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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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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/mm^3 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/mm^3 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/mm^3 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/mm^3. 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.[10] The Centers for Disease Control and Prevention (CDC) estimates that 1 million persons in the United States were living with HIV infection in 2016.[11] In 2015, an estimated 15 percent of infected persons were unaware of their infection.[12] This represents a decrease since 2008, when approximately 20 percent of infected persons were estimated to be unaware of their positive status,[13-15] and from 2010, when 17.1 percent were estimated to be unaware of their status.[16] 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 to 38,281 in 2017.[10,11] 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.[12]

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.[17] 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.[11] 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.[11] 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.[18,19] 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).[20]

The primary HIV infection syndrome usually develops 2 to 4 weeks following initial exposure to HIV.[21] Acute infection is associated with nonspecific symptoms such as fever and fatigue that may resemble infectious mononucleosis, but is often unrecognized.[22,23] Very early after acute infection, there is rapid virus production that declines to a variable set point as the host immune

system responds, although continuous rapid virus production and clearance occurs at all stages of infection.[24-29]

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.[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.[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^3 per year.[32] Most patients with CD4 counts greater than 200 cells/mm^3 are either asymptomatic or have mild disease,[33] although research indicates an increased risk of AIDS or even death in patients with CD4 counts greater than 500 cells/mm^3.[34] Patients with CD4 counts less than 200 cells/mm^3 have advanced immune deficiency and are at markedly increased risk of AIDS-related opportunistic infections, other AIDS-related complications, and AIDS-associated mortality.[35-37]

A higher HIV viral load is a strong independent predictor of more rapid progression to AIDS.[35-40] Other predictors of more rapid progression include older age at the time of infection,[30,31,35,36,39,41,42] more severe symptoms at the time of primary HIV infection,[43] and other clinical and genetic factors. One factor associated with slow progression is the C-C chemokine receptor type 5 delta32 genotype.[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.[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.[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)[52] that reduce the risk of progression to AIDS, AIDS-defining clinical events, and mortality.[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.[66,67] 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.[72] 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.[12] 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.[73] 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.[74]

In 2009, the American College of Physicians issued a guidance statement on HIV screening consistent with the CDC approach,[75] and the Infectious Diseases Society of America recommended routine HIV screening for all sexually active adults.[76] 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.[77] 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.[78] The American Academy of Family Physicians follows the 2013 USPSTF recommendation, except it recommends that routine screening not begin until age 18 years.[79]

Chapter 2. Methods

Key Questions and Analytic Framework

Using the methods developed by the USPSTF,[80] 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**).[61] 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.[61] We focused on studies on initiation of ART in patients with baseline CD4 counts greater than 350 cells/mm^3, 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.[1,52] 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**).[80] 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.[80] 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.[80]

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,[11] 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/mm^3:

- The prior USPSTF review found inconsistent effects of initiation of ART in persons infected with HIV with CD4 counts greater than 500 cells/mm^3 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/mm^3 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/mm^3 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/mm^3 or greater:

- 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 after approximately 1.5 years compared with initiation at CD4 counts less than 250 cells/mm^3, 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]).[55,89] 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).[55]
- 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/mm^3 or greater to less than 550 cells/mm^3 associated with decreased risk of AIDS-related events versus initiation at CD4 counts less than 250 cells/mm^3 (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 (RR, 0.87 [95% CI, 0.79 to 0.95]) and 10-year (RR, 0.93 [95% CI, 0.86 to 1.00]) mortality 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/mm^3. We identified longer-term (up to 5.5 years) followup data from the HPTN 052 trial,[90,93] 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 Canada[87,88,95,96] 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/mm^3 (median, 651 cells/mm^3) at baseline to immediate initiation of ART versus deferred initiation at CD4 counts less than 350 cells/mm^3.[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/mm^3 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/mm^3 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/mm^3, WHO clinical stage 4, or a CD4 count of 200 to 350 cells/mm^3 and WHO clinical stage 2 or 3. At the end of the trial, the criteria were a CD4 count less than 350 cells/mm^3 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 3**).[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 outcomes[87] and subgroup

analyses for adults older than age 50 years.[95] The other two studies evaluated cohorts from Canada (n=4,120; mean age, 42 years)[96] and the United States (n=3,532; approximately half of subjects ages 18 to 34 years).[88] 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/mm^3

In the prior review, evidence on effects of initiating ART at CD4 counts greater than 500 cells/mm^3 versus delayed initiation was limited to observational studies and inconsistent in showing beneficial effects.[81-84] Two new RCTs found early initiation of ART associated with beneficial effects on clinical outcomes in this population (**Table 3; Appendix B Table 2**).[85,86] In the START trial, immediate initiation of ART in persons with CD4 counts greater than 500 cells/mm^3 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/mm^3.[85] 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**).[85] 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/mm^3 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]).[86] 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/mm^3. An analysis of the HIV CAUSAL Collaboration (n=55,826; median baseline CD4 count, 376 cells/mm^3) found ART initiation at CD4 counts less than 350 cells/mm^3 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.[87] 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.[95] 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**).[96] 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**).[55,89] 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**).[81,82,84,92]

Longer-term followup from the HPTN 052 trial (n=1,763) is now available (**Table 3; Appendix B Table 2**).[90,93] 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/mm^3, initiation at less than 200 cells/mm^3 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/mm^3 (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/mm^3 versus initiation at less than 250 cells/mm^3, 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/mm^3 and discontinue when CD4 count >350 cells/mm^3) (1.1% vs. 1.8%; RR, 0.64 [95% CI, 0.41 to 1.0]). 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 studies,[97-100] 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 UPSTF 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) data[103] (**Table 4**). Other new evidence on longer-term harms include a systematic review,[105] a D:A:D analysis,[107] and two cohort studies[106,108] 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 deaths[121] (**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 with 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]).[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).[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.[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.[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,[107] and an analysis on a large (n=19,983) U.S. administrative cohort found no association between inititation of efavirenz and increased risk of suicidal ideation.[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]).[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]).[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]).[110] However, the risk of ART-related liver deaths in the D:A:D cohorts was low (0.04/1,000 person-years).[117] 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.[111] After discontinuation, the incidence of renal impairment decreased, suggesting that effects depend on ongoing exposure.[123] 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]).[119] 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/1.73m^2) in another (n=1,043) observational study with up to 10 years of followup (HR, 1.63 [95% CI, 1.26 to 2.10]).[118] 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]).[120]

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.[112] 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]).[120]

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.[121]

Chapter 4. Discussion

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.[2] 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,[101] 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).[102,103] 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.[126] A new analysis from D:A:D found no association between the currently used protease inhibitor atazanavir and risk of cardiovascular events.[104] 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.[85,89] The SMART trial, in which ART was initiated at CD4 counts greater than 350 cells/mm^3, 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^3, 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.[127]

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,[105] other studies found no clear association between efavirenz use and death from suicide or suicidal ideation.[106-108] 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.[111,112,117-120,123] 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.[61]

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.[10,12,128,129] 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.[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.[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.[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.[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.[133] Some short-term studies have reported potential neuropsychiatric effects of the integrase inhibitor dolutegravir, but longer-term studies are lacking.[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.[85] 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%).[12,128] However, rates of ART use and viral suppression appear similar across racial/ethnic groups.[128] 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.[95]

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.[137]

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/mm^3, 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/mm^3. 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

1. Chou R, Selph S, Dana T, et al. Screening for HIV: systematic review to update the U.S. Preventive Services Task Force recommendation. Evidence synthesis No. 95. AHRQ publication No. 12-05173-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; November 2012.
2. Chou R, Shelley S, Dana T, et al. Screening for HIV: Systematic review to update the 2005 U.S. Preventive Services Task Force recommendation. Ann Intern Med. 2012;157:706-18. PMID: 23165662.
3. Moyer VA, on behalf of the U.S. Preventive Services Task Force. Screening for HIV: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2013;159(1):51-60. doi: 10.7326/0003-4819-159-1-201307020-00645. PMID: 23698354.
4. Selph SS, Bougatsos C, Dana T, Grusing S, Chou R. Screening for HIV Infection in Pregnant Women: A Systematic Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 177. AHRQ Publication No. 18-05246-EF-2. Rockville, MD: Agency for Healthcare Research and Quality; 2019.
5. US Preventive Services Task Force. Screening for HIV: Recommendation statement. Ann Intern Med. 2005 Jul 5;143(1):32-7. PMID: 15998753.
6. Sanders GD, Bayoumi AM, Holodniy M, et al. Cost-effectiveness of HIV screening in patients older than 55 years of age. Ann Intern Med. 2008 Jun 17;148(12):889-903. PMID: 18559840.
7. Paltiel AD, Walensky RP, Schackman BR, et al. Expanded HIV screening in the United States: effect on clinical outcomes, HIV transmission, and costs.. Ann Intern Med. 2006 Dec 5;145(11):797-806. PMID: 17146064.
8. Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep. 1992 December 18;41(RR-17). PMID: 1361652.
9. Centers for Disease Control and Prevention. HIV-2 surveillance- United States, 1987-2009. 2011. www.cdc.gov/mmwr/preview/mmwrhtml/mm6029a3.htm. Accessed October 31, 2016.
10. Centers for Disease Control and Prevention. HIV Surveillance Report. Volume 28. Diagnoses of HIV Infection in the United States and Dependent Areas, 2016. 2016. www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2016-vol-28.pdf. Accessed December 8, 2017.
11. Centers for Disease Control and Prevention. HIV Surveillance Report - Diagnoses of HIV Infection in the United States and Dependent Areas, 2017. 2017. https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2017-vol-29.pdf. Accessed January 31, 2019.
12. Dailey AF, Hoots BE, Hall HI, et al. Vital signs: Human immunodeficiency virus testing and diagnosis delays - United States. MMWR. 2017 Dec 1;66(47):1300-6. doi: 10.15585/mmwr.mm6647e1. PMID: 29190267.
13. Centers for Disease Control and Prevention. HIV in the United States. 2011. www.cdc.gov/hiv/resources/factsheets/us.htm. Accessed October 31, 2016.
14. Centers for Disease Control and Prevention. HIV surveillance - United States, 1981-2008. MMWR. 2011;60(21):689-93. PMID: 21637182.

