vs. 23% 49% vs. 50% female Geographic region:* 16% vs. 15% South America; 30% vs. 30% Africa; 54% vs. 55% Asia CD4 count: 442 (IQR, 373-522) vs. 428 (IQR, 357 to 522) HIV-1 RNA: 4.4 (IQR, 8.8 to 4.9) vs. 4.4 (IQR, 3.9 to 4.9) log₁₀ copies/mL (4.4 log₁₀ copies/mL = 24,119 copies/mL)</td>
<td>Screened: 5,419 couples Eligible: 1,763 HIV-1 infected partners Enrolled: 1,763 Analyzed: 1,701 Lost to followup: 2% (34/176)</td>
<td></td>
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<tr>
<td><strong>HPTN 052</strong> Cohen 2016</td>
<td>Same as Grinsztejn, 2014</td>
<td>Same as Grinsztejn, 2014</td>
<td>Median 5.5 years</td>
<td>Same as Grinsztejn, 2014; HIV uninfected partner: A. Immediate ART (n=901) B. Delayed ART (n=888)</td>
<td>HIV uninfected member of serodiscordant couple</td>
<td>Same as Grinsztejn, 2014; demographic and clinical characteristics of uninfected partners NR</td>
<td>Same as Grinsztejn, 2014</td>
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<tr>
<td><strong>TEMPRANO</strong></td>
<td>RCT</td>
<td>Ivory Coast</td>
<td>30 months</td>
<td>A. Early ART: Age ≥18 years,</td>
<td>A vs. B</td>
<td>Screened: French National Agency for Fair</td>
<td>Same as Grinsztejn, 2014</td>
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</tbody>
</table>
Appendix B Table 1. Key Question 4: Evidence Table of Trials of Initiating Antiretroviral Therapy at Different CD4 Counts on Clinical Outcomes—Study Characteristics

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<th>Population characteristics</th>
<th>Screened Eligible Enrolled Analyzed Lost to followup</th>
<th>Funding source</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANRS 12136 Study TEMPRA</td>
<td>immediate ART initiation upon study enrollment (n=1,033)</td>
<td>HIV-1 infection or dual infection with HIV-1 and HIV-2, CD4 count &lt;800 cells/mm³, met no criteria for starting ART according to the most recent WHO guidelines</td>
<td>Median age 35 vs. 35 years, 80% vs. 77% female</td>
<td>Race NR; study conducted in Africa</td>
<td>CD4 459 (IQR, 359 to 575) vs. 466 cells/mm³ (IQR, 369 to 584)</td>
<td>HIV-RNA 4.6 (IQR, 4.0 to 5.2) vs. 4.7 (IQR, 4.0 to 5.3) log₁₀ copies/mL (39,811 vs. 50,119)</td>
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<tr>
<td>ANRS Study Group, 2015</td>
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<tr>
<td>B. Delayed ART</td>
<td>ART initiation according to criteria described below (n=1,023)</td>
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<tr>
<td>1. From March 1, 2008 to November 30, 2009, criteria for ART initiation were: 1 CD4 count &lt;200 cells/mm³ or WHO clinical stage 4; or 1 CD4 count 200 to 350 cells/mm³ and WHO clinical stage 2 or 3</td>
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<tr>
<td>2. From December 1, 2009 to July 31, 2013, criteria for ART initiation were: 2 consecutive CD4 counts &lt;350 cells/mm³ regardless of WHO clinical stage; or WHO clinical stage 3 or 4</td>
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</tbody>
</table>

Research on AIDS and Viral Hepatitis

Screened: 2,962
Eligible: 2,560
Enrolled: 2,076
Analyzed: 2,056
Lost to followup: 3% (58/2076)
Appendix B Table 1. Key Question 4: Evidence Table of Trials of Initiating Antiretroviral Therapy at Different CD4 Counts on Clinical Outcomes—Study Characteristics

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<th>Screened Eligible</th>
<th>Enrolled</th>
<th>Analyzed</th>
<th>Lost to followup</th>
<th>Funding source</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMPRANO ANRS 12136 Study TEMPRANO ANRS Study Group, 2015[6] Cont’d</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>3. From August 1, 2013 to study cessation, 2 consecutive CD4 counts &lt;350 cells/mm³, regardless of WHO clinical stage; or WHO clinical stage 3 or 4; or ART may be proposed to persons who have not yet reached the WHO criteria, if their partner is known to be HIV seronegative</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
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</tbody>
</table>

**Abbreviations**: ANRS=Agence Nationale de Recherche sur le SIDA; ART=antiretroviral therapy; CD4=cluster of differentiation 4; HTPN=HIV Prevention Trials Network; IQR=interquartile range; MSM=men who have sex with men; NR=not reported; PWID=persons who inject drugs; RCT=randomized, controlled trial; RNA=ribonucleic acid; START=Strategic Timing of Antiretroviral Treatment; U.S.=United States; WHO=World Health Organization.
## Appendix B Table 2. Key Question 4: Evidence Table of Trials of Initiating Antiretroviral Therapy at Different CD4 Counts on Clinical Outcomes—Results

<table>
<thead>
<tr>
<th>Study name</th>
<th>Treatment groups</th>
<th>Clinical outcomes*</th>
<th>Adverse events</th>
</tr>
</thead>
</table>
| **START**  | A. Immediate ART: CD4 >500 cells/mm³ (n=2,326) B. Deferred ART: CD4 <350 cells/mm³ (n=2,359) | A vs. B  
Primary outcome (serious AIDs or non–AIDS-related event or death): 1.8% (42/2,326) vs. 4.1% (96/2,359); HR, 0.43 (95% CI, 0.30 to 0.62); RR, 0.44 (95% CI, 0.31 to 0.63)  
All-cause mortality: 0.5% (12/2,326) vs. 0.9% (21/2,359); HR, 0.58 (95% CI, 0.28 to 1.17); RR, 0.58 (95% CI, 0.21 to 1.18)  
Serious AIDs-related event: 0.6% (14/2,326) vs. 2.1% (50/2,359); HR, 0.28 (95% CI, 0.15 to 0.50); RR, 0.28 (95% CI, 0.16 to 0.51)  
Tuberculosis: 0.3% (6/2,326) vs. 0.8% (20/2,359); HR, 0.29 (95% CI, 0.12 to 0.73); RR, 0.30 (95% CI, 0.12 to 0.76)  
Grade 4 bacterial infection: 0.6% (14/2,326) vs. 1.5% (36/2,359); HR, 0.38 (95% CI, RR, 0.39 (95% CI, 0.21 to 0.73)  
Grade 4 viral infection: 0.5% (12/2,326) vs. 0.6% (15/2,359); HR, 0.81 (95% CI, 0.38 to 1.72); RR, 0.81 (95% CI, 0.38 to 1.73)  
Grade 4 unspecified infection: 2.8% (64/2,326) vs. 2.8% (65/2,359); HR, 0.99 (95% CI, 0.70 to 1.40); RR, 1.00 (95% CI, 0.71 to 1.40)  
Malignant lymphoma: 0.1% (3/2,326) vs. 0.4% (10/2,359); RR, 0.30 (95% CI, 0.08 to 1.10)  
Cancer not related to AIDS: 0.4% (9/2,326) vs. 0.8% (18/2,359); RR, 0.51 (95% CI, 0.23 to 1.13)  
No evidence of interaction (p>0.05) for any subgroup analysis including: age, sex, race/ethnicity, geographic region, baseline CD4 count, baseline HIV RNA, smoking status, or Framingham 10-year CHD risk | A vs. B  
CVD: 0.5% (12/2,326) vs. 0.6% (14/2,359); RR, 0.87 (95% CI, 0.40 to 1.88)  
Suicidal or self-injurious behavior: 1.2% (27/2,326) vs. 1.0% (24/2,359); RR, 1.20 (95% CI, 0.71 to 2.05)  
End-stage renal disease: <0.01% (1/2,326) vs. 0% (0/2,359); RR, 3.04 (95% CI, 0.47 to 19) |
| O'Connor, 2015 | Same as Lundgren, 2015 | A vs. B  
Serious bacterial infection (grade 4 event or infection requiring unscheduled hospitalization or death): 1.5% (34/2,326) vs. 3.6% (86/2,359); HR, 0.39 (95% CI, 0.26 to 0.57); RR, 0.40 (95% CI, 0.27 to 0.59) | Same as Lundgren, 2015 |
Appendix B Table 2. Key Question 4: Evidence Table of Trials of Initiating Antiretroviral Therapy at Different CD4 Counts on Clinical Outcomes—Results

<table>
<thead>
<tr>
<th>Study name</th>
<th>Author, Year</th>
<th>Treatment groups</th>
<th>Clinical outcomes*</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPTN 052</strong>&lt;sup&gt;Grinsztejn, 2014&lt;/sup&gt;&lt;sup&gt;80&lt;/sup&gt;</td>
<td></td>
<td>A. Immediate ART: CD4 ≥350 to &lt;550 cells/mm&lt;sup&gt;3&lt;/sup&gt; (n=886) B. Delayed ART: CD4 ≤250 cells/mm&lt;sup&gt;3&lt;/sup&gt; (n=877)</td>
<td>A vs. B Primary event (any death, new-onset WHO clinical stage 4 HIV-1 disease, tuberculosis, severe bacterial infection, serious CV or vascular event, serious liver disease, end-stage renal disease, new-onset DM, non-AIDS-defining malignant disease): 6.4% (57/886) vs 8.8% (77/875); HR, 0.73 (95% CI, 0.52 to 1.03); RR, 0.73 (95% CI, 0.53 to 1.02); no difference according to geographical region, sex, baseline CD4 count All-cause mortality: 1.2% (11/886) vs 1.7% (15/875); HR, 0.73 (95% CI, 0.34 to 1.59); RR, 0.72 (95% CI, 0.33 to 1.57) Mortality due to AIDS-related event: 0.1% (1/886) vs 0.5% (4/875); RR, 0.25 (95% CI, 0.03 to 2.20) Any AIDS-related event: 4.5% (40/886) vs 7.0% (61/875); HR, 0.64 (95% CI, 0.43 to 0.96); RR, 0.65 (95% CI, 0.4 to 0.95) Serious bacterial infection: 2.3% (20/886) vs 1.5% (13/875); RR, 1.52 (95% CI, 0.76 to 3.04) Tuberculosis: 1.9% (17/886) vs 3.9% (34/875); HR 0.49 (95% CI, 0.28 to 0.89); RR, 0.49 (95% CI, 0.28 to 0.88)</td>
<td>A vs. B Serious CVD or vascular disease: 0.3% (3/886) vs. 0.1% (1/875); RR, 2.96 (95% CI, 0.31 to 28) New-onset DM: 0.5% (4/886) vs. 0.6% (5/875); RR, 0.79 (95% CI, 0.21 to 2.93) Serious liver disease: 0.2% (2/886) vs. 0% (0/875); RR, 4.94 (95% CI, 0.24 to 103) End-stage renal disease: 0% (0/886) vs. 0% (0/875)</td>
</tr>
<tr>
<td><strong>HPTN 052</strong>&lt;sup&gt;Cohen 2016&lt;/sup&gt;&lt;sup&gt;84&lt;/sup&gt;</td>
<td></td>
<td>Same as Grinsztejn, 2014; HIV uninfected partner: A. Immediate ART (n=901) B. Delayed ART (n=888)</td>
<td>A vs. B Any HIV transmission: 2.1% (19/901) vs 6.6% (59/888); HR, 0.31 (95% CI, 0.19 to 0.53); RR, 0.32 (95% CI, 0.19 to 0.53) Linked HIV transmission: 0.3% (3/901) vs 4.8% (43/888); HR, 0.07 (95% CI, 0.02 to 0.22); RR, 0.07 (95% CI, 0.02 to 0.22)</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Appendix B Table 2: Key Question 4: Evidence Table of Trials of Initiating Antiretroviral Therapy at Different CD4 Counts on Clinical Outcomes—Results