15. Campsmith ML, Rhodes PH, Hall I, et al. Undiagnosed HIV prevalence among adults and adolescents in the United States at the end of 2006. J Acquir Immune Defic Syndr. 2010;53:619-24. PMID: 19838124
16. Satcher Johnson A, Song R, Hall HI. Estimated HIV incidence, prevalence, and undiagnosed infections in US states and Washington, DC, 2010-2014. J Acquir Immune Defic Syndr. 2017 Oct 1;76(2):116-22. doi: 10.1097/qai.0000000000001495. PMID: 28700407.
17. Prejean J, Song R, Hernandez A, et al. Estimated HIV incidence in the United States, 2006–2009. PLoS One. 2011 Aug 3;6(8):e17502. doi:10.1371/journal.pone.0017502. PMID: 21826193.
18. Quinn TC, Wawer MJ, Sewankambo NK, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. N Engl J Med. 2000;342(13):921-9. PMID: 10738050.
19. Gray RH, Wawer MJ, Brookmeyer R, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. Lancet. 2001;357(9263):1149-53. doi: 10.1016/s0140-6736(00)04331-2. PMID: 11323041.
20. Doherty MC, Garfein RS, Monterroso E, et al. Correlates of HIV infection among young adult short-term injection drug users. AIDS. 2000 Apr 14;14(6):717-26. PMID: 10807195.
21. Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. N Engl J Med. 1998;339(1):33-9. doi: 10.1056/NEJM199807023390107. PMID: 9647878.
22. Schacker T, Collier AC, Hughes J, et al. Clinical and epidemiologic features of primary HIV infection. Ann Intern Med. 1996 Aug 15;125(4):257-64. PMID: 8678387.
23. Vanhems P, Allard R, Cooper DA, et al. Acute human immunodeficiency virus type 1 disease as a mononucleosis-like illness: is the diagnosis too restrictive? Clin Infect Dis. 1997;24(5):965-70. doi: 10.1093/clinids/24.5.965. PMID: 9142802.
24. Daar ES, Moudgil T, Meyer RD, et al. Transient high levels of viremia in patients with primary human immunodeficiency virus type 1 infection. N Engl J Med. 1991;324(14):961-4. doi: 10.1056/NEJM199104043241405. PMID: 1823118.
25. Henrard DR, Phillips JF, Muenz LR, et al. Natural history of HIV-1 cell-free viremia. JAMA. 1995 Aug 16;274(7):554-8. PMID: 7629984.
26. Ho DD, Neumann AU, Perelson AS, et al. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature. 1995 Jan 12;373(6510):123-6. doi: 10.1038/373123a0. PMID: 7816094.
27. Schacker TW, Hughes JP, Shea T, et al. Biological and virologic characteristics of primary HIV infection. Ann Intern Med. 1998 Apr 15;128(8):613-20. PMID: 9537934.
28. Touloumi G, Pantazis N, Babiker AG, et al. Differences in HIV RNA levels before the initiation of antiretroviral therapy among 1864 individuals with known HIV-1 seroconversion dates. AIDS. 2004 Aug 20;18(12):1697-705. PMID: 15280781.
29. Wei X, Ghosh SK, Taylor ME, et al. Viral dynamics in human immunodeficiency virus type 1 infection. Nature. 1995 Jan 12;373(6510):117-22. doi: 10.1038/373117a0. PMID: 7529365.
30. Collaborative Group on AIDS Incubation and HIV Survival including the CASCADE EU Concerted Action. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. Lancet. 2000 Apr 1;355(9210):1131-7. PMID: 10791375.

31. Koblin B, van Benthem B, Buchbinder S, et al. Long-term survival after infection with human immunodeficiency virus type 1 (HIV-1) among homosexual hen in hepatitis B vaccine trial cohorts in Amsterdam, New York City, and San Francisco, 1978–1995. Am J Epidemiol. 1999 November 15, 1999;150(10):1026-30. PMID: 10568617.
32. Stein DS, Korvick JA, Vermund SH. CD4+ lymphocyte cell enumeration for prediction of clinical course of human immunodeficiency virus disease: a review. J Infect Dis. 1992 Feb;165(2):352-63. PMID: 1346152.
33. Kaslow RA, Phair JP, Friedman HB, et al. Infection with the human immunodeficiency virus: clinical manifestations and their relationship to immune deficiency. A report from the Multicenter AIDS Cohort Study. Ann Intern Med. 1987 Oct;107(4):474-80. PMID: 2957944.
34. Phillips A, Gazzard B, Gilson R, et al. Rate of AIDS diseases or death in HIV-infected antiretroviral therapy-naive individuals with high CD4 cell count. AIDS. 2007;21(13):1717 - 21. PMID: 17690569.
35. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet. 2002 Jul 13;360(9327):119-29. PMID: 12126821.
36. Phillips A, Pezzotti P. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. AIDS. 2004 Jan 2;18(1):51-8. PMID: 15090829.
37. Phillips AN, Lee CA, Elford J, et al. Serial CD4 lymphocyte counts and development of AIDS. Lancet. 1991 Feb 16;337(8738):389-92. PMID: 1671424.
38. Mellors JW, Kingsley LA, Rinaldo CR, Jr., et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. Ann Intern Med. 1995 Apr 15;122(8):573-9. PMID: 7887550.
39. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med. 1997 Jun 15;126(12):946-54. PMID: 9182471.
40. Phair JP, Mellors JW, Detels R, et al. Virologic and immunologic values allowing safe deferral of antiretroviral therapy. AIDS. 2002 Dec 6;16(18):2455-9. PMID: 12461420.
41. Babiker AG, Peto T, Porter K, et al. Age as a determinant of survival in HIV infection. J Clin Epidemiol. 2001 Dec;54 Suppl 1:S16-21. PMID: 11750205.
42. Vella S, Giuliano M, Floridia M, et al. Effect of sex, age and transmission category on the progression to AIDS and survival of zidovudine-treated symptomatic patients. AIDS. 1995 Jan;9(1):51-6. PMID: 7893441.
43. Pedersen C, Lindhardt BO, Jensen BL, et al. Clinical course of primary HIV infection: consequences for subsequent course of infection. BMJ. 1989;299(6692):154-7. PMID: 2569901.
44. de Roda Husman A-M, Koot M, Cornelissen M, et al. Association between CCR5 genotype and the clinical course of HIV-1 Infection. Ann Intern Med. 1997 November 15, 1997;127(10):882-90. PMID: 9382366.
45. Ioannidis JP, Rosenberg PS, Goedert JJ, et al. Effects of CCR5-Delta32, CCR2-64I, and SDF-1 3'A alleles on HIV-1 disease progression: an international meta-analysis of individual-patient data. Ann Intern Med. 2001 Nov 6;135(9):782-95. PMID: 11694103.
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

patients receiving nucleoside therapy. J Infect Dis. 2001 Dec 1;184(11):1402-11. doi: 10.1086/324427. PMID: 11709782.
47. Marmor M, Sheppard HW, Donnell D, et al. Homozygous and heterozygous CCR5-Delta32 genotypes are associated with resistance to HIV infection. J Acquir Immune Defic Syndr. 2001 Aug 15;27(5):472-81. PMID: 11511825.
48. Nolan D, Gaudieri S, John M, et al. Impact of host genetics on HIV disease progression and treatment: new conflicts on an ancient battleground. AIDS. 2004 Jun 18;18(9):1231-40. PMID: 15362655.
49. Baggaley RF, Boily MC, White RG, et al. Risk of HIV-1 transmission for parenteral exposure and blood transfusion: a systematic review and meta-analysis. AIDS. 2006 Apr 4;20(6):805-12. doi: 10.1097/01.aids.0000218543.46963.6d. PMID: 16549963.
50. Moore RD. Epidemiology of HIV infection in the United States: implications for linkage to care. Clin Infect Dis. 2011 Jan 15;52 Suppl 2:S208-13. doi: 10.1093/cid/ciq044. PMID: 21342909.
51. US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States - 2017 update: A clinical practice guideline. 2017. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf. Accessed January 31, 2019.
52. Chou R, Huffman LH, Fu R, et al. Screening for HIV: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2005 Jul 5;143(1):55-73. PMID: 15998755.
53. Zakher B, Blazina I, Chou R. Association between knowledge of HIV-positive status or use of antiretroviral therapy and high-risk transmission behaviors: Systematic review. AIDS Care. 2014 2014/04/03;26(4):514-21. doi: 10.1080/09540121.2013.832723. PMID: 24007512.
54. Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. JAMA. 2016 Jul 12;316(2):171-81. doi: 10.1001/jama.2016.5148. PMID: 27404185.
55. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011 Aug 11;365(6):493-505. doi: 10.1056/NEJMoa1105243. PMID: 21767103.
56. Skarbinski J, Rosenberg E, Paz-Bailey G, et al. Human immunodeficiency virus transmission at each step of the care continuum in the United States. JAMA Intern Med. 2015 Apr;175(4):588-96. doi: 10.1001/jamainternmed.2014.8180. PMID: 25706928.
57. Gopalappa C, Farnham PG, Chen YH, et al. Progression and transmission of HIV/AIDS (PATH 2.0). Med Decis Making. 2017 Feb;37(2):224-33. doi: 10.1177/0272989x16668509. PMID: 27646567.
58. Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States—2014: a clinical practice guideline. www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf Accessed October 31, 2016.
59. Chou R, Evans C, Hoverman A, Sun C, Dana T, Bougatsos C, Grusing S, Korthuis PT. Pre-Exposure Prophylaxis for the Prevention of HIV Infection: A Systematic Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 178. AHRQ Publication No. 18-05247-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2019.

60. U.S. Department of Health and Human Services. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. 2018. aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0. Accessed January 3, 2018.
61. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Version October 25, 2018.; 2018. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed October 25, 2018.
62. McNaghten AD, Hanson DL, Jones JL, et al. Effects of antiretroviral therapy and opportunistic illness primary chemoprophylaxis on survival after AIDS diagnosis. AIDS. 1999;13(13):1687-95. PMID: 10509570.
63. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed December 21, 2017.
64. Centers for Disease Control and Prevention. Quick reference guide - Laboratory testing for the diagnosis of HIV infection: updated recommendations. 2014. stacks.cdc.gov/view/cdc/23447. Accessed October 31, 2016.
65. Delaney KP, Hanson DL, Masciotra S, et al. Time until emergence of HIV test reactivity following infection with HIV-1: Implications for interpreting test results and retesting after exposure. Clin Infect Dis. 2017 Jan 1;64(1):53-9. doi: 10.1093/cid/ciw666. PMID: 27737954.
66. Bennett B, Neumann D, Fordan S, et al. Performance of the new HIV-1/2 diagnostic algorithm in Florida's public health testing population: a review of the first five months of utilization. J Clin Virol. 2013 Dec;58 Suppl 1:e29-33. doi: 10.1016/j.jcv.2013.08.016. PMID: 24342476.
67. Chen DJ, Yao JD. Comparison of turnaround time and total cost of HIV testing before and after implementation of the 2014 CDC/APHL Laboratory Testing Algorithm for diagnosis of HIV infection. J Clin Virol. 2017 Jun;91:69-72. doi: 10.1016/j.jcv.2017.04.004. PMID: 28461133.
68. Centers for Disease Control and Prevention. Interpretation and use of the western blot assay for serodiagnosis of human immunodeficiency virus type 1 infections JAMA. 1989;262(24):3395-7. PMID: 2685380.
69. Centers for Disease Control and Prevention. Update: serologic testing for HIV-1 antibody--United States, 1988 and 1989. M. 1990;39(22):380-3. PMID: 2111436.
70. Centers for Disease Control and Prevention. Rapid HIV tests suitable for use in non-clinical settings (CLIA-waived). 2016. https://www.cdc.gov/hiv/pdf/testing/rapid-hiv-tests-non-clinical.pdf Accessed February 6, 2018.
71. Centers for Disease Control and Prevention. CDC Fact sheet: HIV testing in the United States. 2016. www.cdc.gov/nchhstp/newsroom/docs/factsheets/hiv-testing-us-508.pdf. Accessed October 31, 2016.

72. Van Handel M, Kann L, Olsen EO, et al. HIV testing among US high school students and young adults. Pediatrics. 2016 Feb;137(2):e20152700. doi: 10.1542/peds.2015-2700. PMID: 26787047.
73. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep. 2006 Sep 22;55(RR-14):1-17. PMID: 16988643.
74. DiNenno EA, Prejean J, Irwin K, et al. Recommendations for HIV screening of gay, bisexual, and other men who have sex with men - United States, 2017. MMWR. 2017 Aug 11;66(31):830-2. doi: 10.15585/mmwr.mm6631a3. PMID: 28796758.
75. Qaseem A, Snow V, Shekelle P, et al. Screening for HIV in health care settings: a guidance statement from the American College of Physicians and HIV Medicine Association. Ann Intern Med. 2009;150(2):125-31. doi: 10.1059/0003-4819-150-2-200901200-00300. PMID: 19047022.
76. Lubinski C, Aberg J, Bardeguez AD, et al. HIV policy: the path forward--a joint position paper of the HIV Medicine Association of the Infectious Diseases Society of America and the American College of Physicians. Clin Infect Dis. 2009 May 15;48(10):1335-44. PMID: 19385087.
77. American College of Obstetricians and Gynecologists. Committee opinion: routine HIV screening. 2014. www.acog.org/-/media/Committee-Opinions/Committee-on-Gynecologic-Practice/co596.pdf?dmc=1&ts=20161013T1844591209. Accessed October 31, 2016.
78. American Academy of Pediatrics. Policy statement: adolescents and HIV infection: The pediatrician's role in promoting routine testing. Pediatrics. 2011;128(5):1023–9. PMID: 22042816
79. American Academy of Family Physicians. Clinical preventive service recommendation: human immunodeficiency virus (HIV). 2013. www.aafp.org/patient-care/clinical-recommendations/all/hiv.html. Accessed October 31, 2016.
80. U.S. Preventive Services Task Force Procedure Manual. Rockville, MD; https://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual Accessed December 8, 2018.
81. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med. 2009 Apr 30;360(18):1815-26. doi: 10.1056/NEJMoa0807252. PMID: 19339714.
82. Ray M, Logan R, Sterne J, et al. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. AIDS. 2010;24(1):123-37. doi: 10.1097/QAD.0b013e3283324283. PMID: 19770621.
83. Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. Lancet. 2009 Apr 18;373(9672):1352-63. doi: 10.1016/s0140-6736(09)60612-7. PMID: 19361855.
84. Writing Committee for the CASCADE Collaboration. Timing of HAART initiation and clinical outcomes in human immunodeficiency virus type 1 seroconverters. Arch Intern Med. 2011 Sep 26;171(17):1560-9. doi: 10.1001/archinternmed.2011.401. PMID: 21949165.

85. Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015 Aug 27;373(9):795-807. doi: 10.1056/NEJMoa1506816. PMID: 26192873.
86. TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med. 2015 Aug 27;373(9):808-22. doi: 10.1056/NEJMoa1507198. PMID: 26193126.
87. Lodi S, Phillips A, Logan R, et al. Comparative effectiveness of immediate antiretroviral therapy versus CD4-based initiation in HIV-positive individuals in high-income countries: observational cohort study. Lancet HIV. 2015 Aug;2(8):e335-43. doi: 10.1016/S2352-3018(15)00108-3. PMID: 26423376.
88. Edwards JK, Cole SR, Westreich D, et al. Age at entry into care, timing of antiretroviral therapy initiation, and 10-year mortality among HIV-seropositive adults in the United States. Clin Infect Dis. 2015 Oct 1;61(7):1189-95. doi: 10.1093/cid/civ463. PMID: 26082505.
89. Emery S, Neuhaus JA, Phillips AN, et al. Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. J Infect Dis. 2008;197(8):1133-44. doi: 10.1086/586713. PMID: 18476292.
90. Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. Lancet Infect Dis. 2014 Apr;14(4):281-90. doi: 10.1016/s1473-3099(13)70692-3. PMID: 24602844.
91. Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. N Engl J Med. 2010 Jul 15;363(3):257-65. doi: 10.1056/NEJMoa0910370. PMID: 20647201.
92. May M, Sterne JA, Sabin C, et al. Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies. AIDS. 2007 May 31;21(9):1185-97. doi: 10.1097/QAD.0b013e328133f285. PMID: 17502729.
93. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. N Engl J Med. 2016 Sep 1;375(9):830-9. doi: 10.1056/NEJMoa1600693. PMID: 27424812.
94. O'Connor J, Vjecha MJ, Phillips AN, et al. Effect of immediate initiation of antiretroviral therapy on risk of severe bacterial infections in HIV-positive people with CD4 cell counts of more than 500 cells per muL: secondary outcome results from a randomised controlled trial. Lancet HIV. 2017 Mar;4(3):e105-e12. doi: 10.1016/s2352-3018(16)30216-8. PMID: 28063815.
95. Lodi S, Costagliola D, Sabin C, et al. Effect of immediate initiation of antiretroviral treatment in HIV-positive individuals aged 50 years or older. J Acquir Immune Defic Syndr. 2017 Nov 01;76(3):311-8. doi: 10.1097/qai.0000000000001498. PMID: 28746165.
96. Lima VD, Reuter A, Harrigan PR, et al. Initiation of antiretroviral therapy at high CD4+ cell counts is associated with positive treatment outcomes. AIDS. 2015 Sep 10;29(14):1871-82. doi: 10.1097/QAD.0000000000000790. PMID: 26165354.
97. 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

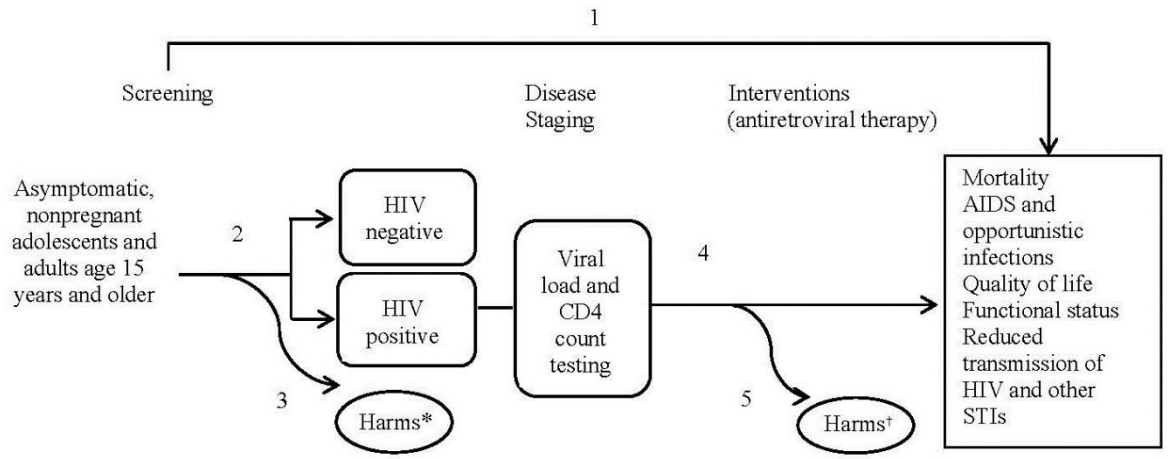
classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. J Infect Dis. 2010 Feb 1;201(3):318-30. doi: 10.1086/649897. PMID: 20039804.
98. Bedimo RJ, Westfall AO, Drechsler H, et al. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era. Clin Infect Dis. 2011 Jul 1;53(1):84-91. doi: 10.1093/cid/cir269. PMID: 21653308.
99. Obel N, Farkas DK, Kronborg G, et al. Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. HIV Med. 2010 Feb;11(2):130-6. doi: 10.1111/j.1468-1293.2009.00751.x. PMID: 19682101.
100. Ribaudo HJ, Benson CA, Zheng Y, et al. No risk of myocardial infarction associated with initial antiretroviral treatment containing abacavir: short and long-term results from ACTG A5001/ALLRT. Clin Infect Dis. 2011 Apr 1;52(7):929-40. doi: 10.1093/cid/ciq244. PMID: 21427402.
101. Ding X, Andraca-Carrera E, Cooper C, et al. No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis. J Acquir Immune Defic Syndr. 2012 Dec 1;61(4):441-7. doi: 10.1097/QAI.0b013e31826f993c. PMID: 22932321.
102. Sabin CA, Reiss P, Ryom L, et al. Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with HIV? A cohort collaboration. BMC Med. 2016 Mar 31;14:61. doi: 10.1186/s12916-016-0588-4. PMID: 27036962.
103. Desai M, Joyce V, Bendavid E, et al. Risk of cardiovascular events associated with current exposure to HIV antiretroviral therapies in a US veteran population. Clin Infect Dis. 2015 Aug 1;61(3):445-52. doi: 10.1093/cid/civ316. PMID: 25908684.
104. Monforte A, Reiss P, Ryom L, et al. Atazanavir is not associated with an increased risk of cardio- or cerebrovascular disease events. AIDS. 2013 Jan 28;27(3):407-15. doi: 10.1097/QAD.0b013e32835b2ef1. PMID: 23291539.
105. Ford N, Shubber Z, Pozniak A, et al. Comparative safety and neuropsychiatric adverse events associated with efavirenz use in first-line antiretroviral therapy: A systematic review and meta-analysis of randomized trials. J Acquir Immune Defic Syndr. 2015 Aug 1;69(4):422-9. doi: 10.1097/QAI.0000000000000606. PMID: 25850607.
106. Nkhoma ET, Coumbis J, Farr AM, et al. No evidence of an association between efavirenz exposure and suicidality among HIV patients initiating antiretroviral therapy in a retrospective cohort study of real world data. Medicine (Baltimore). 2016;95(3):e2480. doi: 10.1097/MD.0000000000002480. PMID: 26817882.
107. Smith C, Ryom L, d'Arminio Monforte A, et al. Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study. J Int AIDS Soc. 2014 11/02;17(4 Suppl 3):19512. doi: 10.7448/IAS.17.4.19512. PMID: 25394021.
108. Chang JL, Tsai AC, Musinguzi N, et al. Depression and suicidal ideation among HIV-infected adults receiving efavirenz versus nevirapine in Uganda: A prospective cohort study. Ann Intern Med. 2018 Jun 26doi: 10.7326/m17-2252. PMID: 29946683.
109. Bruyand M, Ryom L, Shepherd L, et al. Cancer risk and use of protease inhibitor or nonnucleoside reverse transcriptase inhibitor-based combination antiretroviral therapy: the D: A: D study. J Acquir Immune Defic Syndr. 2015 Apr 15;68(5):568-77. doi: 10.1097/qai.0000000000000523. PMID: 25763785.