<table>
<thead>
<tr>
<th>Study name</th>
<th>Treatment groups</th>
<th>Clinical outcomes*</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEMPRANO</strong></td>
<td>A: Early ART: immediate ART initiation upon study enrollment (n=1,033)</td>
<td>A vs. B&lt;br&gt;Patients with baseline CD4 ≥500 cells/mm³: Primary endpoint: 5.3% (23/436) vs. 9.2% (38/413); aHR, 0.56 (95% CI, 0.33 to 0.94); RR, 0.57 (95% CI, 0.35 to 0.95)</td>
<td>A vs. B&lt;br&gt;Patients with CD4 ≥500 cells/mm³ at baseline: Any Grade 3 or 4 adverse event: 6.2% (27/436) vs. 7.3% (30/413); RR, 0.85 (95% CI, 0.52 to 1.41)</td>
</tr>
</tbody>
</table>
| **ANRS Study** | B: Delayed ART: ART initiation according to criteria described below (n=1,023):<br>1. From March 1, 2008 to November 30, 2009, the criteria for ART initiation were: 1 CD4 count <200 cells/mm³ or WHO clinical stage 4; or 1 CD4 count 200 to 350 cells/mm³ and WHO clinical stage 2 or 3.<br>2. From December 1, 2009 to July 31, 2013, the criteria for ART initiation were: 2 consecutive CD4 counts <350 cells/mm³ regardless of WHO clinical stage; or WHO clinical stage 3 or 4.<br>3. From August 1, 2013 to study cessation, 2 consecutive CD4 counts <350 cells/mm³, regardless of WHO clinical stage; or WHO clinical stage 3 or 4; or ART may be proposed to persons who have not yet reached the WHO criteria, if their partner is known to be HIV seronegative | All-cause mortality: 1.1% (5/436) vs. 1.5% (6/413); RR, 0.79 (95% CI, 0.24 to 2.57)<br>Death or progression to AIDS: 4.4% (19/436) vs. 7.3% (30/413); aHR, 0.59 (95% CI, 0.33 to 1.06); RR, 0.60 (95% CI, 0.34 to 1.05)<br>Progression to AIDS: 3.2% (14/436) vs. 5.8% (24/413); aHR, 0.55 (95% CI, 0.28 to 1.05); RR, 0.55 (95% CI, 0.29 to 1.05)<br>Tuberculosis: 2.8% (12/436) vs. 5.1% (21/413); aHR, 0.54 (95% CI, 0.26 to 1.09); RR, 0.54 (95% CI, 0.27 to 1.09)<br>Invasive bacterial disease: 1.1% (5/436) vs. 1.9% (8/413); aHR, 0.61 (95% CI, 0.20 to 1.88); RR, 0.59 (95% CI, 0.20 to 1.80)<br>Patients with baseline CD4 <500 cells/mm³: Primary endpoint: 6.9% (41/597) vs. 12.0% (73/610); aHR, 0.56 (95% CI, 0.38 to 0.83); RR, 0.57 (95% CI, 0.40 to 0.83)<br>Death or progression to AIDS: 5.2% (31/597) vs. 8.9% (54/610); aHR, 0.58 (95% CI, 0.37 to 0.90); RR, 0.59 (95% CI, 0.38 to 0.90)<br>Progression to AIDS: 3.2% (19/597) vs. 6.7% (41/610); aHR, 0.47 (95% CI, 0.27 to 0.81); RR, 0.47 (95% CI, 0.28 to 0.81)<br>Tuberculosis: 2.7% (16/597) vs. 5.6% (34/610); aHR, 0.48 (95% CI, 0.27 to 0.87); RR, 0.48 (95% CI, 0.27 to 0.86)<br>Invasive bacterial disease: 1.5% (9/597) vs. 4.6% (28/610); aHR, 0.33 (95% CI, 0.15 to 0.69); RR, 0.33 (95% CI, 0.16 to 0.69)<br>Primary endpoint (all-cause mortality, AIDS-defining disease, non–AIDS-defining cancer, or non–AIDS-defining invasive bacterial disease): 6.2% (64/1,033) vs. 10.9% (111/1,023); aHR, 0.56 (95% CI, 0.41 to 0.76); RR, 0.57 (95% CI, 0.43 to 0.77)<br>All-cause mortality: 2.0% (21/1,033) vs. 2.5% (26/1,023); aHR, 0.80 (95% CI, 0.45 to 1.40); RR, 0.79 (95% CI, 0.24 to 2.57)<br>Death or progression to AIDS: 4.8% (50/1,033) vs. 8.2% (84/1,023); aHR, 0.58 (95% CI, 0.41 to 0.83); RR, 0.59 (95% CI, 0.42 to 0.83)<br>Progression to AIDS: 3.2% (33/1,033) vs. 6.4% (65/1,023); aHR, 0.50 (95% CI, 0.33 to 0.76); RR, 0.50 (95% CI, 0.33 to 0.76)<br>Tuberculosis: 2.7% (28/1,033) vs. 5.4% (55/1,023); aHR, 0.50 (95% CI, 0.32 to 0.79); RR, 0.50 (95% CI, 0.32 to 0.79)<br>Invasive bacterial disease: 1.4% (14/1,033) vs. 1.5% (36/2,332); aHR, 0.39 (95% CI, 0.21 to 0.71); RR, 0.39 (95% CI, 0.21 to 0.71) | All patients: Any Grade 3 or 4 adverse event: 6.8% (70/1,033) vs. 7.2% (74/1,023); RR, 0.94 (95% CI, 0.68 to 1.28)<br>Grade 3 or 4 cardiovascular event: 0.3% (3/1,033) vs. 0.6% (6/1,023); RR, 0.99 (95% CI, 0.20 to 4.90)<br>Grade 3 or 4 renal event: 0.1% (1/1,033) vs. 1.2% (12/1,023); RR, 0.08 (95% CI, 0.01 to 0.63)<br>Grade 3 or 4 hepatic event: 1.0% (10/1,033) vs. 1.5% (15/1,023); RR, 0.66 (95% CI, 0.30 to 1.46)

*RRs were calculated based on available data.
Appendix B Table 2. Key Question 4: Evidence Table of Trials of Initiating Antiretroviral Therapy at Different CD4 Counts on Clinical Outcomes—Results

**Abbreviations:** aHR=adjusted hazard ratio; ANRS=Agence Nationale de Recherche sur le SIDA; ART=antiretroviral therapy; CD4=cluster of differentiation 4; CHD=coronary heart disease; CI=confidence interval; CVD=cardiovascular disease; DM=diabetes mellitus; HR=hazard ratio; HTPN=HIV Prevention Trials Network; NR=not reported; RNA=ribonucleic acid; RR=risk ratio; START=Strategic Timing of Antiretroviral Treatment; WHO=World Health Organization.
### Appendix B Table 3. Key Question 4: Quality Assessment of Randomized, Controlled Trials

<table>
<thead>
<tr>
<th>Study name Author, year</th>
<th>Randomization adequate?</th>
<th>Allocation concealment adequate?</th>
<th>Groups similar at baseline?</th>
<th>Eligibility criteria specified?</th>
<th>Outcome assessors masked?</th>
<th>Care provider masked?</th>
<th>Patient masked?</th>
<th>Attrition and withdrawals reported?</th>
<th>Loss to followup: differential (&gt;10%)/high (&gt;20%)?</th>
<th>Analyze persons in the groups in which they were randomized?</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>START85</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>HPTN 05290</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>TEMPRANO ANRS, 201586</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
</tbody>
</table>

**Abbreviations:** ANRS=Agence Nationale de Recherche sur le SIDA; HTPN=HIV Prevention Trials Network; START=Strategic Timing of Antiretroviral Treatment.
### Appendix B Table 4: Key Question 4: Evidence Table of Cohort Studies of Initiating Antiretroviral Therapy at Different CD4 Counts on Clinical Outcomes—Study Characteristics

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Setting/ Data source</th>
<th>Cohorts</th>
<th>Duration of followup</th>
<th>Inclusion criteria</th>
<th>Number analyzed</th>
<th>Comparison groups</th>
<th>Population characteristics</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards, 2015</td>
<td>U.S., Centers for AIDS Research Network of Integrated Clinical Systems</td>
<td>Centers for AIDS Research Network of Integrated Clinical Systems enrollees from 1 of 8 sites</td>
<td>10 years</td>
<td>ART naïve, age ≥19 years enrolled in Centers for AIDS Research Network of Integrated Clinical Systems sites from January 1 1998 to December 31 2013</td>
<td>3,532</td>
<td>A. Initiation of ART at &lt;500 cells/mm³</td>
<td>Data not stratified according to intervention group &lt;br&gt; Mean age NR: 49% 18 to 34 years &lt;br&gt; 32% 35 to 44 years &lt;br&gt; 19% 45 to 65 years &lt;br&gt; 18% female &lt;br&gt; 9% Hispanic; other race/ethnicity NR</td>
<td>Fair</td>
</tr>
<tr>
<td>Lima, 2015</td>
<td>British Columbia (Canada) Centre for Excellence in HIV/AIDS Drug Treatment Programme</td>
<td>DTP enrollees between January 1 2000 and December 31 2012</td>
<td>Median 5 years</td>
<td>ART naïve, age ≥19 years enrolled in DTP during specified time frame</td>
<td>4,120</td>
<td>A. Initiation of ART at ≥500 cells/mm³ &lt;br&gt; B. Initiation of ART at &lt;500 cells/mm³ &lt;br&gt; C. Initiation of ART at ≥350 cells/mm³ &lt;br&gt; D. Initiation of ART at &lt;350 cells/mm³</td>
<td>Data not stratified according to intervention group &lt;br&gt; Mean age NR: 42 years (IQR, 35 to 49) &lt;br&gt; 20% female &lt;br&gt; Race/ethnicity NR: 36% history of PWID &lt;br&gt; CD4 count: 44% &lt;200 cells/mm³; 32% 200 to 349 cells/mm³; 14% 350 to 499 cells/mm³; 10% ≥500 cells/mm³</td>
<td>Fair</td>
</tr>
<tr>
<td>Lodi, 2015</td>
<td>Pooled national health care data from 12 European cohorts</td>
<td>HIV-CAUSAL collaboration of cohorts in Europe and the U.S.</td>
<td>7 years</td>
<td>Age ≥18 years; HIV diagnosis on or after Jan 1, 2000; AIDS-free; ART naïve; CD4 cell count and HIV-RNA measurements within 3 months of each other and within 6 months of the date of HIV diagnosis. Excluded: Individuals with no CD4 or HIV RNA measures after baseline</td>
<td>55,826</td>
<td>A. Initiation of ART at ≥500 cells/mm³ &lt;br&gt; B. Initiation of ART at &lt;500 cells/mm³ &lt;br&gt; C. Initiation of ART at &lt;350 cells/mm³</td>
<td>A vs. B &lt;br&gt; Mean age 35 (IQR, 28 to 44) vs. 38 (IQR, 31 to 46) &lt;br&gt; 22% vs. 24% female &lt;br&gt; Transmission group: 30% vs. 40% heterosexual; 56% vs. 44% homosexual or bisexual; 2 vs. 3% PWID; 11% vs. 14% other/unknown &lt;br&gt; Geographic origin: 78% vs. 67% Western country; 11% vs. 20% sub-Saharan Africa; 8% vs. 9% rest of the world; 4% vs. 5% unknown</td>
<td>Fair</td>
</tr>
</tbody>
</table>
## Appendix B Table 4. Key Question 4: Evidence Table of Cohort Studies of Initiating Antiretroviral Therapy at Different CD4 Counts on Clinical Outcomes—Study Characteristics

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Setting/ Data source</th>
<th>Cohorts</th>
<th>Duration of followup</th>
<th>Inclusion criteria</th>
<th>Number analyzed</th>
<th>Comparison groups</th>
<th>Population characteristics</th>
<th>Quality rating</th>
</tr>
</thead>
</table>
| Lodi, 2017   | Cohorts from Europe, Brazil, Canada and the U.S. | HIV CAUSAL Collaboration cohorts (general HIV population) and Veterans Aging Cohort Study (VA population) | 5 years | Ages 50 to 70 years, who had at least 1 CD4 cell count and 1 HIV-RNA measurement within 3 months of each other, whereas ART-naive and AIDS-free after December 31, 2004 | 9,599 | A. Initiation of ART at ≥500 cells/mm³  
B. Initiation of ART at <500 cells/mm³  
C. Initiation of ART at <350 cells/mm³ | Data not stratified according to intervention group  
General HIV population  
Age 55 years (IQR, 52 to 59)  
21% female  
Transmission group: 45% heterosexual; 43% homosexual; 2% PWID; 9% unknown  
Geographic origin: 63% Western country; 6% sub-Saharan Africa; 9% rest of world; 22% unknown  
CD4 count: 12% <100 cells/mm³; 13% 100 to 200 cells/mm³; 25% 200 to 349 cells/mm³; 22% 350 to 499 cells/mm³; 29% ≥500 cells/mm³  
HIV RNA: 23% <10,000 copies/mL; 41% 10,000 to 100,000 copies/mL; 36% >100,000 copies/mL  
VA population  
Age 56 years (IQR, 53 to 60)  
2% female  
CD4 count: 20% <100 cells/mm³; 16% 100 to 200 cells/mm³; 23% 200 to 349 cells/mm³; 19% 350 to 499 cells/mm³; 22% ≥500 cells/mm³  
HIV RNA: 26% <10,000 copies/mL; 47% 10,000 to 100,000 copies/mL; 27% >100,000 copies/mL | Fair |

**Abbreviations:** ART=antiretroviral therapy; CD4=cluster of differentiation 4; DTP=drug treatment program; IQR=interquartile range; MSM=men who have sex with men; NR=not reported; PWID=persons who inject drugs; RNA=ribonucleic acid; U.S.=United States; VA=U.S. Department of Veterans Affairs.
### Appendix B Table 5. Key Question 4: Evidence Table of Cohort Studies of Initiating Antiretroviral Therapy at Different CD4 Counts on Clinical Outcomes—Results

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Comparison groups</th>
<th>Adjusted variables for statistical analysis</th>
<th>Clinical outcomes</th>
</tr>
</thead>
</table>
| Edwards, 2015<sup>86</sup> | A. Initiation of ART at <500 cells/mm<sup>3</sup>  
B. Initiation of ART at <350 cells/mm<sup>3</sup>  
C. Initiation of ART at <200 cells/mm<sup>3</sup> | Sex, race/ethnicity, injection drug use, MSM status, age, year, CD4 cell count, viral load, AIDS status | All-cause mortality, 5-year risk:  
B vs. A: RR, 1.15 (95% CI, 1.05 to 1.26); RD, 0.67 (95% CI, 0.23 to 1.11)  
C vs. A: RR, 1.33 (95% CI, 1.15 to 1.54); RD, 1.54 (95% CI, 0.72 to 2.36)  
Ages 18 to 34 years:  
B vs. A: RR, 1.05 (95% CI, 0.87 to 1.27); RD, 0.11 (95% CI, -0.33 to 0.55)  
C vs. A: RR, 1.16 (95% CI, 0.84 to 1.60); RD, 0.34 (95% CI, -0.40 to 1.08)  
Ages 35 to 44 years:  
B vs. A: RR, 1.08 (95% CI, 0.95 to 1.22); RD, 0.42 (95% CI, -0.23 to 1.07)  
C vs. A: RR, 1.13 (95% CI, 0.91 to 1.41); RD, 0.67 (95% CI, -0.59 to 1.93)  
Ages 45 to 65 years:  
B vs. A: RR, 1.23 (95% CI, 1.08 to 1.40); RD, 2.11 (95% CI, 0.80 to 3.42)  
C vs. A: RR, 1.58 (95% CI, 1.31 to 1.90); RD, 5.33 (95% CI, 3.15 to 7.51) | All-cause mortality, 10-year risk:  
B vs. A: RR, 1.08 (95% CI, 1.00 to 1.16); RD, 0.87 (95% CI, 0.07 to 1.67)  
C vs. A: RR, 1.25 (95% CI, 1.08 to 1.44); RD, 2.71 (95% CI, 0.92 to 4.50)  
Ages 18 to 34 years:  
B vs. A: RR, 1.00 (95% CI, 0.87 to 1.15); RD, -0.03 (95% CI, -0.83 to 0.77)  
C vs. A: RR, 1.02 (95% CI, 0.78 to 1.33); RD, 0.14 (95% CI, -1.48 to 1.76)  
Ages 35 to 44 years:  
B vs. A: RR, 1.09 (95% CI, 0.99 to 1.20); RD, 0.99 (95% CI, -0.13 to 2.11)  
C vs. A: RR, 1.19 (95% CI, 1.98 to 1.45); RD, 2.15 (95% CI, -0.39 to 4.69)  
Ages 45 to 65 years:  
B vs. A: RR, 1.12 (95% CI, 1.01 to 1.25); RD, 2.30 (95% CI, 0.23 to 4.37)  
C vs. A: RR, 1.45 (95% CI, 1.21 to 1.71); RD, 8.78 (95% CI, 5.89 to 13.90) |
| Lima, 2015<sup>96</sup> | A. Initiation of ART at ≥500 cells/mm<sup>3</sup>  
B. Initiation of ART at <500 cells/mm<sup>3</sup>  
C. Initiation of ART at ≥350 cells/mm<sup>3</sup>  
D. Initiation of ART at <350 cells/mm<sup>3</sup> | Mortality: Age, sex, history of injection drug use, longitudinal adherence to cART, longitudinal viral load, follow-up time  
AIDS-defining illness: History of injection drug use, longitudinal adherence to cART, longitudinal viral load, follow-up time | All-cause mortality, probability (IQR):  
CD4 <350 cells/mm<sup>3</sup>, 2000–2006: 0.14 (0.08 to 0.22)  
CD4 ≥350 cells/mm<sup>3</sup>, 2000–2006: 0.14 (0.09 to 0.22)  
CD4 <350 cells/mm<sup>3</sup>, 2007–2012: 0.05 (0.03 to 0.08)  
CD4 ≥350 cells/mm<sup>3</sup>, 2007–2012: 0.02 (0.01 to 0.04)  
CD4 <500 cells/mm<sup>3</sup>, 2000–2006: 0.13 (0.08 to 0.22)  
CD4 ≥500 cells/mm<sup>3</sup>, 2000–2006: 0.16 (0.10 to 0.24)  
CD4 <500 cells/mm<sup>3</sup>, 2007–2012: 0.05 (0.03 to 0.02)  
CD4 ≥500 cells/mm<sup>3</sup>, 2007–2012: 0.01 (0.01 to 0.02)  
|
### Appendix B Table 5: Key Question 4: Evidence Table of Cohort Studies of Initiating Antiretroviral Therapy at Different CD4 Counts on Clinical Outcomes—Results

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Comparison groups</th>
<th>Adjusted variables for statistical analysis</th>
<th>Clinical outcomes</th>
</tr>
</thead>
</table>
| Lodi, 2015\textsuperscript{67} | A. Initiation of ART at ≥500 cells/mm\textsuperscript{3}  
B. Initiation of ART at <500 cells/mm\textsuperscript{3}  
C. Initiation of ART at <350 cells/mm\textsuperscript{3} | CD4 count, HIV-RNA, AIDS, calendar period, age of HIV diagnosis, risk group, sex, geographical origin, race/ethnicity, cohort | All-cause mortality, 7-year risk:  
A: 4.0% (95% CI, 3.8 to 4.2); B: 4.0% (95% CI, 3.8 to 4.3); C: 4.2% (95% CI, 4.0 to 4.5)  
All-cause mortality, RR (A=1.0 reference standard):  
B vs. A: 1.02 (95% CI, 1.01 to 1.03); A vs. C: 1.06 (95% CI, 1.03 to 1.10)  
All-cause mortality, RD (A=0 reference standard):  
B vs. A: 0.06% (95% CI, 0.02 to 0.11); A vs. C: 0.25% (95% CI, 0.14 to 0.37)  
All-cause mortality, difference in restricted mean survival time:  
B vs. A: -2 days (95% CI, -2 to -1); A vs. C: -5 days (95% CI, -6 to -4)  
AIDS or death, 7-year risk:  
A: 7.1% (95% CI, 6.8 to 7.3); B: 7.5% (95% CI, 7.2 to 7.8); C: 8.5% (95% CI, 8.2 to 8.8)  
AIDS or death, RR (A=1.0 reference standard):  
B vs. A: 1.06 (95% CI, 1.06 to 1.07); A vs. C: 1.20 (95% CI, 1.17 to 1.23)  
AIDS or death, RD (A=0 reference standard):  
B vs. A: 0.44% (95% CI, 0.37 to 0.51); A vs. C: 1.41% (95% CI, 1.24 to 1.59)  
AIDS or death, difference in restricted mean survival time:  
B vs. A: -7 days (95% CI, -8 to -6); A vs. C: -21 days (95% CI, -23 to -19) |
| Lodi, 2017\textsuperscript{95} | A. Initiation of ART at ≥500 cells/mm\textsuperscript{3}  
B. Initiation of ART at <500 cells/mm\textsuperscript{3}  
C. Initiation of ART at <350 cells/mm\textsuperscript{3} | CD4 cell count, HIV-RNA level, age, sex, mode of acquisition, calendar year, geographical origin, cohort | General HIV population  
All-cause mortality:  
B vs. A: RR, 1.03 (95% CI, 1.01 to 1.06); RD, 0.14 (95% CI, 0.04 to 0.28); C vs. A: RR, 1.07 (95% CI, 1.02 to 1.15); RD, 0.40 (95% CI, 0.10 to 0.71)  
Non-AIDS mortality:  
B vs. A: RR, 1.03 (95% CI, 0.99 to 1.06); RD, 0.07 (95% CI, -0.03 to 0.16); C vs. A: RR, 1.06 (95% CI, 0.97 to 1.16); RD, 0.17 (95% CI, -0.07 to 0.43)  
All-cause mortality, patients with CD4 ≥500 cells/mm\textsuperscript{3}:  
B vs. A: RR, 1.30 (95% CI, 1.03 to 1.72); RD, 0.86 (95% CI, 0.10 to 1.45); C vs. A: RR, 1.56 (95% CI, 1.05 to 2.41); RD, 1.62 (95% CI, 0.17 to 2.92)  
VA population  
All-cause mortality:  
B vs. A: RR, 1.05 (95% CI, 1.02 to 1.08); RD, 0.69 (95% CI, 0.32 to 1.13); C vs. A: RR, 1.11 (95% CI, 1.05 to 1.18); RD, 1.61 (95% CI, 0.79 to 2.67)  
Non-AIDS mortality:  
B vs. A: RR, 1.06 (95% CI, 1.02 to 1.13); RD, 0.40 (95% CI, 0.13 to 0.84); C vs. A: RR, 1.15 (95% CI, 1.04 to 1.30); RD, 1.00 (95% CI, 0.31 to 2.00) |

**Abbreviations:** ART=antiretroviral therapy; cART=combination antiretroviral therapy; CD4=cluster of differentiation 4; CI=confidence interval; IQR=interquartile range; MSM=men who have sex with men; RD=risk difference; RNA=ribonucleic acid; RR=risk ratio; VA=U.S. Department of Veterans Affairs.
## Appendix B Table 6. Key Question 4: Quality Assessment of Cohort Studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Did the study attempt to enrol all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?</th>
<th>Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?</th>
<th>Did the study use accurate methods for ascertaining exposures and potential confounders?</th>
<th>Were outcome assessors and/or data analysts blinded to the exposure being studied?</th>
<th>Did the article report attrition?</th>
<th>Did the study perform appropriate statistical analyses on potential confounders?</th>
<th>Is there important differential loss to followup or overall high loss to followup?</th>
<th>Were outcomes prespecified and defined, and ascertained using accurate methods?</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lodi, 2015</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Lodi, 2017</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Lima, 2015</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Edwards, 2015</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Fair</td>
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</table>
### Appendix B Table 7. Key Question 5: Evidence Table of Systematic Reviews of Harms While Using Antiretroviral Therapy—Study Characteristics

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Databases and time period covered</th>
<th>Number of studies/Number of patients</th>
<th>Characteristics of identified articles: study designs</th>
<th>Characteristics of identified articles: populations</th>
<th>Characteristics of identified articles: interventions</th>
<th>Funding</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ding, 2012 U.S. Food and Drug Administration</td>
<td>International Pharmaceutical Abstracts, Intelesos, Embase, Scopus (searches conducted by U.S. Food and Drug Administration and GlaxoSmithKline) Inception to 2009</td>
<td>26 RCTs included in meta-analysis N=9,868 (5,028 ABC vs. 4,840 non-ABC) Trials, sample size &gt;50 (Observational studies excluded)</td>
<td>HIV+ individuals, adults, studies not conducted in Africa ABC vs. non-ABC: GlaxoSmithKline trials N: 2,341 vs. 2,367 % Male: 78% vs. 76% Age: 36 vs. 37 years CD4 count: 360 vs. 360 cells/mm³ Log viral load: 4.38 vs. 4.38 log₁₀ copies/mL AIDS Clinical Trials Group trials N: 1,985 vs. 1,610 % Male: 81% vs. 83% Age: 38 vs. 39 years CD4 count: 237 vs. 235 cells/mm³ Log viral load: 4.72 vs. 4.7 log₁₀ copies/mL Other trials N: 702 vs. 863 % Male: 82% vs. 66% Age: 42 vs. 42 years CD4 count: 255 vs. 250 cells/mm³ Log viral load: 5.03 vs. 4.94 log₁₀ copies/mL</td>
<td>ABC, randomized as part of a combined antiretroviral regimen, vs. non-ABC regimens Reports no funding or conflicts of interest</td>
<td>Fair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ford, 2015</td>
<td>MEDLINE, Embase, LILACS, Cochrane Central Register of Controlled Trials Inception to 2014</td>
<td>42 trials 37 included in meta-analysis N=18,097 (8,466 EFV vs. 9,631 other) Randomized trials and quasirandomized trials Mean study N: 303 (range, 47 to 1,771) Mean study duration: 78 weeks (range, 12 to 280 weeks)</td>
<td>HIV+ adults and children (although no pediatric trials met inclusion criteria) No geographical restrictions</td>
<td>EFV vs. other regimens as first-line therapy Two authors received funding from various pharmaceutical companies; the other authors report no funding or conflicts of interest</td>
<td>Fair</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ABC=abacavir; CD4=cluster of differentiation 4; EFV=efavirenz; RCT=randomized, controlled trial, U.S.=United States.
## Appendix B Table 8. Key Question 5: Evidence Table of Systematic Reviews of Harms While Using Antiretroviral Therapy—Results