110. Ryom L, Lundgren JD, De Wit S, et al. Use of antiretroviral therapy and risk of end-stage liver disease and hepatocellular carcinoma in HIV-positive persons. AIDS. 2016 Jul 17;30(11):1731-43. doi: 10.1097/qad.0000000000001018. PMID: 26752282.
111. Mocroft A, Lundgren JD, Ross M, et al. Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: a prospective international cohort study. Lancet HIV. 2016 Jan;3(1):e23-32. doi: 10.1016/s2352-3018(15)00211-8. PMID: 26762990.
112. Borges AH, Hoy J, Florence E, et al. Antiretrovirals, fractures, and osteonecrosis in a large international HIV cohort. Clin Infect Dis. 2017 May 15;64(10):1413-21. doi: 10.1093/cid/cix167. PMID: 28329090.
113. Friis-Moller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med. 2007 Apr 26;356(17):1723-35. doi: 10.1056/NEJMoa062744. PMID: 17460226.
114. Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet. 2008 Apr 26;371(9622):1417-26. doi: 10.1016/s0140-6736(08)60423-7. PMID: 18387667.
115. Arribas JR, Thompson M, Sax PE, et al. Brief report: Randomized, double-blind comparison of tenofovir alafenamide (TAF) vs tenofovir disoproxil fumarate (TDF), each coformulated eith elvitegravir, cobicistat, and emtricitabine (E/C/F) for initial HIV-1 treatment: Week 144 results. J Acquir Immune Defic Syndr. 2017 Jun 01;75(2):211-8. doi: 10.1097/QAI.0000000000001350. PMID: 28282300.
116. Rockstroh JK, DeJesus E, Lennox JL, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. J Acquir Immune Defic Syndr. 2013 May 1;63(1):77-85. doi: 10.1097/QAI.0b013e31828ace69. PMID: 23412015.
117. Kovari H, Sabin CA, Ledergerber B, et al. Antiretroviral drug-related liver mortality among HIV-positive persons in the absence of hepatitis B or C virus coinfection: the data collection on adverse events of anti-HIV drugs study. Clin Infect Dis. 2013 Mar;56(6):870-9. doi: 10.1093/cid/cis919. PMID: 23090925.
118. Laprise C, Baril J-G, Dufresne S, et al. Association between tenofovir exposure and reduced kidney function in a cohort of HIV-positive patients: results from 10 years of follow-up. Clin Infect Dis. 2013;56(4):567-75. doi: 10.1093/cid/cis937. PMID: 23143096.
119. Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS. 2012 Apr 24;26(7):867-75. doi: 10.1097/QAD.0b013e328351f68f. PMID: 22313955.
120. Nkhoma ET, Rosenblatt L, Myers J, et al. Real-world assessment of renal and bone safety among patients with HIV infection exposed to tenofovir disoproxil fumarate-containing single-tablet regimens. PLoS One. 2016;11(12):e0166982. doi: 10.1371/journal.pone.0166982. PMID: 27941989.
121. Kowalska JD, Reekie J, Mocroft A, et al. Long-term exposure to combination antiretroviral therapy and risk of death from specific causes: no evidence for any previously unidentified increased risk due to antiretroviral therapy. AIDS. 2012 Jan 28;26(3):315-23. doi: 10.1097/QAD.0b013e32834e8805. PMID: 22112597.

122. Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: An analysis of trial data. Ann Intern Med. 2014;161(1):1-10. PMID: 24979445.
123. Ryom L, Mocroft A, Kirk O, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. J Infect Dis. 2013 May 1;207(9):1359-69. doi: 10.1093/infdis/jit043. PMID: 23382571.
124. Siegfried N, Uthman OA, Rutherford GW. Optimal time for initiation of antiretroviral therapy in asymptomatic, HIV-infected, treatment-naive adults. Cochrane Database Syst Rev. 2011(2)doi: 10.1002/14651858.CD008272.pub2. PMID: 20238364.
125. Anglemyer A, Rutherford GW, Easterbrook PJ, et al. Early initiation of antiretroviral therapy in HIV-infected adults and adolescents: a systematic review. AIDS. 2014 Mar;28 Suppl 2:S105-18. doi: 10.1097/QAD.0000000000000232. PMID: 24849469.
126. Bavinger C, Bendavid E, Niehaus K, et al. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. PLoS One. 2013;8(3):e59551. doi: 10.1371/journal.pone.0059551. PMID: 23555704.
127. Siedner MJ. START or SMART? Timing of antiretroviral therapy initiation and cardiovascular risk for people with human immunodeficiency virus infection. Open Forum Infect Dis. 2016 Jan;3(1):ofw032. doi: 10.1093/ofid/ofw032. PMID: 26989755.
128. Bradley H, Hall HI, Wolitski RJ, et al. Vital Signs: HIV diagnosis, care, and treatment among persons living with HIV--United States, 2011. MMWR. 2014;63(47):1113-7. PMID: 25426654.
129. Tillison AS, Avery AK. Evaluation of the impact of routine HIV screening in primary care. J Int Assoc Provid AIDS Care. 2017 Jan/Feb;16(1):18-22. doi: 10.1177/2325957416666677. PMID: 27596961.
130. Hutchinson AB, Farnham PG, Sansom SL, et al. Cost-effectiveness of frequent HIV testing of high-risk populations in the United States. J Acquir Immune Defic Syndr. 2016 Mar 1;71(3):323-30. doi: 10.1097/qai.0000000000000838. PMID: 26361172.
131. Lucas A, Armbruster B. The cost-effectiveness of expanded HIV screening in the United States. AIDS. 2013 Mar 13;27(5):795-801. doi: 10.1097/QAD.0b013e32835c54f9. PMID: 23169333.
132. Long EF. HIV screening via fourth-generation immunoassay or nucleic acid amplification test in the United States: a cost-effectiveness analysis. PLoS One. 2011;6(11):e27625. doi: 10.1371/journal.pone.0027625. PMID: 22110698.
133. U.S. Department of Health and Human Services. HIV Treatment. FDA-Approved HIV Medicines. 2017. aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/21/58/fda-approved-hiv-medicines. Accessed December 21, 2017.
134. Cid-Silva P, Llibre JM, Fernández-Bargiela N, et al. Clinical experience with the integrase inhibitors dolutegravir and elvitegravir in HIV-infected patients: Efficacy, safety and tolerance. Basic Clin Pharmacol Toxicol. 2017;121(5):442-6. doi: 10.1111/bcpt.12828. PMID: 28627771.
135. Cailhol J, Rouyer C, Alloui C, et al. Dolutegravir and neuropsychiatric adverse events: a continuing debate. AIDS. 2017;31(14):2023-4. doi: 10.1097/qad.0000000000001596. PMID: 28857781.

136. Hoffmann C, Welz T, Sabranski M, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med. 2017 Jan;18(1):56-63. doi: 10.1111/hiv.12468. PMID: 27860104.
137. Grulich A. HIV treatment prevents HIV transmission in male serodiscordant couples in Australia, Thailand and Brazil. 2017. programme.ias2017.org/Abstract/Abstract/5469. Accessed February 6, 2018.

Figure 1. Analytic Framework and Key Questions



* Harms of screening include false-positive results, anxiety and effects of labeling, and partner discord, abuse, or violence.
† Harms of treatment include adverse effects associated with antiretroviral therapy, including cardiometabolic outcomes.

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

Study	Mortality	AIDS-related events
CASCADE Collaboration 2011[84] *Included in prior report*	**≥350 to <500 cells/mm^3 vs. no treatment initiation** All-cause mortality: HR, 0.51 (95% CI, 0.33 to 0.80) **≥500 cells/mm^3 vs. no treatment initiation** All-cause mortality: HR, 1.02 (95% CI, 0.49 to 2.12)	**≥350 to <500 cells/mm^3 vs. no treatment initiation** Progression to AIDS or death: HR, 0.75 (95% CI, 0.49 to 1.14) **≥500 cells/mm^3 vs. no treatment initiation** Progression to AIDS or death: HR, 1.10 (95% CI, 0.67 to 1.79)
Kitahata 2009[81] *Included in prior report*	**≥350 to 500 vs. <350 cells/mm^3** All-cause mortality: RR, 0.61 (95% CI, 0.46 to 0.83) **>500 vs. ≤500 cells/mm^3** All-cause mortality: RR, 0.54 (95% CI, 0.35 to 0.83)	NR
May 2007[92] *Included in prior report*	**≥350 vs <250 cells/mm^3** All-cause mortality: HR, 0.34 (95% CI, 0.27 to 0.44)	**≥350 vs. <250 cells/mm^3** Progression to AIDS or death: HR, 0.23 (95% CI, 0.19 to 0.27)
Ray 2010[82] *Included in prior report*	**500 vs. 350 cells/mm^3** All-cause mortality: HR, 0.99 (95% CI, 0.82 to 1.19)	**500 vs. 350 cells/mm^3** Progression to AIDS or death: HR, 0.72 (95% CI, 0.64 to 0.81)
Sterne 2009[83] *Included in prior report*	**>450 to 550 vs. ≥350 to 450 cells/mm^3** All-cause mortality: HR, 0.93 (95% CI, 0.6 to 1.40)	**>450 to 550 vs. ≥350 to 450 cells/mm^3** Progression to AIDS or death: HR, 0.90 (95% CI, 0.76 to 1.29)
Lodi 2015[87]	**≥500 vs. <500 cells/mm^3** All-cause mortality: RR, 0.98 (95% CI, 0.97 to 0.99) **≥500 vs. <350 cells/mm^3** All-cause mortality: RR, 0.94 (95% CI, 0.91 to 0.97)	**≥500 vs. <500 cells/mm^3** Progression to AIDS or death: RR, 0.94 (95% CI, 0.93 to 0.94) **≥500 vs. <350 cells/mm^3** Progression to AIDS or death: RR, 0.83 (95% CI, 0.81 to 0.85) **Subgroup of patients with baseline CD4 count >500 cells/mm^3 vs. entire sample** Progression to AIDS or death: 7.1% vs. 4.9%; RR, 1.52 (95% CI, 1.34 to 1.77)
Lodi 2017[95]	**≥500 vs. <500 cells/mm^3** All-cause mortality, general HIV population: RR, 0.97 (95% CI, 0.94 to 0.99) All-cause mortality, general HIV population patients with CD4 ≥500 cells/mm^3: RR, 0.76 (95% CI, 0.58 to 0.97) All-cause mortality, VA population: RR, 0.95 (95% CI, 0.93 to 0.98) **≥500 vs. <350 cells/mm^3** All-cause mortality, general HIV population: RR, 0.93 (95% CI, 0.87 to 0.98) All-cause mortality, general HIV population patients with CD4 ≥500 cells/mm^3: RR, 0.64 (95% CI, 0.41 to 0.95) All-cause mortality, VA population: RR, 0.90 (95% CI, 0.85 to 0.95)	NR
Lima 2015[96]	All-cause mortality, probability (IQR): CD4 <350 cells/mm^3, 2007–2012: 0.05 (0.03 to 0.08) CD4 ≥350 cells/mm^3, 2007–2012: 0.02 (0.01 to 0.04) CD4 <500 cells/mm^3, 2007–2012: 0.05 (0.03 to 0.02) CD4 ≥500 cells/mm^3, 2007–2012: 0.01 (0.01 to 0.02)	AIDS-defining illness, probability (IQR): CD4 <350 cells/mm^3, 2007–2012: 0.05 (0.03 to 0.08) CD4 ≥350 cells/mm^3, 2007–2012: 0.03 (0.01 to 0.05) CD4 <500 cells/mm^3, 2007–2012: 0.03 (0.01 to 0.04) CD4 ≥500 cells/mm^3, 2007–2012: 0.01 (0.00 to 0.01)

Table 1. Cohort Studies of Early vs. Delayed Antiretroviral Therapy

Study	Mortality	AIDS-related events
Edwards 2015[88]	**<500 vs. <350 cells/mm^3** 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 2. Characteristics of Studies Published Since the Prior USPSTF Review of Immediate vs. Delayed Antiretroviral Therapy

Study design	Study name Author, year Duration Geographic setting N	Intervention groups	Population
RCT	*START* Lundgren 2015[85] 3 years Africa, Europe, Israel, North America, South America, Mexico, Australia n=4,685	A. Immediate ART (n=2,326): CD4 >500 cells/mm^3 B. Deferred ART (n-2,359): CD4 <350 cells/mm^3	**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^3
RCT	*HPTN 052* Grinsztejn 2014[90] 2 to 5.5 years* Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, United States, Zimbabwe n=1,763	A. Immediate ART (n=886): CD4 ≥350 to <550 cells/mm^3 B. Delayed ART (n=877): CD4 ≤250 cells/mm^3	**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^3
RCT	*TEMPRANO ANRS 12136 Study* TEMPRANO ANRS Study Group 2015[86] 30 months Ivory Coast n=2,076	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^3 or WHO clinical stage 4; or one CD4 count 200 to 350 cells/mm^3 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^3 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^3, 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^3 (IQR, 369 to 584)