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Harms</th>
</tr>
</thead>
</table>
| Ding, 2012<sup>101</sup> U.S. Food and Drug Administration | MI events  
ABC vs. non-ABC: 1.43 vs. 1.49 person-years of followup  
Overall: 0.48% (24/5,028) vs. 0.46% (22/4,840); RD: 0.008% (95% CI, -0.26% to 0.27%); OR: 1.02 (95% CI, 0.56 to 1.84)  
GlaxoSmithKline trials: 0.26% (6/2,341) vs. 0.38% (9/2,367); RD: -0.11% (95% CI, 0.43% vs. 0.21%); OR: 0.70 (95% CI, 0.25 to 2.00)  
AIDS Clinical Trials Group trials: 0.60% (12/1,985) vs. 0.89% (9/1,016); RD: 0.03% (95% CI, -0.45% to 0.51%); OR: 1.06 (95% CI, 0.43 to 2.61)  
Other trials: 0.85% (6/702) vs. 0.46% (4/863); RD: 0.31% (95% CI, -0.53% to 1.16%); OR: 1.60 (95% CI, 0.46 to 5.62) |
| Ford, 2015<sup>105</sup> | Central nervous system events in patients receiving EFV regimens  
Overall (13 studies, N=3,954): 29.6% (95% CI, 21.9 to 37.3)  
Severe (23 studies, N=5,246): 6.1% (95% CI, 4.3 to 7.9)  
Insomnia (10 studies, N=3,306): 6.0% (95% CI, 3.3 to 8.6)  
Abnormal dreams (10 studies, N=2,273): 8.4% (95% CI, 4.3 to 12.5)  
Dizziness (16 studies, N=4,399): 12.8% (95% CI, 9.1 to 16.5)  
Impaired concentration (5 studies, N=2,370): 2.9% (95% CI, 0.9 to 5.0)  
Depression (16 studies, N=5,149): 3.3% (95% CI, 2.2 to 4.3)  
Anxiety (16 studies, N=1,763): 3.4% (95% CI, 1.3 to 5.5)  
Headache (18 studies, N=6,037): 6.8% (95% CI, 4.5 to 9.10)  
Suicide ideation (6 studies, N=1,304): 0.6% (95% CI, 0.2 to 1.1) |
| | Severe central nervous system events, efavirenz vs. other regimen as specified  
Nevirapine: RR, 1.7 (95% CI, 0.9 to 3.0); RD, 1.1 (95% CI, -0.2 to 2.5)  
EFV, low-dose: RR, 5.2 (95% CI, 0.3 to 107.7); RD, 0.6 (95% CI, -0.4 to 1.7)  
RPV: RR, 2.9 (95% CI, 0.9 to 10.0); RD, 1.0 (95% CI, -0.3 to 2.4)  
ETR: RR, 5.1 (95% CI, 0.6 to 42.4); RD, 5.1 (95% CI, -0.8 to 11.1)  
ABC: RR, 12.9 (95% CI, 0.8 to 216.3); RD, 6.0 (95% CI, 2.4 to 9.6)  
ATV/r: RR, 2.4 (95% CI, 1.5 to 3.8); RD, 3.7 (95% CI, 1.8 to 5.5)  
LPV/r: RR, 1.2 (95% CI, 0.6 to 2.7); RD, 1.4 (95% CI, -2.5 to 5.2)  
DTG: RR, 16.7 (95% CI, 2.0 to 137.8); RD, 3.0 (95% CI, 1.4 to 4.6)  
MVC: RR, 5.3 (95% CI, 1.6 to 18.1); RD, 3.6 (95% CI, 1.3 to 5.9) |
| | Severe adverse events: No statistically significant difference in the risk of severe clinical adverse events for any drug comparison |

**Abbreviations:** ABC=abacavir; ATV/r=atazanavir/ritonavir; CI=confidence interval; DTG=dolutegravir; EFV=efavirenz; ETR=etravirine; LPV/r=lopinavir/ritonavir; MI=myocardial infarction; MVC=maraviroc; OR=odds ratio; RD=risk difference; RPV=rilpivirine; RR=risk ratio; U.S.=United States.
## Appendix B Table 9. Key Question 5: Quality Assessment of Systematic Reviews

<table>
<thead>
<tr>
<th>Author Year</th>
<th>A priori design provided?</th>
<th>Duplicate study selection and data extraction? a. Study selection b. Data extraction</th>
<th>Comprehensive literature search performed?</th>
<th>Searched for more than published studies?</th>
<th>List of studies (included and excluded) provided?</th>
<th>Characteristics of the included studies provided?</th>
<th>Scientific quality of included studies assessed and documented?</th>
<th>Scientific quality of the included studies used appropriately in formulating conclusions?</th>
<th>Methods used to combine the findings of studies appropriate?</th>
<th>Likelihood of publication bias assessed?</th>
<th>Conflict of interest stated? a) Systematic Review b) Individual Studies</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ding, 2012&lt;sup&gt;101&lt;/sup&gt;</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes/No</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Yes/No</td>
<td>Yes/No</td>
<td>Fair</td>
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<tr>
<td>Ford, 2015&lt;sup&gt;105&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes/Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes/No</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes/No</td>
<td>Yes/No</td>
<td>Yes/No</td>
<td>Fair</td>
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</tbody>
</table>
# Appendix B Table 10: Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

<table>
<thead>
<tr>
<th>Harm category</th>
<th>Study Author, year</th>
<th>Study design</th>
<th>Number of centers, Country</th>
<th>Study duration Mean followup</th>
<th>Intervention</th>
<th>Inclusion criteria</th>
<th>Patient characteristics</th>
<th>N</th>
<th>Funding source</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple</td>
<td>Arribas 2017</td>
<td>RCT</td>
<td>GS-US-292-0104: 134 sites North America, Europe, Australia, Japan, and Thailand GS-US-292-0111: 128 sites North America, Europe, and Latin America</td>
<td>2 years</td>
<td>A. TAF + EVG/COBI/FTC (n=866) B. TDF + EVG/COBI/FTC (n=867)</td>
<td>Age ≥18 years, HIV-1 and no previous antiretroviral treatment, had HIV-1 RNA concentration ≥1,000 copies/mL, and eGFR ≥50 mL/min. Eligible patients had a screening HIV-1 genotype showing sensitivity to EVG, FTC, and tenofovir.</td>
<td>A vs. B Median age: 33 vs. 35 years % Male: 85% vs. 85% Black/African heritage: 26% vs. 25%; Asian: 11% vs. 10%; Hispanic/Latino: 19% vs. 19%; Median CD4 count: 404 vs. 406 cells/mm³ HIV-1 RNA &gt;100,000 copies/mL: 23% vs. 22% Median eGFR (Cockcroft-Gault): 117 vs. 114 mL/min</td>
<td>1,733</td>
<td>Gilead Sciences, Inc.</td>
<td>Good</td>
</tr>
<tr>
<td>Multiple</td>
<td>Rockstroh 2013</td>
<td>RCT</td>
<td>67 centers Australia, Brazil, Canada, Columbia, Germany, India, Italy, Mexico, Peru, Spain, Thailand, U.S.</td>
<td>4.6 years</td>
<td>A. RAL + TDF-FTC (n=281) B. EFV + TDF-FTC (n=282)</td>
<td>Treatment-naive HIV-infected patients age ≥18 years were eligible if their viral load was &gt;5,000 RNA copies/mL without genotypic resistance to tenofovir, FTC, or EFV. Patients with stable chronic hepatitis could be enrolled if their serum aminotransferase levels were &gt;5 xULN, patients with acute or decompensated chronic hepatitis excluded.</td>
<td>A vs. B Mean age: 38 vs. 37 years % Male: 81% vs. 82% 41% vs. 44% white; 12% vs. 8% black; 13% vs. 11% Asian; 21% vs. 24% Hispanic; 0.4% vs. 0.4% Native American; 13% vs. 13% multiracial</td>
<td>563</td>
<td>Merck</td>
<td>Good</td>
</tr>
</tbody>
</table>
### Appendix B Table 10. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

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<th>Quality rating</th>
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</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Kowalska, 2012</td>
<td>EuroSIDA Study Prospective cohort, single arm</td>
<td>103 centers Europe, Israel, Argentina</td>
<td>Followed from time of starting ART or study entry until death or 6 months after last followup visit</td>
<td>cART</td>
<td>All patients recruited to EuroSIDA cohort after January 1996 who were on ART at some point while under followup, and had at least 1 CD4 count measurement available at or prior to baseline</td>
<td>Age: 38.2 years % Male: 74.6% Ethnicity: 88% white Mode of HIV acquisition: MSM 40.6%, PWID 22.2%, heterosexual 29.3% HBV status: positive 5.5%, negative 73.1%, unknown 21.4% HCV status: positive 21.6%, negative 53.0%, unknown 25.4% Smoking: current 41.0%, previous 17.0%, never 20.3%, unknown 21.7% Hypertension: yes 10.2%, no 31.8%, unknown 58.0% Diabetes: yes 2.3%, no 84.0%, unknown 13.7% CD4 count: 288 cells/mm³ HIV RNA viral load: 2.84 log₁₀ copies/mL Median time of exposure to cART: 4.4 years</td>
<td>12,069</td>
<td>European Commission BIOMED 1, BIOMED 2, the 5th Framework, 6th Framework, and 7th Framework programs; grants by Gilead, Pfizer, Bristol-Myers Squibb, and Merck; the Swiss National Science Foundation</td>
<td>Fair</td>
</tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction</td>
<td>Sabin 2016 D:A:D Study</td>
<td>Prospective cohort</td>
<td>11 cohorts Europe, Australia, U.S.</td>
<td>Followed from study entry until MI, death, February 2013, or 6 months after last visit</td>
<td>ABC vs. not on ABC</td>
<td>HIV-1 positive patients followed prospectively during visits to outpatient clinics as part of regular medical care. Patients were enrolled into D:A:D consecutively as they were seen in the clinic from the time the D:A:D study was implemented in each of the participating cohorts. At enrollment and at least every 8 months thereafter standardized data collection forms are completed. Enrollment took place in 3 phases: cohort I (1999–2000), cohort II (added in 2004), cohort III (added in 2009)</td>
<td>Those under followup in 2012 (N=31,112): Male: 73.6% Median age: 50 years Previous AIDS: 27.8% 10-year CVD risk: low 71.7%, moderate 71.7%, high 6.0%, unknown 11.1% Known smoking status: current smoker 39.8%, ex-smoker 30.6%, never smoked 29.6% Family history of CVD: 7.8% Diabetes: 6.3% Median TC: 5.0 mmol/L Median high-density lipoprotein cholesterol: 1.2 mmol/L Median triglycerides: 1.5 mmol/L Median CD4: 566 cells/mm³ Median viral load: 1.7 log₁₀ copies/mL</td>
<td>49,717</td>
<td>See table note</td>
<td>Good</td>
</tr>
</tbody>
</table>
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<th>Funding source</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction</td>
<td>Monforte, 2013</td>
<td>D:A:D Study Prospective cohort</td>
<td>Same as Sabin 2016</td>
<td>Followed from study entry until MI, stroke, death, February 2011, or 6 months after last visit</td>
<td>ATV, boosted or unboosted by RTV</td>
<td>Same as Sabin 2016</td>
<td>ATV vs. other regimen vs. no ART Total person-years: 27,115 vs. 187,027 vs. 87,765 Male: 73.5% vs. 75.7% vs. 69.4% Mode of HIV acquisition: MSM 45.3% vs. 46.0% vs. 41.9% PWID 16.1% vs. 14.5% vs. 17.6% Heterosexual 31.6% vs. 31.8% vs. 34.1% Other/unknown 6.9% vs. 7.8% vs. 8.5% Ethnicity: White 52.0% vs. 50.9% vs. 51.0% Black 7.2% vs. 8.1% vs. 9.0% Other 2.4% vs. 2.7% vs. 2.3% Unknown 38.4% vs. 38.2% vs. 37.7% Age: 30–39 years: 21.0% vs. 29.8% vs. 16.4% 40–49 years 44.2% vs. 39.3% vs. 11.8% 50–59 years 21.2% vs. 17.6% vs. 3.8% Family history of MI: 9.3% vs. 8.1% vs. 7.0% Smoking history: Current smoker 41.3% vs. 37.8% vs. 41.4% Ex-smoker 24.3% vs. 22.1% vs. 17.5% Previous CVD event: 3.0% vs. 2.3% vs. 1.4% Diabetes: 6.8% vs. 4.9% vs. 3.5%</td>
<td>49,734</td>
<td>See table note</td>
<td>Same as Sabin 2016</td>
</tr>
</tbody>
</table>
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<th>Funding source</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction</td>
<td>Monforte, 2013104</td>
<td>D:A:D Study</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>Framingham score: Low (&lt;10%) 60.3% vs. 50.3% vs. 49.1% Moderate (10%–20%) 19.8% vs. 14.0% vs. 8.9% High (&gt;20%) 8.6% vs. 6.7% vs. 3.7% Unknown 11.3% vs. 29.0% vs. 38.3%</td>
<td>Mean age: 46.5 years (SD, 10.1) % Male: 97.6% 83.8% white; 42.4% black; 1.2% other; 22.6% missing race data; 5.5% Hispanic; 22.5% missing ethnicity data 47.1% ever smokers 11.6% diabetes 8.7% chronic kidney disease 0.36% history of stroke 0.42% history of MI 0.13% history of percutaneous coronary intervention 0.09% history of coronary artery bypass surgery 0.87% history of any cardiovascular event</td>
<td>104</td>
<td>See above</td>
<td>See above</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>Desai 2015103</td>
<td>Retrospective cohort</td>
<td>Database analysis U.S.</td>
<td>Enrolled from 1996–2009 Mean followup varied according to study drug</td>
<td>Current ART exposure vs. no exposure</td>
<td>Patients with evidence of a positive HIV lab test on or after January 1, 1996, who also received subsequent medical care in the VA</td>
<td>See above</td>
<td>103</td>
<td>National Institutes of Health; Patient-Centered Outcomes Research Institute</td>
<td>Fair</td>
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</table>
Appendix B Table 10. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

<table>
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<tr>
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<th>N</th>
<th>Funding source</th>
<th>Quality rating</th>
</tr>
</thead>
</table>
| Cancer/Liver Disease | Bruyand, 2015 | Same as Sabin 2016 | Followed from study entry or January 2004 until cancer diagnosis, February 2012, or 6 months after last visit | Any cART vs. PIs vs. NNRTIs | Same as Sabin 2016 | Male: 73.6%  
Median age: 39 years  
Mode of HIV acquisition: MSM 43.8%, PWID 14.5%, heterosexual 35.2%, other/unknown 6.5%  
Ethnicity: white 49.9%, black African 7.0%, other 2.0%, unknown 41.1%  
Smoking status: current smoker 39.8%, ex-smoker 17.7%, never smoker 24.8%, unknown 17.7%  
Median CD4 count: 433 cells/mm³  
Median plasma HIV RNA: 2.3 log₁₀ copies/mL  
HCV: positive 10.5%, negative 63.0%, unknown 26.5%  
HBV: positive 4.2%, negative 96.0%, unknown 29.8%  
Previous cancer: 5.6%  
Any exposure to cART: 89.7%  
Median years of exposure: 7.1 years  
Any exposure to PIs: 68.7%  
Median years of exposure: 4.9 years  
Any exposure to NNRTIs: 68.7%  
Median years of exposure: 3.8 years | 41,762 | See table note | Same as Sabin 2016 |
| Harm category       | Study Author, year | Study design | Number of centers, Country | Study duration Mean followup | Intervention | Inclusion criteria | Patient characteristics | N        | Funding source | Quality rating |
|--------------------|--------------------|--------------|-----------------------------|----------------------------|--------------|--------------------|--------------------------|----------|----------------|----------------|}
| Cancer/Liver Disease | Ryom, 2016113      | D:A:D Study  | Same as Sabin 2016          | Followed from study entry or February 2004 until the first of end-stage liver disease, or Hepato-cellular carcinoma, death, February 2014, or 6 months after last visit | cART         | Same as Sabin 2016 | White ethnicity: 49.6%, Male: 73.5% | 45,544   | See table note | Same as Sabin 2016 |
| Cancer/Liver Disease | Kovari, 2013117    | D:A:D Study  | Same as Sabin 2016          | Followed from date of study entry until death or February 2010, or 6 months after last visit Followup: 114,478 person-years; median 4.9 years | cART         | Same as Sabin 2016 | All participants with negative HCV and HBV status | 22,910   | See table note | Same as Sabin 2016 |
### Appendix B Table 10. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

<table>
<thead>
<tr>
<th>Harm category</th>
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<th>Patient characteristics</th>
<th>N</th>
<th>Funding source</th>
<th>Quality rating</th>
</tr>
</thead>
</table>
| Kidney Disease | Ryom, 2013[1-3]    | D:A:D Study  | Same as Sabin 2016          | Followed from January 2004 until they had a confirmed eGFR of ≤70 mL/min or ≤60 mL/min or until last eGFR during followup Median followup of 4.5 years | cART         | Same as Sabin 2016 All participants with normal baseline renal function eGFR of ≥90 mL/min | % Male: 73%  
Ethnicity: white 47%, African ancestry 8%, unknown 43%  
Mean age: 39 years  
Mode of HIV acquisition: MSM 44%, PWID 14%, heterosexual 36%  
Prior AIDS-defining illness: 20%  
Mean CD4 count: 440 cells/mm³  
Mean HIV RNA load: 2.1 log₁₀ copies/mL  
Mean duration of HIV positivity: 5.2 years  
HBV positive: 12%  
HCV positive: 12%  
Hypertension: 8%  
Diabetes: 3%  
Prior cardiovascular event: 2%  
Smoking: 42%  
cART exposure: 63%  
ART use:  
Tenofovir: 5,366 patients, 2,015 person-years followup, median 0 years  
LPV/r: 4,963 patients, 3,358 person years followup, median 0.1 years  
ABC: 4,937 patients, 5,613 person-years followup, median 0.3 years  
ATV/r: 1,055 patients, 296 person-years followup, median 0 years  
ATV: 352 patients, 192 person-years followup, median 0.1 years  
Other RTV-boosted PI: 2,216 patients, 3,669 person-years followup, median 1.1 years  
IDV: 4,567 patients, 9,135 patient-years followup, median 1.5 years | 22,603 | See table note | Same as Sabin 2016 |
### Appendix B Table 10. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

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<tr>
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<th>N</th>
<th>Funding source</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney Disease</td>
<td>Mocroft, 2016 D:A:D Study Prospective cohort</td>
<td>Same as Sabin 2016</td>
<td>Followed from January 2004 until they had a confirmed eGFR of &lt;60 mL/min per 1.73 m² or until last eGFR during followup or February 2014</td>
<td>cART (TDF, ATV/r, LPV/r, other RTV-boosted PIs, ABC)</td>
<td>Same as Sabin 2016 All participants with normal baseline renal function eGFR of ≥90 mL/min per 1.73 m²</td>
<td>Median age: 39 years % Male: 73% Ethnicity: white 46%, black 8%, other 2%, unknown 44% Risk factor: MSM 45%, PWID 13%, heterosexual 36%, other 8% HBV status: negative 88%, positive 5%, unknown 7% HCV status: negative 72%, positive 18%, unknown 10% Mean baseline eGFR: 110 mL/min (IQR, 100–125)</td>
<td>23,905</td>
<td>See table note</td>
<td>Same as Sabin 2016</td>
</tr>
<tr>
<td>Kidney Disease</td>
<td>Laprise 2013 Retrospective cohort</td>
<td>Single center Canada Enrollment 2002–2012 Median followup 7.9 years</td>
<td>A. TDF exposure B. Nonexposure Other ART comparisons: NRTI, NNRTI, PI exposure vs. nonexposure</td>
<td>Enrolled after January 2002 with eGFR measures</td>
<td>A vs. B Median age: 39.3 years (total cohort) % Male: 95.9% vs. 96.7% 95.9% vs. 96.7% white; 2.3% vs. 3.9% black; 5.4% vs. 5.2% other Duration of HIV infection: 6.54 vs. 6.47 years Median eGFR: 104.9 vs. 103.5 mL/min/1.73 m²</td>
<td>1,043</td>
<td>None reported</td>
<td>Fair</td>
<td></td>
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</tbody>
</table>
### Appendix B Table 10. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

<table>
<thead>
<tr>
<th>Harm category</th>
<th>Study Author, year</th>
<th>Study design</th>
<th>Number of centers, Country</th>
<th>Study duration Mean followup</th>
<th>Intervention</th>
<th>Inclusion criteria</th>
<th>Patient characteristics</th>
<th>N</th>
<th>Funding source</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney Disease</td>
<td>Nkhoma 2016b</td>
<td>Database analysis U.S.</td>
<td>Enrollment 2008–2014 Mean followup 2.5 years</td>
<td>A. EVF + TDF-FTC B. RPV + TDF-FTC C. EVG + COBI + TDF-FTC</td>
<td>Age ≥18 years with at least 1 medical record with a diagnosis of HIV-1 and treatment with EFV/TDF-FTC, RPV/TDF-FTC, or EVG/COBI/TDF-FTC; ≥6 months continuous enrollment prior to initiation of the index regimen</td>
<td>A vs. B vs. C Renal outcomes (defined as ≥2 medical insurance claims that were associated with ICD-9-CM diagnosis codes for renal disease with the exclusion of codes associated with calculus of the kidney and ureter) Mean age 43.5 (10.5) vs. 42.3 (10.9) vs. 43.5 years (10.8) % Male: 87% vs. 84% vs. 89% Race/ethnicity NR</td>
<td>120</td>
<td>Bristol-Myers Squibb, authors are employees of and own stock in Bristol-Myers Squibb</td>
<td>Fair</td>
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<tr>
<td>Kidney Disease</td>
<td>Scherzer 2012</td>
<td>National database U.S.</td>
<td>Enrollment from 1997–2007 Median followup 3.9–5.5 years (varied according to outcome)</td>
<td>A. Tenofovir exposure (n=4,303) B. Nonexposure (n=6,538)</td>
<td>Treatment-naive HIV-infected veterans at the time they entered clinical care in the VA system, who subsequently received monotherapy or cART with regular care and laboratory monitoring</td>
<td>A vs. B Mean age 45 vs. 47 years % Male: 97% vs. 98% 46% vs. 39% white; 47% vs. 51% black; 7% vs. 11% other race/ethnicity Median eGFR: 97 (IQR, 82–113) vs. 96 (IQR, 82–114) mL/min per 1.73 m² Proportion with eGFR &lt;60 mL/min per 1.73 m²: 4.7% vs. 7.3% Proteinuria: 19% vs. 21%</td>
<td>108</td>
<td>National Institutes of Health, the National Center for Research Resources, the American Heart Association Established Investigator Award, and the Veterans Affairs Public Health Strategic Healthcare Group</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Suicidality</td>
<td>Chang 2018</td>
<td>Single center Uganda</td>
<td>Enrollment 2005–2015 Mean followup 2 years</td>
<td>A. EFV, any use (n=305) B. NVP only (n=389)</td>
<td>Age ≥18 years, ART-naive, and living within 60 km (about 37.3 miles) of the clinic</td>
<td>A vs. B Median age: 32 vs. 34 years 66% vs. 73% female Race NR 7% vs. 7% suicidal ideation at enrollment 33% vs. 33% probably depression at enrollment</td>
<td>59</td>
<td>National Institutes of Health, Harvard and San Francisco Centers for AIDS Research, and Doris Duke Charitable Foundation</td>
<td>Fair</td>
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</tbody>
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### Appendix B Table 10. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