Table 2. Characteristics of Studies Published Since the Prior USPSTF Review of Immediate vs. Delayed Antiretroviral Therapy

Study design	Study name Author, year Duration Geographic setting N	Intervention groups	Population
Cohort	*HIV CAUSAL Collaboration* Lodi 2015[87] France, Greece, The Netherlands, Spain, Switzerland, United Kingdom, United States 7 years n=55,826	A. Initiation of ART at ≥500 cells/mm^3 B. Initiation of ART at <500 cells/mm^3 C. Initiation of ART at <350 cells/mm^3	**A vs. B** 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[95] Brazil, Canada, France, Greece, The Netherlands, Spain, Switzerland, United Kingdom, United States 5 years n=9,599	A. Initiation of ART at ≥500 cells/mm^3 B. Initiation of ART at <500 cells/mm^3 C. Initiation of ART at <350 cells/mm^3	*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/mm^3): 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 $\log_{10}$ copies/mL **VA population** Age 56 years (IQR, 53 to 60) 2% female CD4 count (cells/mm^3): 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 $\log_{10}$ copies/mL
Cohort	Lima 2015[96] Canada 5 years n=4,120	A. Initiation of ART at ≥500 cells/mm^3 B. Initiation of ART at <500 cells/mm^3 C. Initiation of ART at ≥350 cells/mm^3 D. Initiation of ART at <350 cells/mm^3	*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/mm^3): 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

Study design	Study name Author, year Duration Geographic setting N	Intervention groups	Population
Cohort	Edwards 2015[88] United States 10 years n=3,532	A. Initiation of ART at <500 cells/mm^3 B. Initiation of ART at <350 cells/mm^3	*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^3

*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

Baseline CD4 count	Study name	Primary composite outcome	Mortality	AIDS-related events	Tuberculosis or bacterial infection	HIV transmission
>500 cells/mm^3	START[85]	All-cause mortality, serious AIDS-related events, and serious non–AIDS-related events: RR, 0.44 (95% CI, 0.31 to 0.63)	All-cause mortality: RR, 0.58 (95% CI, 0.29 to 1.18) Mortality due to AIDS-related event: RR, 0.25 (95% CI, 0.03 to 2.27)	Serious AIDS-related event: RR, 0.28 (95% CI, 0.16 to 0.51)	Tuberculosis: RR, 0.30 (95% CI, 0.12 to 0.76) Grade 4 bacterial infection: RR, 0.39 (95% CI, 0.21 to 0.73)	NR
>500 cells/mm^3	TEMPRANO ANRS[86]	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)	All-cause mortality: RR, 0.79 (95% CI, 0.24 to 2.57)	Progression to AIDS: RR, 0.55 (95% CI, 0.29 to 1.05)	Tuberculosis: RR, 0.54 (95% CI, 0.27 to 1.09) Invasive bacterial disease: RR, 0.59 (95% CI, 0.20 to 1.80)	NR
≥350 to 550 cells/mm^3	HPTN 052, 2011*[55,90]	All-cause mortality, serious AIDS-related events, and serious non–AIDS-related events: RR, 0.73 (95% CI, 0.53 to 1.02)	All-cause mortality, 1.7-year followup: RR, 0.76 (95% CI, 0.34 to 1.73) All-cause mortality, 2.1-year followup: RR, 0.72 (95% CI, 0.33 to 1.57) Mortality due to AIDS-related event: RR, 0.25 (95% CI, 0.03 to 2.20)	Any AIDS-related event: RR, 0.65 (95% CI, 0.4 to 0.95)	Tuberculosis: RR, 0.49 (95% CI, 0.28 to 0.88) Serious bacterial infection: RR, 1.52 (95% CI, 0.76 to 3.04)	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) 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)
≥350 to 500 cells/mm^3	SMART*[89]	All-cause mortality or opportunistic disease: RR, 0.31 (95% CI, 0.11 to 0.83)	All-cause mortality: RR, 0.26 (95% CI, 0.05 to 1.25)	Any opportunistic disease: RR, 0.33 (95% CI, 0.11 to 1.03)	Tuberculosis: RR, 0.46 (95% CI, 0.04 to 5.02)	NR

*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 Managment of Antiretroviral Therapy; START=Strategic Timing of Antiretroviral Treatment.

Table 4. New Studies on the Association Between Antiretroviral Therapy and Long-Term Cardiovascular Harms

Author, Year Study Quality	Study details N Overall duration of followup	Intervention	Results
D:A:D Study Monforte, 2013[104] Good	Prospective analysis of 11 cohorts Europe, Australia, and United States N=49,734 Participants were followed for a total of 301,907 person-years of followup for MI, and 303,118 person-years of followup for stroke	ATV, boosted or unboosted by RTV	MI: Overall events: 844/49,734; incidence, 0.28/100 person-years followup (95% CI, 0.26 to 0.30) >3 years exposure to ATV: 0.20 (95% CI, 0.12 to 0.32)/100 person-years followup No exposure to ATV: 0.28 (95% CI, 0.26 to 0.30)/100 person-years followup 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 follow up, 95% CI 0.16 to 0.19 >3 years exposure to ATV: 0.17 (95% CI 0.10 to 0.27)/100 person years followup No exposure to ATV: 0.17 (95% CI 0.16 to 0.19)/100 person years follow up 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)
D:A:D Study Sabin, 2016[102] Good	Prospective analysis of 11 cohorts Europe, Australia, United States N=49,717 Median followup: 7 years	ABC vs. non-ABC	MI: 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 Overall: 941/367,559 person-years (rate, 0.26 [95% CI, 0.24 to 0.27])/100 person-years Currently on ABC: 341/71,971 person-years (rate, 0.47 [95% CI, 0.42 to 0.52])/100 person-years Currently not on ABC: 600/295,642 person-years (rate, 0.20 [95% CI, 0.19 to 0.22])/100 person-years Stratified by calendar period (D:A:D publication from 2008 showed 90% increase in risk of MI for patients on ABC) Pre-March 2008: Currently on ABC: 247/40,833 person-years (rate, 0.61 [95% CI, 0.53 to 0.68])/100 person-years Currently not on ABC: 425/169,417 person-years (rate, 0.25 [95% CI, 0.23 to 0.28])/100 person-years Post-March 2008 Currently on ABC: 94/31,084 person-years (rate, 0.30 [95% CI, 0.24 to 0.36])/100 person-years Currently not on ABC: 175/126,225 person-years (rate, 0.14 [95% CI, 0.12 to 0.16])/100 person-years 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

Table 4. New Studies on the Association Between Antiretroviral Therapy and Long-Term Cardiovascular Harms

Author, Year Study Quality	Study details N Overall duration of followup	Intervention	Results
Desai 2015[103]	Retrospective analysis of VA data N=24,510 Mean duration of followup varied according to study drug (results for interventions with <2 years followup not shown)	Current ART exposure vs. nonexposure	Cardiovascular event (MI, stroke, or cardiovascular procedure) ABC: OR, 1.50 (95% CI, 1.26 to 1.79) EFV: OR, 1.40 (95% CI, 1.19 to 1.66) 3TC: OR, 1.53 (95% CI, 1.34 to 1.75) NVP: OR, 0.91 (95% CI, 0.70 to 1.18) D4T: OR, 1.14 (95% CI, 0.95 to 1.37) Tenofovir: OR, 1.10 (95% CI, 0.93 to 1.30) ZDV: OR, 1.41 (95% CI, 1.22 to 1.63)
Ding, 2012[101] U.S. Food and Drug Administration Fair	Systematic review of 26 RCTs included in meta-analysis N=9,868 Mean followup (ABC vs. non-ABC): 1.43 vs. 1.49 person-years	ABC vs. non-ABC	MI events: 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) 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) 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)

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 5. Summary of Evidence

KQ	No. of studies (k) Number of participants (n) 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
KQ 1. Benefits of HIV screening vs. no screening	No studies	--	--	--	--	--	--
KQ 2. Yield of repeat vs. one-time HIV screening, or HIV screening at different intervals	No studies	--	--	--	--	--	--
KQ 3. Harms of HIV screening vs. no screening	No studies	--	--	--	--	--	--
KQ 4. Benefits of immediate vs. delayed ART • CD4 count >500 cells/mm^3	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])	Four observational studies in the prior USPSTF review found inconsistent evidence on effects of initiation of ART in patients with CD4 counts >500 cells/mm^3 vs. delayed initiation. Two new RCTs found initiation of ART in patients with CD4 counts >500 cells/mm^3 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 >500 cells/mm^3 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]).	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.	Fair	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 >500 cells/mm^3 (41% of study population).	Moderate	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/mm^3 in one trial and in the other trial baseline CD4 count ranged from 500 to 800 mm/cells^3 (average CD4 count not reported in the subgroup of patients with a CD4 count >500 cells/mm^3 at baseline). Patients were randomized between 2008 and 2013 in the trials. The observational studies were conducted in U.S. and European cohorts.

Table 5. Summary of Evidence

KQ	No. of studies (k) Number of participants (n) 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
KQ 4. Benefits of immediate vs. delayed ART • CD4 count >350 to <500 or 550 cells/mm^3	2012 USPSTF review: k=6 (2 RCTs [n=2,012] and 4 observational studies [n=71,460]) New evidence: k=1 observational study (n=3,532), plus longer-term followup from RCT included in 2012 review	Two RCTs in the prior USPSTF review found initiation of ART at CD4 counts >350 cells/mm^3 associated with decreased risk of death or AIDS events after ~1.5 years compared with initiation at CD4 counts <250 cells/mm^3 (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]). Longer-term (2.1 years) followup from one RCT included in the prior review reported decreased risk of AIDS-related events (RR, 0.65 [95% CI, 0.44 to 0.95]); effects on the primary composite outcome (death, AIDS events, and non-AIDS events) favored early initiation of ART, but the effect was not statistically significant (RR, 0.73 [95% CI, 0.53 to 1.02]); beneficial effects on HIV transmission remained present at 5.5 years followup (RR, 0.07 [95% CI, 0.02 to 0.22] for virologically-linked transmission). One observational study reported consistent findings on clinical outcomes.	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/mm^3 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/mm^3. 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

KQ	No. of studies (k) Number of participants (n) 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
KQ 5. Long-term harms of ART	2012 USPSTF review: k=4 observational studies (n>60,500*) 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)	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]).	Some inconsistency between RCT and observational data regarding cardiovascular risks of ABC. Findings reasonably precise. No reporting bias detected.	Fair	All studies were observational.	Low to moderate	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.