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<tbody>
<tr>
<td>Suicidality</td>
<td>Smith, 2014&lt;sup&gt;107&lt;/sup&gt;</td>
<td>D:A:D Study (abstract only) Prospective cohort</td>
<td>Same as Sabin 2016</td>
<td>Followed from study entry until death, February 2013, or last study visit</td>
<td>cART, including efavirenz-containing regimens vs. other</td>
<td>Same as Sabin 2016</td>
<td>NR, but see above for patient characteristics from other D:A:D publications</td>
<td>49,717</td>
<td>See table note</td>
<td>Same as Sabin 2016</td>
</tr>
<tr>
<td>Suicidality</td>
<td>Nkhoma, 2016&lt;sup&gt;108&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Unclear U.S.</td>
<td>Followed from study entry until death, end of exposure to anchor agent, disenrollment of insurance, or 2013 (end of study period)</td>
<td>cART, including: A. EFV-containing regimens (n=11,187 commercial database) B. EFV-containing regimens (n=2,224 Medicaid database) C. EFV-free regimens (n=8,796 commercial database) D. EFV-free regimens (n=2,930 Medicaid database)</td>
<td>U.S. administrative claims data for commercially-insured (Truven Health MarketScan Commercial Claims and Encounters database) and Medicaid-insured (Multi State Medicaid database of 15 states) individuals; ART-naive patients age ≥12 years initiating an EFV-containing or EFV-free antiretroviral regimen with 6 months of continuous insurance enrollment prior to ART initiation period, 2007 to 2013</td>
<td>A vs. B vs. C vs. D Mean age: 40.1 vs. 41.7 vs. 40.8 vs. 39.7 years % Male: 86.0% vs. 56.7% vs. 79.1% vs. 50.2% Ethnicity (Medicaid data only available): 16 to 17% white, 69 to 70% black, 1.2 to 1.3% Hispanic, 12 to 13% unknown, 06% other Depression: 16.7% vs. 29.0% vs. 20.0% vs. 34.8% Drug dependence: 0.6% vs. 5.3% vs. 0.9% vs. 8.1% Anxiety: 2.3% vs. 3.8% vs. 3.1% vs. 5.5% Attention deficit hyperactivity disorder: 0.4% vs. 0.4% vs. 0.6% vs. 0.5% Bipolar disorder: 0.6% vs. 3.5% vs. 1.3% vs. 5.8% Personality disorder: 0.1% vs. 0.7% vs. 0.2% vs. 1.2% Schizophrenia: 0.04% vs. 3.7% vs. 0.1% vs. 7.0% Suicidality: 0.2% vs. 1.3% vs. 0.4% vs. 2.9% Suicide attempt: 0.01% vs. 0.1% vs. 0.03% vs. 0.3% Suicide attempt (expanded): 0.1% vs. 0.3% vs. 0.1% vs. 0.8%</td>
<td>25,137</td>
<td>Bristol-Myers Squibb Authors are employees of Bristol-Myers Squibb and Truven Health Analytics</td>
<td>Fair</td>
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<tbody>
<tr>
<td>Fracture</td>
<td>Borges 2017</td>
<td>Prospective cohort</td>
<td>11 cohorts (Europe, Australia, U.S.)</td>
<td>Enrollment from 2004; mean followup unclear (total 86,118 person-years)</td>
<td>TDF exposure vs. no TDF exposure</td>
<td>Age ≥16 years with baseline data on CD4 counts and viral loads with prospective followup</td>
<td>Total population</td>
<td>Mean age: 49 years; % Male: 75%; 86% white; 6% black; 2% Asian; 8% other</td>
<td>11,820</td>
<td>Bristol-Myers Squibb, European Union 7th Framework Programme; Gilead; GlaxoSmithKline; Janssen Research and Development; Merck; Pfizer; Swiss National Science Foundation; Danish National Research Foundation</td>
<td>Fair</td>
</tr>
<tr>
<td>Fracture</td>
<td>Nkhoma 2016b</td>
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<td>A. EVF + TDF-FTC B. RPV + TDF-FTC C. EVG + COBI + TDF-FTC</td>
<td>Age ≥18 years with at least 1 medical record with a diagnosis of HIV-1 and treatment with EFV/TDF-FTC, RPV/TDF-FTC, or EVG/COBI/TDF-FTC; 66 months continuous enrollment prior to initiation of the index regimens</td>
<td>A vs. B vs. C Fracture (defined as ICD-9-CM diagnosis codes for bone fracture)</td>
<td>Mean age: 43 (10.6) vs. 42 (11.0) vs. 43 years (11.1); % Male: 87% vs. 84% vs. 89%; Race/ethnicity NR</td>
<td>10,383</td>
<td>Bristol-Myers Squibb, authors are employees of and own stock in Bristol-Myers Squibb</td>
<td>Fair</td>
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**Abbreviations:** 3TC=lamivudine; ABC=abacavir; ART=antiretroviral therapy; ATV=atazanavir; ATV/r=ritonavir-boosted atazanavir; cART=combination antiretroviral therapy; CD4=cluster of differentiation 4; COBI=cobicistat; CVD=cardiovascular disease; D4L=stavudine; D:A:D Study=Data Collection on Adverse Events of Anti-HIV Drugs Study; ddl=didanosine; eGFR=estimated glomerular filtration rate; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; HBV=hepatitis B virus; HCV=hepatitis C virus; ICD-9-CM=International Classification of Diseases, 9th Revision, Clinical Modification; IDV=indinavir; IQR=interquartile range; LPV=lopinavir; LPV/r=ritonavir-boosted lopinavir; MI=myocardial infarction; MSM=men who have sex with men; NFV=nelfinavir; NNRTI=nonnucleoside reverse transcriptase inhibitors; NR=not reported; NRTI=nucleoside reverse transcriptase inhibitors; NVP=nevirapine; PI=protease inhibitor; PWID=persons who inject drugs; RAL=raltegravir; RCT=randomized, controlled trial; RNA=ribonucleic acid; RPV=rilpivirine; RTV=ritonavir; SD=standard deviation; SQV=saquinavir; STARTMRK=Phase III Noninferiority Trial of Raltegravir-Based Versus Efavirenz-Based Therapy in Treatment-Naïve Patients; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; ULN=upper limit of normal; U.S.=United States; VA=U.S. Department of Veterans Affairs; ZDV=zidovudine.

**Note:** The D:A:D study was supported by the Highly Active Antiretroviral Therapy Oversight Committee (HAARTOC), a collaborative committee with representation from academic institutions, the European Agency for the Evaluation of Medicinal Products, the U.S. Food and Drug Administration, the patient community, and pharmaceutical companies with licensed anti-HIV drugs in the European Union (AbbVie, Bristol-Myers Squibb, Gilead Sciences Inc., ViV Healthcare, Merck & Co Inc., and Janssen...
Appendix B Table 10: Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

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Appendix B Table 11. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Results

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<th>Adverse events</th>
</tr>
</thead>
</table>
| Multiple      | Arribas 2017\textsuperscript{115} | RCT          | A. TAF + EVG/COBI/FTC (n=866) B. TDF-FTC + EVG/COBI (n=867) | A vs. B
Withdrawal due to adverse events: 1.3% (11/866) vs. 3.3% (29/867); RR, 0.38 (95% CI, 0.19 to 0.76)
Withdrawal due to renal adverse event: 0% (0/866) vs. 1.4% (12/867); RR, 0.04 (95% CI, 0.00 to 0.68)
Serious adverse events: 14.0% (121/866) vs. 14.3% (124/867); RR, 0.98 (95% CI, 0.77 to 1.23)
Grade 3 or 4 laboratory abnormalities: 32.9% (285/866) vs. 30.8% (267/867); RR, 1.07 (95% CI, 0.93 to 1.23)
Serious cardiovascular or cerebrovascular event: 0.6% (5/866) vs. 0.7% (6/867); RR, 0.83 (95% CI, 0.26 to 2.72)
Fracture: 0.7% (6/866) vs. 1.8% (16/867); RR, 0.38 (95% CI, 0.15 to 0.95)
Elevated creatine kinase: 11.5% (100/866) vs. 10.1% (88/867); RR, 1.14 (95% CI, 0.87 to 1.49)
Decrease of ≥25% from baseline in creatinine clearance: 17.6% (152/866) vs. 33.4% (290/867); RR, 0.52 (95% CI, 0.44 to 0.62)
Clinically significant proteinuria (urine protein to creatinine ratio >200 mg/g): 2.5% (22/866) vs. 4.6% (40/867); RR, 0.55 (95% CI, 0.33 to 0.92)
Proximal renal tubulopathy: 0% (0/866) vs. 0.8% (7/867); RR, 0.07 (95% CI, 0.00 to 1.17) |
| Multiple      | Rockstroh 2013\textsuperscript{116} | RCT          | A. RAL+ TDF-FTC (n=281) B. EFV + TDF-FTC (n=282) | A vs. B
Mortality: 1.8% (5/281) vs. 1.8% (5/282); RR, 1.00 (95% CI, 0.29 to 3.43)
Withdrawal due to adverse events: 5% (14/281) vs. 9.9% (28/282); RR, 0.50 (95% CI, 0.27 to 0.93)
Serious adverse events: 20.3% (57/281) vs. 20.2% (57/282); RR, 1.00 (95% CI, 0.72 to 1.39)
Myocardial infarction: 0% (0/281) vs. 0.4% (1/282); RR, 0.33 (95% CI, 0.01 to 8.18)
Suicidal ideation or attempt: 1.8% (5/281) vs 0.4% (1/282); RR, 5.02 (95% CI, 0.59 to 43) |
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Kowalska, 2012</td>
<td>EuroSIDA Study</td>
<td>cART</td>
<td>Mortality overall</td>
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<tr>
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<td>Prospective cohort, single arm</td>
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<td>1,297 patients died during 70,613 person-years of followup; crude incidence rate, 18.3/1,000 person-years followup (95% CI, 17.4 to 19.4)</td>
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<td>Specific causes of death</td>
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<td>AIDS-related: 32% (413/1,297); crude incidence rate, 5.85/1,000 person-years followup (95% CI, 5.28 to 6.14)</td>
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<td>Non–AIDS-related: 68% (884/1,297); crude incidence rate, 12.5/1,000 person-years followup (95% CI, 11.7 to 13.3)</td>
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<td>Non–AIDS-related infection: 9% (121/1,297)</td>
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<td>Liver-related: 14% (182/1,297)</td>
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<td>Non–AIDS-defining malignancies: 10% (125/1,297)</td>
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<td>Cardiovascular disease: 9% (122/1,297)</td>
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<td>Violent: 7% (90/1,297)</td>
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<td>Other: 7% (90/1,297)</td>
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<td>Unknown: 12% (153/1,297)</td>
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<td>After adjustment for confounding variables, there was a significant decrease in the rate of all cause and AIDS-related death between 2 and 3.99 years and longer exposure time, but no significant difference in the rate of non–AIDS-related deaths.</td>
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<td>When time on cART was fitted as a continuous variable from 2 years of exposure onwards: 5% decrease in the risk of all cause death (IRR, 0.95 [95% CI, 0.92 to 0.97]); 14% decrease in the risk of AIDS-related death (IRR, 0.86 [95% CI, 0.81 to 0.91])</td>
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<td>Non–AIDS-related: IRR, 0.97 (95% CI, 0.95 to 1.00)</td>
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<td>Non–AIDS-related infection: IRR, 0.97 (95% CI, 0.90 to 1.05)</td>
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<td>Liver-related: IRR, 0.94 (95% CI, 0.89 to 1.00)</td>
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<td>Non–AIDS-defining malignancies: IRR, 1.07 (95% CI, 1.00 to 1.04)</td>
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<td>Cardiovascular disease: IRR, 0.99 (95% CI, 0.93 to 1.06)</td>
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<td>Violent: IRR, 0.90 (95% CI, 0.81 to 0.99)</td>
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<td>Other: IRR, 1.01 (95% CI, 0.94 to 1.09)</td>
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<td></td>
<td>Unknown: IRR, 0.94 (95% CI, 0.86 to 1.01)</td>
</tr>
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<tr>
<td>Myocardial Infarction</td>
<td>Sabin, 2016(^{102})</td>
<td>ABC vs. not on ABC</td>
<td>After adjustment for potential confounders, current ABC use was associated with a 98% increase in MI rate (aRR, 1.98 [95% CI, 1.72 to 2.29]), with no difference in the pre-2008 (aRR, 1.97 [95% CI, 1.68 to 2.33]) and post-2008 (aRR, 1.97 [95% CI, 1.43 to 2.72]) periods; p=0.74 for interaction MI events: Overall: 941/367,559 person-years (rate, 0.26/100 person-years [95% CI, 0.24 to 0.27]) Currently on ABC: 341/71,971 person-years (rate, 0.47/100 person-years [95% CI, 0.42 to 0.52]) Currently not on ABC: 600/295,642 person-years (rate 0.20/100 person-years [95% CI, 0.19 to 0.22]) Stratified by calendar period (D:A:D publication from 2008 showed 90% increase in risk of MI for those on ABC): Pre-March 2008: Currently on ABC: 247/40,833 person-years (rate, 0.61/100 person-years [95% CI, 0.53 to 0.68]) Currently not on ABC: 425/169,417 person-years (rate, 0.25/100 person-years [95% CI, 0.23 to 0.28]) Post-March 2008 Currently on ABC: 94/31,084 person-years (rate, 0.30/100 person-years [95% CI, 0.24 to 0.36]) Currently not on ABC: 175/126,225 person-years (rate, 0.14/100 person-years [95% CI, 0.12 to 0.16]) Results unchanged after stratifying by Framingham risk group or after further adjusting for factors potentially on the causal pathway, including renal function, dyslipidemia, and hypertension</td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>Monforte, 2013(^{104})</td>
<td>ATV, boosted or unboosted by RTV</td>
<td>MI Overall events: 844/49,734 (incidence, 0.28/100 person-years followup [95% CI, 0.26 to 0.30]) &gt;3 years exposure to ATV: 0.20/100 person-years followup (95% CI, 0.12 to 0.32) No exposure to ATV: 0.28/100 person-years followup (95% CI, 0.26 to 0.30) No association between cumulative exposure to ATV and MI risk: univariate relative rate/year, 0.96 (95% CI, 0.88 to 1.04); multivariable relative rate/year, 0.95 (95% CI, 0.87 to 1.05) Stroke Overall events: 523/49,734 (incidence, 0.18/100 person-years followup [95% CI, 0.16 to 0.19]) &gt;3 years exposure to ATV: 0.17/100 person-years followup (95% CI, 0.10 to 0.27) No exposure to ATV: 0.17/100 person-years followup (95% CI, 0.16 to 0.19) No association between cumulative exposure to ATV and stroke risk: univariate relative rate/year, 1.02 (95% CI, 0.98 to 1.05); multivariable relative rate/year, 0.95 (95% CI, 0.87 to 1.05)</td>
<td></td>
</tr>
</tbody>
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<td>Myocardial Infarction</td>
<td>Desai 2015</td>
<td>Retrospective cohort</td>
<td>Current ART exposure vs. no exposure</td>
<td>Cardiovascular event (MI, stroke, or cardiovascular procedure)</td>
</tr>
<tr>
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<td>ABC: OR, 1.50 (95% CI, 1.26 to 1.79)</td>
</tr>
<tr>
<td></td>
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<td>EFV: OR, 1.40 (95% CI, 1.19 to 1.66)</td>
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<td>3TC: OR, 1.53 (95% CI, 1.34 to 1.75)</td>
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<td>NVP: OR, 0.91 (95% CI, 0.70 to 1.18)</td>
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<td>D4L: OR, 1.14 (95% CI, 0.95 to 1.37)</td>
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<td>Tenofovir: OR, 1.10 (95% CI, 0.93 to 1.30)</td>
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<td>ZDV: OR, 1.41 (95% CI, 1.22 to 1.63)</td>
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<td>Other drugs and ART combinations had &lt;2 years mean followup</td>
</tr>
</tbody>
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</thead>
</table>
| Cancer/ Liver Disease | Bruyand, 2015<sup>109</sup> D:A:D Study Prospective cohort | cART vs. PIs vs. NNRTIs | Cancer, overall events: 1,832/41,762 (incidence rate, 0.76/100 person-years [95% CI, 0.72 to 0.79])<br>Association between cART use (per year longer exposure) and cancer<br>AIDS-defining cancer (n=718):<br>Any cART: aRR, 0.88 (95% CI, 0.85 to 0.92)<br>PI-based ART: aRR, 0.96 (95% CI, 0.92 to 1.00)<br>NNRTI-based ART: aRR, 0.86 (95% CI, 0.81 to 0.91)<br>Kaposi Sarcoma (n=341):<br>Any cART: aRR, 0.84 (95% CI, 0.78 to 0.89)<br>PI-based ART: aRR, 0.93 (95% CI, 0.87 to 1.00)<br>NNRTI-based ART: aRR, 0.81 (95% CI, 0.74 to 0.90)<br>Non–AIDS-defining cancer (n=1,114):<br>Any cART: aRR, 0.84 (95% CI, 0.51 to 1.37)<br>PI-based ART: aRR, 0.93 (95% CI, 0.59 to 1.44)<br>NNRTI-based ART: aRR, 0.91 (95% CI, 0.58 to 1.45)<br>Lung cancer (n=195):<br>Any cART: aRR, 0.99 (95% CI, 0.95 to 1.03)<br>PI-based ART: aRR, 1.01 (95% CI, 0.97 to 1.05)<br>NNRTI-based ART: aRR, 0.97 (95% CI, 0.93 to 1.02)<br>Anal cancer (n=131):<br>Any cART: aRR, 1.06 (95% CI, 1.01 to 1.11)<br>PI-based ART: aRR, 1.08 (95% CI, 1.04 to 1.13)<br>NNRTI-based ART: aRR, 0.97 (95% CI, 0.97 to 1.09)<br>Hodgkin Lymphoma (n=107):<br>Any cART: aRR, 0.91 (95% CI, 0.85 to 0.97)<br>PI-based ART: aRR, 0.99 (95% CI, 0.92 to 1.06)<br>NNRTI-based ART: aRR, 0.90 (95% CI, 0.82 to 0.99)<br>Head and neck cancer (n=97):<br>Any cART: aRR, 1.01 (95% CI, 0.96 to 1.07)<br>PI-based ART: aRR, 1.01 (95% CI, 0.96 to 1.07)<br>NNRTI-based ART: aRR, 1.03 (95% CI, 0.97 to 1.10)
<table>
<thead>
<tr>
<th>Harm category</th>
<th>Study author, year*</th>
<th>Study design</th>
<th>Intervention</th>
<th>Adverse events</th>
</tr>
</thead>
</table>
| Cancer/ Liver Disease | Ryom, 2016 | D:A:D Study Prospective cohort | cART | End-stage liver disease/hepatocellular carcinoma  
Overall, median followup of 8.4 years: 319 events (incidence rate, 1.01/1,000 person-years of followup [95% CI, 0.90 to 1.12]), with a 1-year mortality rate of 62.6%  
Cumulative (per 5 years) exposure by drug, adjusted for potential confounders:  
D4L: relative rate, 1.46 (95% CI, 1.20 to 1.77)  
ddI: relative rate, 1.32 (95% CI, 1.07 to 1.63)  
Tenofovir: relative rate, 1.46 (95% CI, 1.11 to 1.93)  
FPV: relative rate, 1.47 (95% CI, 1.00 to 2.15)  
FTC: relative rate, 0.51 (95% CI, 0.32 to 0.83)  
NVP: relative rate, 0.76 (95% CI, 0.58 to 0.98)  
Stratified by viral hepatitis status, per 1,000 person-years of followup:  
HCV positive: 229 events (incidence rate, 3.59 [95% CI, 3.13 to 4.06])  
HBV positive active: 59 events (incidence rate, 4.57 [95% CI, 3.40 to 5.74]) |
| Cancer/ Liver Disease | Kovari, 2013 | D:A:D Study Prospective cohort | cART | Liver-related deaths: 12 events (incidence rate, 0.10/1,000 person-years [95% CI, 0.05 to 0.18]); 7 events due to severe alcohol and 5 events due to established ART-related toxicity  
Rate of ART-related deaths in treatment-experienced persons: rate, 0.04 with 5 events/1,000 person-years (95% CI, 0.01 to 0.10) |
### Appendix B Table 11: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Results