*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

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

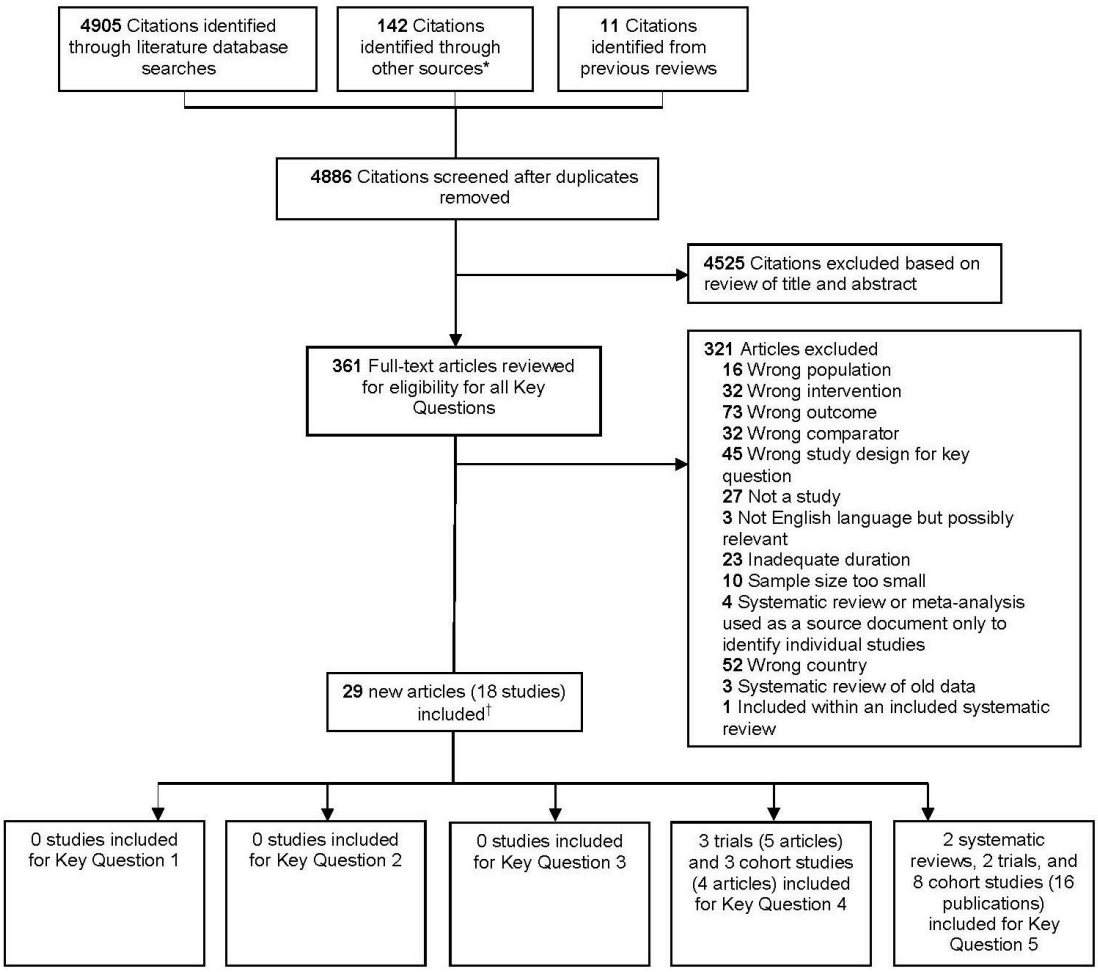
Appendix A2. Inclusion and Exclusion Criteria

Category	Include	Exclude
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



*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

Arribas JR, Thompson M, Sax PE, et al. Brief report: Randomized, double-blind comparison of tenofovir alafenamide (TAF) vs tenofovir disoproxil fumarate (TDF), each coformulated eith elvitegravir, cobicistat, and emtricitabine (E/C/F) for initial HIV-1 treatment: Week 144 results. J Acquir Immune Defic Syndr. 2017;75(2):211-8. doi: 10.1097/QAI.0000000000001350. PMID: 28282300.

Borges AH, Hoy J, Florence E, et al. Antiretrovirals, fractures, and osteonecrosis in a large international HIV cohort. Clin Infect Dis. 2017;64(10):1413-21. doi: 10.1093/cid/cix167. PMID: 28329090.

Bruyand M, Ryom L, Shepherd L, et al. Cancer risk and use of protease inhibitor or nonnucleoside reverse transcriptase inhibitor-based combination antiretroviral therapy: the D: A: D study. J Acquir Immune Defic Syndr. 2015;68(5):568-77. doi: 10.1097/qai.0000000000000523. PMID: 25763785.

Chang JL, Tsai AC, Musinguzi N, et al. Depression and suicidal ideation among HIV-infected adults receiving efavirenz versus nevirapine in Uganda: A prospective cohort study. Ann Intern Med. 2018 doi: 10.7326/m17-2252. PMID: 29946683.

Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. N Engl J Med. 2016;375(9):830-9. doi: 10.1056/NEJMoa1600693. PMID: 27424812.

Desai M, Joyce V, Bendavid E, et al. Risk of cardiovascular events associated with current exposure to HIV antiretroviral therapies in a US veteran population. Clin Infect Dis. 2015;61(3):445-52. doi: 10.1093/cid/civ316. PMID: 25908684.

Ding X, Andraca-Carrera E, Cooper C, et al. No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis. J Acquir Immune Defic Syndr. 2012;61(4):441-7. doi: 10.1097/QAI.0b013e31826f993c. PMID: 22932321.

Edwards JK, Cole SR, Westreich D, et al. Age at entry into care, timing of antiretroviral therapy initiation, and 10-year mortality among HIV-seropositive adults in the United States. Clin Infect Dis. 2015;61(7):1189-95. doi: 10.1093/cid/civ463. PMID: 26082505.

Ford N, Shubber Z, Pozniak A, et al. Comparative safety and neuropsychiatric adverse events associated with efavirenz use in first-line antiretroviral therapy: A systematic review and meta-analysis of randomized trials. J Acquir Immune Defic Syndr. 2015;69(4):422-9. doi: 10.1097/QAI.0000000000000606. PMID: 25850607.

Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. Lancet Infect Dis. 2014;14(4):281-90. doi: 10.1016/s1473-3099(13)70692-3. PMID: 24602844.

Kovari H, Sabin CA, Ledergerber B, et al. Antiretroviral drug-related liver mortality among HIV-positive persons in the absence of hepatitis B or C virus coinfection: the data collection on adverse events of anti-HIV drugs study. Clin Infect Dis. 2013;56(6):870-9. doi: 10.1093/cid/cis919. PMID: 23090925.

Kowalska JD, Reekie J, Mocroft A, et al. Long-term exposure to combination antiretroviral therapy and risk of death from specific causes: no evidence for any previously unidentified increased risk due to antiretroviral therapy. AIDS. 2012;26(3):315-23. doi: 10.1097/QAD.0b013e32834e8805. PMID: 22112597.

Laprise C, Baril J-G, Dufresne S, et al. Association between tenofovir exposure and reduced kidney function in a cohort of HIV-positive patients: results from 10 years of follow-up. Clin Infect Dis. 2013;56(4):567-75. doi: 10.1093/cid/cis937. PMID: 23143096.

Lima VD, Reuter A, Harrigan PR, et al. Initiation of antiretroviral therapy at high CD4+ cell counts is associated with positive treatment outcomes.[Erratum appears in AIDS. 2016 Feb 20;30(4):677]. AIDS. 2015;29(14):1871-82. doi: 10.1097/QAD.0000000000000790. PMID: 26165354.

Lodi S, Costagliola D, Sabin C, et al. Effect of immediate initiation of antiretroviral treatment in HIV-positive individuals aged 50 years or older. J Acquir Immune Defic Syndr. 2017;76(3):311-8. doi: 10.1097/qai.0000000000001498. PMID: 28746165.

Lodi S, Phillips A, Logan R, et al. Comparative effectiveness of immediate antiretroviral therapy versus CD4-based initiation in HIV-positive individuals in high-income countries: observational cohort study. Lancet HIV. 2015;2(8):e335-43. doi: 10.1016/S2352-3018(15)00108-3. PMID: 26423376.

Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;373(9):795-807. doi: 10.1056/NEJMoa1506816. PMID: 26192873.

Mocroft A, Lundgren JD, Ross M, et al. Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: a prospective international cohort study. Lancet HIV. 2016;3(1):e23-32. doi: 10.1016/s2352-3018(15)00211-8. PMID: 26762990.

Monforte A, Reiss P, Ryom L, et al. Atazanavir is not associated with an increased risk of cardio- or cerebrovascular disease events. AIDS. 2013;27(3):407-15. doi: 10.1097/QAD.0b013e32835b2ef1. PMID: 23291539.

Appendix A4. Included Studies List

Nkhoma ET, Coumbis J, Farr AM, et al. No evidence of an association between efavirenz exposure and suicidality among HIV patients initiating antiretroviral therapy in a retrospective cohort study of real world data. Medicine (Baltimore). 2016;95(3):e2480. doi: 10.1097/MD.0000000000002480. PMID: 26817882.

Nkhoma ET, Rosenblatt L, Myers J, et al. Real-world assessment of renal and bone safety among patients with HIV infection exposed to tenofovir disoproxil fumarate-containing single-tablet regimens. PLoS One. 2016;11(12):e0166982. doi: 10.1371/journal.pone.0166982. PMID: 27941989.

O'Connor J, Vjecha MJ, Phillips AN, et al. Effect of immediate initiation of antiretroviral therapy on risk of severe bacterial infections in HIV-positive people with CD4 cell counts of more than 500 cells per muL: secondary outcome results from a randomised controlled trial. Lancet HIV. 2017;4(3):e105-e12. doi: 10.1016/s2352-3018(16)30216-8. PMID: 28063815.

Rockstroh JK, DeJesus E, Lennox JL, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. J Acquir Immune Defic Syndr. 2013;63(1):77-85. doi: 10.1097/QAI.0b013e31828ace69. PMID: 23412015.

Ryom L, Lundgren JD, De Wit S, et al. Use of antiretroviral therapy and risk of end-stage liver disease and hepatocellular carcinoma in HIV-positive persons. AIDS. 2016;30(11):1731-43. doi: 10.1097/qad.0000000000001018. PMID: 26752282.

Ryom L, Mocroft A, Kirk O, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. J Infect Dis. 2013;207(9):1359-69. doi: 10.1093/infdis/jit043. PMID: 23382571.

Sabin CA, Reiss P, Ryom L, et al. Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with HIV? A cohort collaboration. BMC Med. 2016;14:61. doi: 10.1186/s12916-016-0588-4. PMID: 27036962.

Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS. 2012;26(7):867-75. doi: 10.1097/QAD.0b013e328351f68f. PMID: 22313955.

Smith C, Ryom L, d'Arminio Monforte A, et al. Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study. J Int AIDS Soc. 2014;17(4 Suppl 3):19512. doi: 10.7448/IAS.17.4.19512. PMID: 25394021.

TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med. 2015;373(9):808-22. doi: 10.1056/NEJMoa1507198. PMID: 26193126.

Appendix A5. Excluded Studies List

Achhra AC, Mocroft A, Ross MJ, et al. Kidney disease in antiretroviral-naive HIV-positive adults with high CD4 counts: prevalence and predictors of kidney disease at enrolment in the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med. 2015 Apr;16 Suppl 1:55-63. doi: 10.1111/hiv.12234. PMID: 25711324. Excluded: Wrong study design for Key Question.

Adebayo AM, Ilesanmi OS, Omotoso BA, et al. Disclosure to sexual partner and condom use among HIV positive clients attending ART clinic at a tertiary health facility in South West Nigeria. Pan Afr Med J. 2014;18:245. doi: 10.11604/pamj.2014.18.245.4371. PMID: 25426203. Excluded: Wrong country.

Adetokunboh OO, Schoonees A, Balogun TA, et al. Efficacy and safety of abacavir-containing combination antiretroviral therapy as first-line treatment of HIV infected children and adolescents: a systematic review and meta-analysis. BMC Infect Dis. 2015;15:469. doi: 10.1186/s12879-015-1183-6. PMID: 26502899. Excluded: Wrong country.

Adewumi OM, Odaibo GN, Olaleye OD. Baseline CD4 T cell level predicts recovery rate after initiation of ART in HIV infected Nigerians. J Immunoassay Immunochem. 2016;37(2):109-18. doi: 10.1080/15321819.2015.1057738. PMID: 26065646. Excluded: Wrong country.

Ahmadi M, Khalili H, Abbasian L, et al. Effect of valerian in preventing neuropsychiatric adverse effects of efavirenz in HIV-positive patients: A pilot randomized, placebo-controlled clinical trial. Ann Pharmacother. 2017 Jun;51(6):457-64. doi: 10.1177/1060028017696105. PMID: 28478716. Excluded: Wrong intervention.

Aho I, Kivela P, Haukka J, et al. Declining prevalence of cytological squamous intraepithelial lesions of the cervix among women living with well-controlled HIV - Most women living with HIV do not need annual PAP smear screening. Acta Obstet Gynecol Scand. 2017 Nov;96(11):1330-7. doi: 10.1111/aogs.13207. PMID: 28832899. Excluded: Wrong study design for Key Question.

Amin J, Boyd MA, Kumarasamy N, et al. Raltegravir non-inferior to nucleoside based regimens in second-line therapy with lopinavir/ritonavir over 96 weeks: a randomised open label study for the treatment of HIV-1 infection.[Erratum appears in PLoS One. 2015;10(10):e0140623; PMID: 26451848]. PLoS One. 2015;10(2):e0118228. doi: 10.1371/journal.pone.0118228. PMID: 25723472. Excluded: Wrong population.

Anderson D, DeMasi R, DeLaitsch L, et al. Week 96 outcomes of patients with less treatment experience versus more treatment experience receiving etravirine in the DUET trials. Curr HIV Res. 2012 Apr;10(3):256-61. PMID: 22497697. Excluded: Wrong comparator.

Anglemyer A, Rutherford GW, Easterbrook PJ, et al. Early initiation of antiretroviral therapy in HIV-infected adults and adolescents: a systematic review. AIDS. 2014 Mar;28 Suppl 2:S105-18. doi: 10.1097/QAD.0000000000000232. PMID: 24849469. Excluded: Systematic review or meta-analysis used as a source document only to identify individual studies.

Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. N Engl J Med. 2016 Dec 01;375(22):2121-32. doi: 10.1056/NEJMoa1506110. PMID: 26900902. Excluded: Wrong intervention.

Baker JV, Engen NW, Huppler Hullsiek K, et al. Assessment of arterial elasticity among HIV-positive participants with high CD4 cell counts: a substudy of the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med. 2015 Apr;16 Suppl 1:109-18. doi: 10.1111/hiv.12239. PMID: 25711329. Excluded: Wrong outcome.

Banhegyi D, Katlama C, da Cunha CA, et al. Week 96 efficacy, virology and safety of darunavir/r versus lopinavir/r in treatment-experienced patients in TITAN. Curr HIV Res. 2012 Mar;10(2):171-81. PMID: 22339125. Excluded: Wrong population.

Bavinger C, Bendavid E, Niehaus K, et al. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. PLoS One. 2013;8(3):e59551. doi: 10.1371/journal.pone.0059551. PMID: 23555704. Excluded: Systematic review of old data.

Bavinton B, Grinsztejn B, Phanuphak N, et al. HIV treatment prevents HIV transmission in male serodiscordant couples in Australia, Thailand and Brazil. J Int AIDS Soc. 2017. Int AIDS Society Avenue de France 23, Geneva, 1202, Switzerland; 20. Excluded: Wrong study design for Key Question.

Bavinton BR, Jin F, Prestage G, et al. The Opposites Attract Study of viral load, HIV treatment and HIV transmission in serodiscordant homosexual male couples: design and methods. BMC Public Health. 2014 Sep 4;14:917. doi: 10.1186/1471-2458-14-917. PMID: 25190360. Excluded: Wrong study design for Key Question.

Bedimo R, Maalouf NM, Zhang S, et al. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS. 2012 Apr 24;26(7):825-31. doi: 10.1097/QAD.0b013e32835192ae. PMID: 22301411. Excluded: Wrong study design for Key Question.

Behrens G, Rijnders B, Nelson M, et al. Rilpivirine versus efavirenz with emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV-1-infected patients with HIV-1 RNA <100,000 copies/mL: week 96 pooled ECHO/THRIVE subanalysis. AIDS Patient Care STDS. 2014 Apr;28(4):168-75. doi: 10.1089/apc.2013.0310. PMID: 24660840. Excluded: Sample size too small.

Appendix A5. Excluded Studies List

Benoit AC, Younger J, Beaver K, et al. Increased mortality among Indigenous persons in a multisite cohort of people living with HIV in Canada. Can J Public Health. 2017 Jun 16;108(2):e169-e75. doi: 10.17269/cjph.108.5708. PMID: 28621653. Excluded: Wrong comparator.

Bermudez-Aza EH, Shetty S, Ousley J, et al. Long-term clinical, immunological and virological outcomes of patients on antiretroviral therapy in southern Myanmar. PLoS ONE. 2018;13(2):e0191695. doi: 10.1371/journal.pone.0191695. PMID: 29420652. Excluded: Wrong country.

Bernardino JI, Mocroft A, Mallon PW, et al. Bone mineral density and inflammatory and bone biomarkers after darunavir-ritonavir combined with either raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults with HIV-1: a substudy of the NEAT001/ANRS143 randomised trial. Lancet HIV. 2015 Nov;2(11):e464-73. doi: 10.1016/S2352-3018(15)00181-2. PMID: 26520926. Excluded: Sample size too small.

Blick G, Greiger-Zanlungo P, Gretz S, et al. Long-term efficacy and safety of once-daily fosamprenavir 1400 mg boosted by ritonavir 100 mg: the BOLD100 study. Int J STD AIDS. 2012 Mar;23(3):e18-22. doi: 10.1258/ijsa.2009.009161. PMID: 22581890. Excluded: Wrong outcome.

Boettiger DC, Sabin CA, Grulich A, et al. Is nelfinavir exposure associated with cancer incidence in HIV-positive individuals? AIDS. 2016 Jun 19;30(10):1629-37. doi: 10.1097/qad.0000000000001053. PMID: 26854812. Excluded: Wrong intervention.

Bor J, Ahmed S, Fox MP, et al. Effect of eliminating CD4-count thresholds on HIV treatment initiation in South Africa: An empirical modeling study. PLoS One. 2017;12(6):e0178249. doi: 10.1371/journal.pone.0178249. PMID: 28617805. Excluded: Wrong study design for Key Question.

Bottero J, Boyd A, Gozlan J, et al. Simultaneous hiv-hbv-hcv point-of-care tests improve the screening outcomes. J Hepatol. 2015;62(22). Excluded: Wrong outcome.

Brouwer ES, Napravnik S, Eron JJ, Jr., et al. Effects of combination antiretroviral therapies on the risk of myocardial infarction among HIV patients. Epidemiology. 2014 May;25(3):406-17. doi: 10.1097/EDE.0000000000000041. PMID: 24713880. Excluded: Sample size too small.

Brown TT, Moser C, Currier JS, et al. Changes in bone mineral density after initiation of antiretroviral treatment with tenofovir disoproxil fumarate/emtricitabine plus atazanavir/ritonavir, darunavir/ritonavir, or raltegravir. J Infect Dis. 2015 Oct 15;212(8):1241-9. doi: 10.1093/infdis/jiv194. PMID: 25948863. Excluded: Sample size too small.

Bunupuradah T, Phupitakphol T, Sophonphan J, et al. Prevalence of persistent renal dysfunction in perinatally HIV-infected Thai adolescents. Pediatr Infect Dis J. 2018 Jan;37(1):66-70. doi: 10.1097/INF.0000000000001684. PMID: 28719505. Excluded: Wrong country.

Burt RD, Tinsley J, Glick SN. A decline in HIV testing among persons who inject drugs in the Seattle area, 2004-2015. J Acquir Immune Defic Syndr. 2017 Jul 01;75 Suppl 3:S346-S51. doi: 10.1097/QAI.0000000000001409. PMID: 28604437. Excluded: Wrong outcome.

Campbell TB, Smeaton LM, Kumarasamy N, et al. Efficacy and safety of three antiretroviral regimens for initial treatment of HIV-1: a randomized clinical trial in diverse multinational settings. PLoS Med. 2012;9(8):e1001290. PMID: 22936892. Excluded: Wrong country.

Capetti A, Landonio S, Meraviglia P, et al. 96 Week follow-up of HIV-infected patients in rescue with raltegravir plus optimized backbone regimens: a multicentre Italian experience. PLoS One. 2012;7(7):e39222. doi: 10.1371/journal.pone.0039222. PMID: 22808029. Excluded: Wrong population.

Capetti A, Meraviglia P, Landonio S, et al. Four years data of raltegravir-based salvage therapy in HIV-1-infected, treatment-experienced patients: the SALIR-E Study. Int J Antimicrob Agents. 2014 Feb;43(2):189-94. doi: 10.1016/j.ijantimicag.2013.10.013. PMID: 24315315. Excluded: Wrong population.

Capetti AF, Cossu MV, Paladini L, et al. Dolutegravir plus rilpivirine dual therapy in treating HIV-1 infection. Expert Opin Pharmacother. 2018 Jan;19(1):65-77. doi: 10.1080/14656566.2017.1417984. PMID: 29246084. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Caro-Vega Y, del Rio C, Lima VD, et al. Estimating the impact of earlier ART initiation and increased testing coverage on HIV transmission among men who have sex with men in Mexico using a mathematical model. PLoS One. 2015;10(8):e0136534. doi: 10.1371/journal.pone.0136534. PMID: 26302044. Excluded: Wrong study design for Key Question.

Carr A, Grund B, Neuhaus J, et al. Prevalence of and risk factors for low bone mineral density in untreated HIV infection: a substudy of the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med. 2015 Apr;16 Suppl 1:137-46. doi: 10.1111/hiv.12242. PMID: 25711332. Excluded: Wrong study design for Key Question.

Appendix A5. Excluded Studies List

Caseiro MM, Nelson M, Diaz RS, et al. Vicriviroc plus optimized background therapy for treatment-experienced subjects with CCR5 HIV-1 infection: final results of two randomized phase III trials. J Infect. 2012 Oct;65(4):326-35. doi: 10.1016/j.jinf.2012.05.008. PMID: 22634184. Excluded: Wrong population.

Castagna A, Maggiolo F, Penco G, et al. Dolutegravir in antiretroviral-experienced patients with raltegravir- and/or elvitegravir-resistant HIV-1: 24-week results of the phase III VIKING-3 study. J Infect Dis. 2014 Aug 1;210(3):354-62. doi: 10.1093/infdis/jiu051. PMID: 24446523. Excluded: Wrong study design for Key Question.

Castelnuovo B, Kiragga A, Musaazi J, et al. Outcomes in a cohort of patients started on antiretroviral treatment and followed up for a decade in an urban clinic in Uganda. PLoS One. 2015;10(12):e0142722. doi: 10.1371/journal.pone.0142722. PMID: 26642214. Excluded: Wrong country.