<table>
<thead>
<tr>
<th>Harm category</th>
<th>Study author, year</th>
<th>Study design</th>
<th>Intervention</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney Disease</td>
<td>Ryom, 2013(^2)</td>
<td>D:A:D Study</td>
<td>cART</td>
<td>Renal impairment, median followup duration of 4.5 years: eGFR (\leq) 70 mL/min: 2.1% (468 persons); incidence rate, 4.78/1,000 person-years of followup (95% CI, 4.35 to 5.22) Chronic kidney disease: 0.6% (131 persons); incidence rate, 1.33 cases/1,000 person-years of followup (95% CI, 1.10 to 1.56) Significant predictors of a confirmed eGFR (\leq) 70 mL/min: Cumulative tenofovir use: aIRR, 1.18/year (95% CI, 1.12 to 1.25) Cumulative ritonavir-boosted atazanavir use: aIRR, 1.19/year (95% CI, 1.09 to 1.32) Cumulative ritonavir-boosted lopinavir use: aIRR, 1.11/year (95% CI, 1.05 to 1.07) Significant predictors of chronic kidney disease: Cumulative ritonavir-boosted lopinavir use: aIRR, 1.22/year (95% CI, 1.16 to 1.28) A current eGFR of 60 to 70 mL/min caused significantly higher rates of discontinuation of tenofovir compared with a current eGFR of (\geq) 90 mL/min: aIRR, 1.72 (95% CI, 1.38 to 2.14) After discontinuation, the treatment-associated incidence rates decreased</td>
</tr>
<tr>
<td></td>
<td>Mocroft, 2016(^1)</td>
<td>D:A:D Study</td>
<td>cART (TDF, ATV/r, LPV/r, other PI/r, ABC)</td>
<td>Chronic kidney disease, median followup of 7.2 years: 1% (285/23,905); incidence, 1.76 per 1,000 person-years of followup (95% CI, 1.56 to 1.97) Significant predictors of chronic kidney disease, after adjustment: Yearly TDF use: aIRR, 1.14 (95% CI, 1.10 to 1.19) Yearly ATV/r use: aIRR, 1.20 (95% CI, 1.13 to 1.26) Yearly LPV/r use: aIRR, 1.11 (95% CI, 1.06 to 1.16) Nonsignificant: Yearly other PI/r: aIRR, 1.02 (95% CI, 0.97 to 1.08) Yearly ABC: aIRR, 1.03 (95% CI, 0.99 to 1.08)</td>
</tr>
</tbody>
</table>
### Appendix B Table 11. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Results

<table>
<thead>
<tr>
<th>Harm category</th>
<th>Study author, year</th>
<th>Study design</th>
<th>Intervention</th>
<th>Adverse events</th>
</tr>
</thead>
</table>
| Kidney Disease      | Laprise 2013<sup>118</sup> | Retrospective cohort | A. TDF exposure  
B. Nonexposure  
Other ART comparisons: NRTI, NNRTI, PI exposure vs. nonexposure | A vs. B  
Reduced kidney function (eGFR <90 mL/min/1.73 m²): adjusted HR (time-dependent Cox model), 1.63 (95% CI, 1.26 to 2.10); adjusted OR (generalized estimating equation model), 1.63 (95% CI, 1.48 to 1.79)  
Loss in eGFR, 1 year: −3.05 (95% CI, −5.55 to −0.54); 2 year: −4.05 (95% CI, −6.03 to −2.08); 3 year: −2.42 (95% CI, −4.57 to −0.28); 4 year: −3.09 (95% CI, −6.98 to 0.80); 5 year: −0.12 (95% CI, −3.59 to 3.35); ≥6 year: 0.32 (95% CI, −4.55 to 5.19)  
Other comparisons  
NRTI exposure vs. nonexposure, reduced kidney function (eGFR <90 mL/min/1.73 m²): adjusted HR (time-dependent Cox model), 0.39 (95% CI, 0.18 to 0.86); adjusted OR (generalized estimating equation model), 0.78 (95% CI, 0.58 to 1.04)  
NNRTI exposure vs. nonexposure, reduced kidney function (eGFR <90 mL/min/1.73 m²): adjusted HR (time-dependent Cox model), 0.97 (95% CI, 0.69 to 1.37); adjusted OR (generalized estimating equation model), 0.98 (95% CI, 0.87 to 1.11)  
PI exposure vs. nonexposure, reduced kidney function (eGFR <90 mL/min/1.73 m²): adjusted HR (time-dependent Cox model), 1.46 (95% CI, 1.07 to 2.01); adjusted OR (generalized estimating equation model), 1.82 (95% CI, 1.61 to 2.05) |
|                    |                    |              | A vs. B       | All patients (regardless of intervention):  
Renal adverse events: 4.5% (5,704/126,168); exposure-adjusted incidence rate per 1,000 person-years, 18.0 (95% CI, 17.5 to 18.4)  
A vs. B vs. C:  
Renal adverse events, IR: 9.7 (95% CI, 8.5 to 11.0) vs. 10.5 (95% CI, 6.7 to 16.4) vs. 13.6 (95% CI, 8.1 to 23.0); adjusted IRD, A vs. B: -1.05 (95% CI, -2.90 to 0.53); IRD, A vs. C: -1.78 (95% CI, -2.19 to -1.50) |

### Additional Table

| Kidney Disease      | Nkhoma 2016b<sup>120</sup> (see also Fracture) | Retrospective cohort | A. EVF + TDF-FTC  
B. RPV + TDF-FTC  
C. EVG/COBI + TDF-FTC | All patients (regardless of intervention):  
Renal adverse events: 4.5% (5,704/126,168); exposure-adjusted incidence rate per 1,000 person-years, 18.0 (95% CI, 17.5 to 18.4)  
A vs. B vs. C:  
Renal adverse events, IR: 9.7 (95% CI, 8.5 to 11.0) vs. 10.5 (95% CI, 6.7 to 16.4) vs. 13.6 (95% CI, 8.1 to 23.0); adjusted IRD, A vs. B: -1.05 (95% CI, -2.90 to 0.53); IRD, A vs. C: -1.78 (95% CI, -2.19 to -1.50) |
### Appendix B Table 11. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Results

<table>
<thead>
<tr>
<th>Harm category</th>
<th>Study author, year</th>
<th>Study design</th>
<th>Intervention</th>
<th>Adverse events</th>
</tr>
</thead>
</table>
| **Kidney Disease** | Scherzer 2012<sup>119</sup> | Retrospective cohort | A. Tenofovir exposure (n=4,303)  
B. Nonexposure (n=6,538) | A vs. B  
Cumulative exposure to tenofovir, per year  
Chronic kidney disease (eGFR <60 mL/min/1.73m<sup>2</sup>): aHR, 1.36 (95% CI, 1.22 to 1.51)  
Rapid decline in kidney function (3 mL/min/1.73m<sup>2</sup> annual decline): aHR, 1.16 (95% CI, 1.09 to 1.23)  
Proteinuria (2 consecutive urine dipstick measurements 30 mg/dL): aHR, 1.24 (95% CI, 1.17 to 1.32)  
Ever exposure to tenofovir  
Chronic kidney disease: aHR, 1.88 (95% CI, 1.50 to 2.36)  
Rapid decline in kidney function: aHR, 1.50 (95% CI, 1.36 to 1.67)  
Proteinuria: aHR, 1.51 (95% CI, 1.36 to 1.66)  
Cumulative risk according to duration of tenofovir exposure  
Proteinuria, <0.5 years: 1.72 (95% CI, 1.50 to 1.96); 0.5 to 1 years: 1.59 (95% CI, 1.36 to 1.86); 1 to 3 years: 1.68 (95% CI, 1.44 to 1.95); >3 years: 2.17 (95% CI, 1.48 to 3.20)  
Rapid decline in kidney function, <0.5 years: 1.35 (95% CI, 1.16 to 1.56); 0.5 to 1 years: 1.59 (95% CI, 1.38 to 1.84); 1 to 3 years: 1.23 (95% CI, 1.07 to 1.42); >3 years: 1.04 (95% CI, 0.66 to 1.63)  
Chronic kidney disease, <0.5 years: 1.30 (95% CI, 0.91 to 1.86); 0.5 to 1 years: 1.85 (95% CI, 1.35 to 2.53); 1 to 3 years: 1.69 (95% CI, 1.26 to 2.27); >3 years: 1.56 (95% CI, 0.73 to 3.36)  
No evidence of interaction according to patient demographic and clinical characteristics except viral load <100,000 vs. >100,000 copies/mL (p=0.01) |
| **Suicidality** | Chang 2018<sup>108</sup> | Prospective cohort | A. EFV, any use (n=305)  
B. NVP only (n=389) | A vs. B  
Suicidal ideation: 6.2% (19/305) vs. 12.1% (47/389); adjusted HR, 0.47 (95% CI, 0.21 to 1.07); adjusted risk difference at visit, -0.91 (95% CI, -2.1 to 0.3)  
Depression: 20.0% (61/305) vs. 32.1% (125/389); adjusted HR, 0.56 (95% CI, 0.35 to 0.89); adjusted risk difference at visit, -3.1 (95% CI, -5.8 to -0.4) |
### Appendix B Table 11: Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Results

<table>
<thead>
<tr>
<th>Harm category</th>
<th>Study author, year Study design</th>
<th>Intervention</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suicidality</strong></td>
<td>Smith, 2014&lt;sup&gt;10&lt;/sup&gt; D:A:D Study (abstract only) Prospective cohort</td>
<td>cART, including EFV-containing regimens vs. other</td>
<td>Overall deaths: 4,420 over 371,333 person-years; rate, 11.9 per 1,000 person-years (95% CI, 11.6 to 12.3) &lt;br&gt;Deaths with an underlying cause of suicide or psychiatric disease: &lt;br&gt;Overall: 193 deaths/371,333 person-years; rate, 0.52 per 1,000 person years (95% CI, 0.45 to 0.59) &lt;br&gt;EFV-containing regimen: 24 deaths/78,580 person-years; aRR, 0.59 (95% CI, 0.33 to 1.06) &lt;br&gt;Other NNRTI-containing regimen: 31 deaths/64,288 person-years; aRR, 0.93 (95% CI, 0.53 to 1.62) &lt;br&gt;Other ART: 66 deaths/157,664 person-years; aRR, 0.81 (95% CI, 0.49 to 1.32) &lt;br&gt;No ART, naive: 21 deaths/40,454 person-years (reference) &lt;br&gt;No ART, experienced: 51 deaths/30,348 person-years; aRR, 3.24 (95% CI, 1.95 to 5.38) &lt;br&gt;Deaths with suicide or psychiatric disease &quot;mentioned anywhere&quot;: &lt;br&gt;Overall: 482 deaths/371,333 person-years; rate, 1.30 per 1,000-person years (95% CI, 1.18 to 1.41) &lt;br&gt;Efavirenz-containing regimen: 60 deaths/78,580 person-years; aRR, 0.42 (95% CI, 0.28 to 0.63) &lt;br&gt;Other NNRTI-containing regimen: 72 deaths/64,288 person-years; aRR, 0.68 (95% CI, 0.46 to 1.00) &lt;br&gt;Other ART: 162 deaths/157,664 person-years; aRR, 0.52 (95% CI, 0.37 to 0.73) &lt;br&gt;No ART, naive: 82 deaths/40,454 person-years (reference) &lt;br&gt;No ART, experienced: 126 deaths/30,348 person-years; aRR, 2.29 (95% CI, 1.63 to 3.21)</td>
</tr>
<tr>
<td><strong>Suicidality</strong></td>
<td>Nkhoma, 2016&lt;sup&gt;10&lt;/sup&gt; Retrospective cohort</td>
<td>cART, including: &lt;br&gt;A. EFV-containing regimens (n=11,187 Medicaid database) &lt;br&gt;B. EFV-containing regimens (n=2,224 Medicaid database) &lt;br&gt;C. EFV-free regimens (n=8,796 commercial database) &lt;br&gt;D. EFV-free regimens (n=2,930 Medicaid database)</td>
<td>vs. B vs. C vs. D &lt;br&gt;Unadjusted incidence rate per 1,000 person-years: 3.3 (95% CI, 2.4 to 4.4) vs. 25.7 (95% CI, 18.8 to 34.4) vs. 4.0 (95% CI, 2.7 to 5.8) vs. 40.6 (95% CI, 31.9 to 50.9) Propensity score adjusted HR, efavirenz use vs. EFV-free regimen: &lt;br&gt;Commercial: aHR, 1.029 (95% CI, 0.636 to 1.665) &lt;br&gt;Medicaid: aHR, 0.902 (95% CI, 0.617 to 1.319) Propensity score adjusted and inverse probability of censoring HR, EFV use vs. EFV-free regimen: &lt;br&gt;Commercial: aHR, 1.122 (95% CI, 0.686 to 1.836) &lt;br&gt;Medicaid: aHR, 0.935 (95% CI, 0.626 to 1.395) Suicidality Events: 7 vs. 1 vs. 1 vs. 12 Propensity score adjusted HR, EFV use vs. EFV-free regimen: &lt;br&gt;Commercial: aHR, 5.697 (95% CI, 0.688 to 47.147) &lt;br&gt;Medicaid: aHR, 0.113 (95% CI, 0.015 to 0.885) Suicide attempt (expanded) Events: 22 vs. 11 vs. 15 vs. 23 Propensity score adjusted HR, EFV use vs. EFV-free regimen: &lt;br&gt;Commercial: aHR, 1.000 (95% CI, 0.513 to 1.950) &lt;br&gt;Medicaid: aHR, 0.710 (95% CI, 0.334 to 1.509)</td>
</tr>
</tbody>
</table>
### Appendix B Table 11. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Results

<table>
<thead>
<tr>
<th>Harm category</th>
<th>Study author, year Study design</th>
<th>Intervention</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture</td>
<td>Borges 2017†112 EuroSIDA Study</td>
<td>TDF exposure vs. no TDF exposure</td>
<td>Fracture. TDF ever used vs. nonuse: aIRR, 1.40 (95% CI, 1.15 to 1.70) Fracture, current TDF use vs. nonuse: aIRR, 1.25 (95% CI, 1.05 to 1.49) Fracture, cumulative TDF use per 5 years of exposure vs. nonuse: aIRR, 1.08 (95% CI, 0.94 to 1.25) No association between exposure to any of the other investigated antiretrovirals and fracture risk (data not shown)</td>
</tr>
<tr>
<td>Fracture</td>
<td>Nkhoma 2016b120 (see also Kidney Disease) Retrospective cohort</td>
<td>A. EVF + TDF-FTC B. RPV + TDF-FTC C. EVG/COBI + TDF-FTC</td>
<td>All patients (regardless of intervention): Fracture: 1.3% (1,710/131,612); IR, 4.4 (95% CI, 4.2 to 4.6) A vs. B vs. C: Fracture, cumulative TDF use vs nonuse: aIRR, 1.25 (95% CI, 1.02 to 1.49); IRD, A vs. C: -0.85 (95% CI, -1.02 to -0.78)</td>
</tr>
</tbody>
</table>

**Abbreviations:** 3TC=lamivudine; ABC=abacavir; aIRR=adjusted incidence rate ratio; aHR=adjusted hazard ratio; aRR=adjusted rate ratio; ART=antiretroviral therapy; ATV=atazanavir; ATV=r=ritonavir-boosted atazanavir; cART=combination antiretroviral therapy; CI=confidence interval; COBI=cobicistat; D4L=stavudine; D:A:D Study= Data collection on Adverse events of anti-HIV Drugs Study; ddl=didanosine; eGFR=estimated glomerular filtration rate; EFV=efavirenz; EVG=elvitegavir; FPV=fosamprenavir; FTC=emtricitabine; HBV=hepatitis B virus; HCV=hepatitis C virus; HR=hazard ratio; IR=incidence rate; IRD=incidence rate difference; IRR=incidence rate ratio; LPV=r=ritonavir-boosted lopinavir; MI=myocardial infarction; NNRTI=nonnucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; NVP=nevirapine; OR=odds ratio; PI=protease inhibitor; RAL=raltegravir; RCT=randomized, controlled trial; RPV=ritonavir; STARTMRK=Phase III Noninferiority Trial of Raltegravir-Based Versus Efavirenz-Based Therapy in Treatment-Naïve Patients; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; ZDV=zidovudine.

**Note:** The D:A:D study was supported by the Highly Active Antiretroviral Therapy Oversight Committee (HAARTOC), a collaborative committee with representation from academic institutions, the European Agency for the Evaluation of Medical Products, the U.S. Food and Drug Administration, the patient community, and pharmaceutical companies with licensed anti-HIV drugs in the European Union (AbbVie, Bristol-Myers Squibb, Gilead Sciences Inc., ViIV Healthcare, Merck & Co Inc. and Janssen Pharmaceuticals). Supported also by a grant (grant no. DNRFI126) from the Danish National Research Foundation (CHIP & PERSIMUNE); by a grant from the Dutch Ministry of Health, and Sport through the Center for Infectious Disease Control of the National Institute for Public Health and the Environment to Stiching HIV Monitoring (ATHENA); by a grant from the Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS) (Action Coordonnée no. 7, Cohortes) to the Aquitaine Cohort. The Australian HIV Observational Database (AHOD) is funded as part of the Asia Pacific HIV Observational Database, a program of the Foundation for AIDS Research, amfAR, and is supported in part by a grant from the U.S. National Institutes of Health’s National Institute of Allergy and Infectious Diseases (NIAID) (grant no. U01-AI069907) and by unconditional grants from Merck Sharp & Dohme, Gilead Sciences Inc., Bristol-Myers Squibb, Boehringer Ingelheim, Janssen-Cilag, and ViIV Healthcare. The Kirby Institute is funded by the Australian Government Department of Health and Ageing, and is affiliated with the Faculty of Medicine, University of New South Wales; by grants from the Fondo de Investigación Sanitaria (grant no. FIS 99/0887) and Fundación para la Investigación y la Prevención del SIDA en España (grant no. FIPSE 3171/00), to the Barcelona Antiretroviral Surveillance Study (BASS); by NIAID (grant no. 5U01AI042170-10, 5U01AI046362-03), to the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA); by primary funding provided by the Swiss National Science Foundation (grant no. 108787) to the EuroSIDA study; by unrestricted educational grants of AbbVie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Pfizer, and Janssen Pharmaceuticals to the Italian Cohort Naïve to Antiretrovirals (ICONA Foundation); and financed within the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (grant no. 148522) and by the SHCS Research Foundation.
### Appendix B Table 12. Key Question 5: Quality Assessment of Randomized, Controlled Trials

<table>
<thead>
<tr>
<th>Study name Author, year</th>
<th>Randomization adequate?</th>
<th>Allocation concealment adequate?</th>
<th>Groups similar at baseline?</th>
<th>Eligibility criteria specified?</th>
<th>Outcome assessors masked?</th>
<th>Care provider masked?</th>
<th>Patient masked?</th>
<th>Attrition and withdrawals reported?</th>
<th>Loss to followup: differential (&gt;10%)/high (&gt;20%)?</th>
<th>Analyze persons in the groups in which they were randomized?</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arribas 2017115</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Rockstroh 2013116</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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</tr>
</tbody>
</table>
Appendix B Table 13. Key Question 5: Quality Assessment of Single-Arm Cohort Studies

<table>
<thead>
<tr>
<th>Study Author, Year</th>
<th>Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?</th>
<th>Did the study use accurate methods for ascertaining exposures and potential confounders?</th>
<th>Were outcome assessors and/or data analysts blinded to the exposure being studied?</th>
<th>Did the article report attrition?</th>
<th>Is there high attrition?</th>
<th>Were outcomes prespecified and defined, and ascertained using accurate methods?</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>D:A:D Study 102,104,107,109-111,117,123</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Good</td>
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<tr>
<td>Desai 2015103</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
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<tr>
<td>EuroSIDA Study Kowalska, 2012112, Borges 2017112</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
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<tr>
<td>Laprise 2013118</td>
<td>Yes</td>
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<td>No</td>
<td>Unclear</td>
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<tr>
<td>Scherzer 2012119</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
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</tbody>
</table>

Abbreviation: D:A:D=Data Collection on Adverse Events of Anti-HIV Drugs.
### Appendix B Table 14. Key Question 5: Quality Assessment of Comparative Cohort Studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?</th>
<th>Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?</th>
<th>Did the study maintain comparable groups through the study period?</th>
<th>Did the study use accurate methods for ascertaining exposures and potential confounders?</th>
<th>Were outcome assessors and/or data analysts blinded to the exposure being studied?</th>
<th>Did the article report attrition?</th>
<th>Did the study perform appropriate statistical analyses on potential confounders?</th>
<th>Is there important differential loss to followup or overall high loss to followup?</th>
<th>Were outcomes prespecified and defined, and ascertained using accurate methods?</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang 2018&lt;sup&gt;106&lt;/sup&gt;</td>
<td>Yes</td>
<td>No (some variables, such as pregnancy)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Differential: yes; high overall: yes, for NVP group</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Nkhoma, 2016&lt;sup&gt;106&lt;/sup&gt;</td>
<td>Yes</td>
<td>No, significant differences for some variables</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Nkhoma 2016b&lt;sup&gt;120&lt;/sup&gt;</td>
<td>Yes</td>
<td>No; differences in baseline concomitant medications used</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
</tbody>
</table>

**Abbreviation:** NVP=nevirapine.