Castilho JL, Melekhin VV, Sterling TR. Sex differences in HIV outcomes in the highly active antiretroviral therapy era: a systematic review. AIDS Res Hum Retroviruses. 2014 May;30(5):446-56. doi: 10.1089/AID.2013.0208. PMID: 24401107. Excluded: Wrong comparator.

Centers for Disease Control and Prevention. Diagnoses of HIV infection among adults aged 50 years and older in the United States and dependent areas 2011-2016. 2018. https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-23-5.pdf. Accessed January 11, 2019. Excluded: Not a study.

Cettomai D, Kwasa JK, Birbeck GL, et al. Screening for HIV-associated peripheral neuropathy in resource-limited settings. Muscle Nerve. 2013 Oct;48(4):516-24. doi: 10.1002/mus.23795. PMID: 24037693. Excluded: Wrong country.

Chadwick DR, Sarfo FS, Kirk ES, et al. Tenofovir is associated with increased tubular proteinuria and asymptomatic renal tubular dysfunction in Ghana. BMC Nephrol. 2015;16:195. doi: 10.1186/s12882-015-0192-4. PMID: 26627687. Excluded: Wrong country.

Chen J, Han X, An M, et al. Immunological and virological benefits resulted from short-course treatment during primary HIV infection: a meta-analysis. PLoS One. 2013;8(12):e82461. doi: 10.1371/journal.pone.0082461. PMID: 24324793. Excluded: Wrong outcome.

Chen M, Dou Z, Wang L, et al. Gender eifferences in outcomes of antiretroviral treatment among HIV-infected patients in China: A retrospective cohort study, 2010-2015. J Acquir Immune Defic Syndr. 2017 Nov 01;76(3):281-8. doi: 10.1097/QAI.0000000000001500. PMID: 28708809. Excluded: Wrong country.

Chen R, Scherzer R, Hsue PY, et al. Association of tenofovir use with risk of incident heart failure in HIV-infected patients. J Am Heart Assoc. 2017 Apr 24;6(4)doi: 10.1161/jaha.116.005387. PMID: 28438737. Excluded: Wrong outcome.

Chen YQ, Masse B, Wang L, et al. Statistical considerations for the HPTN 052 Study to evaluate the effectiveness of early versus delayed antiretroviral strategies to prevent the sexual transmission of HIV-1 in serodiscordant couples. Contemp Clin Trials. 2012 Nov;33(6):1280-6. doi: 10.1016/j.cct.2012.07.007. PMID: 22813645. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Cheret A, Nembot G, Melard A, et al. Intensive five-drug antiretroviral therapy regimen versus standard triple-drug therapy during primary HIV-1 infection (OPTIPRIM-ANRS 147): a randomised, open-label, phase 3 trial. Lancet Infect Dis. 2015 Apr;15(4):387-96. doi: 10.1016/S1473-3099(15)70021-6. PMID: 25701561. Excluded: Wrong comparator.

Clotet B, Feinberg J, van LJ, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet. 2014;383(9936):2222-31. PMID: 24698485. Excluded: Inadequate duration.

Cohen CJ, Molina JM, Cassetti I, et al. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials. AIDS. 2013 Mar 27;27(6):939-50. doi: 10.1097/QAD.0b013e32835cee6e. PMID: 23211772. Excluded: Wrong outcome.

Conway DP, Holt M, McNulty A, et al. Multi-centre evaluation of the Determine HIV Combo assay when used for point of care testing in a high risk clinic-based population.[Erratum appears in PLoS One. 2014;9(7):e103399]. PLoS One. 2014;9(4):e94062. doi: 10.1371/journal.pone.0094062. PMID: 24714441. Excluded: Wrong outcome.

Cooper DA, Heera J, Ive P, et al. Efficacy and safety of maraviroc vs. efavirenz in treatment-naive patients with HIV-1: 5-year findings. AIDS. 2014 Mar 13;28(5):717-25. doi: 10.1097/QAD.0000000000000131. PMID: 24983542. Excluded: Wrong comparator.

Copeland B, Shah B, Wheatley M, et al. Diagnosing HIV in men who have sex with men: an emergency department's experience. AIDS Patient Care STDS. 2012 Apr;26(4):202-7. doi: 10.1089/apc.2011.0303. PMID: 22356726. Excluded: Wrong study design for Key Question.

Cornell M, Schomaker M, Garone DB, et al. Gender differences in survival among adult patients starting antiretroviral therapy in South Africa: a multicentre cohort study. PLoS Med. 2012;9(9):e1001304. PMID: 22973181. Excluded: Wrong country.

Appendix A5. Excluded Studies List

Corrao S, Prestileo T, Di Lorenzo F. Antiretroviral therapy in early HIV infection [Comment on "Initiation of antiretroviral therapy in early asymptomatic HIV infection"]. N Engl J Med. 2016 Jan 28;374(4):393-4. doi: 10.1056/NEJMc1513311#SA2. PMID: 26816021. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Costello JF, Sliney A, MacLeod C, et al. Implementation of routine HIV testing in an acute care hospital in Rhode Island: a nurse-initiated opt-out pilot project. J Assoc Nurses AIDS Care. 2013 Sep-Oct;24(5):460-8. doi: 10.1016/j.jana.2012.09.007. PMID: 23270811. Excluded: Wrong study design for Key Question.

Cruciani M, Mengoli C, Malena M, et al. Virological efficacy of abacavir: systematic review and meta-analysis. J Antimicrob Chemother. 2014 Dec;69(12):3169-80. doi: 10.1093/jac/dku279. PMID: 25074854. Excluded: Systematic review of old data.

da Motta LR, Vanni AC, Kato SK, et al. Evaluation of five simple rapid HIV assays for potential use in the Brazilian national HIV testing algorithm. J Virol Methods. 2013 Dec;194(1-2):132-7. doi: 10.1016/j.jviromet.2013.08.016. PMID: 23994148. Excluded: Wrong intervention.

Da Silva B, Tschampa J, Beron J, et al. Evaluation of myocardial infarction and coronary artery disease in subjects taking lopinavir/ritonavir: a study using clinical trial and pharmacovigilance databases. Int J Clin Pharmacol Ther. 2012 Jun;50(6):391-402. doi: 10.5414/CP201606. PMID: 22541744. Excluded: Wrong intervention.

daCosta DiBonaventura M, Gupta S, Cho M, et al. The association of HIV/AIDS treatment side effects with health status, work productivity, and resource use. AIDS Care. 2012;24(6):744-55. doi: 10.1080/09540121.2011.630363. PMID: 22292729. Excluded: Wrong outcome.

d'Almeida KW, Kierzek G, de Truchis P, et al. Modest public health impact of nontargeted human immunodeficiency virus screening in 29 emergency departments. Arch Intern Med. 2012 Jan 9;172(1):12-20. doi: 10.1001/archinternmed.2011.535. PMID: 22025095. Excluded: Wrong study design for Key Question.

Damtew B, Mengistie B, Alemayehu T. Survival and determinants of mortality in adult HIV/Aids patients initiating antiretroviral therapy in Somali Region, Eastern Ethiopia. Pan Afr Med J. 2015;22:138. doi: 10.11604/pamj.2015.22.138.4352. PMID: 26889319. Excluded: Wrong country.

Danjuma MI, Mohamad-Fadzillah NH, Khoo S. An investigation of the pattern of kidney injury in HIV-positive persons exposed to tenofovir disoproxil fumarate: an examination of a large population database (MHRA database). Int J STD AIDS. 2014 Mar;25(4):273-9. doi: 10.1177/0956462413504747. PMID: 24067251. Excluded: Wrong study design for Key Question.

D'Ascenzo F, Cerrato E, Biondi-Zoccai G, et al. Acute coronary syndromes in human immunodeficiency virus patients: a meta-analysis investigating adverse event rates and the role of antiretroviral therapy. Eur Heart J. 2012 Apr;33(7):875-80. doi: 10.1093/eurheartj/ehr456. PMID: 22187508. Excluded: Wrong outcome.

D'Ascenzo F, Quadri G, Cerrato E, et al. A meta-analysis investigating incidence and features of stroke in HIV-infected patients in the highly active antiretroviral therapy era. J Cardiovasc Med. 2015 Dec;16(12):839-43. doi: 10.2459/JCM.0b013e328365ca31. PMID: 24979113. Excluded: Wrong comparator.

Davies NE, Karstaedt AS. Antiretroviral outcomes in South African prisoners: a retrospective cohort analysis. PLoS One. 2012;7(3):e33309. doi: 10.1371/journal.pone.0033309. PMID: 22470448. Excluded: Wrong country.

Davis DH, Smith R, Brown A, et al. Early diagnosis and treatment of HIV infection: magnitude of benefit on short-term mortality is greatest in older adults. Age Ageing. 2013 Jul;42(4):520-6. doi: 10.1093/ageing/aft052. PMID: 23672932. Excluded: Wrong population.

de Bruyn G, Magaret A, Baeten JM, et al. Mortality in members of HIV-1 serodiscordant couples in Africa and implications for antiretroviral therapy initiation: results of analyses from a multicenter randomized trial. BMC Infect Dis. 2012;12:277. doi: 10.1186/1471-2334-12-277. PMID: 23130818. Excluded: Wrong country.

de Miguel R, Montejano R, Stella-Ascariz N, et al. A safety evaluation of raltegravir for the treatment of HIV. Expert Opin Drug Saf. 2018 Feb;17(2):217-23. doi: 10.1080/14740338.2018.1411903. PMID: 29199485. Excluded: Systematic review or meta-analysis used as a source document only to identify individual studies.

de Waal R, Cohen K, Maartens G. Systematic review of antiretroviral-associated lipodystrophy: lipoatrophy, but not central fat gain, is an antiretroviral adverse drug reaction. PLoS One. 2013;8(5):e63623. doi: 10.1371/journal.pone.0063623. PMID: 23723990. Excluded: Wrong outcome.

Deconinck L, Yazdanpanah Y, Gilson RJ, et al. Time to initiation of antiretroviral therapy in HIV-infected patients diagnosed with an opportunistic disease: a cohort study. HIV Med. 2015 Apr;16(4):219-29. doi: 10.1111/hiv.12201. PMID: 25522796. Excluded: Sample size too small.

Deeks ED. Emtricitabine/rilpivirine/tenofovir disoproxil fumarate single-tablet regimen: a review of its use in HIV infection. Drugs. 2014 Nov;74(17):2079-95. doi: 10.1007/s40265-014-0318-1. PMID: 25352394. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Appendix A5. Excluded Studies List

Dikman AE, Schonfeld E, Srisarajivakul NC, et al. Human immunodeficiency virus-associated diarrhea: Still an issue in the era of antiretroviral therapy. Dig Dis Sci. 2015 Aug;60(8):2236-45. doi: 10.1007/s10620-015-3615-y. PMID: 25772777. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Diop SA, Fortes-Deguenonvo L, Seydi M, et al. [Efficacy and tolerance of tenofovir-lamivudine-efavirenz combination in HIV-1 patients in Fann Teaching Hospital in Dakar]. Bull Soc Pathol Exot. 2013 Feb;106(1):22-6. doi: 10.1007/s13149-012-0272-7. PMID: 23247755. Excluded: Not English language but possibly relevant.

Dolling DI, Goodall RL, Chirara M, et al. The virological durability of first-line ART among HIV-positive adult patients in resource limited settings without virological monitoring: a retrospective analysis of DART trial data. BMC Infect Dis. 2017 Feb 21;17(1):160. doi: 10.1186/s12879-017-2266-3. PMID: 28222702. Excluded: Wrong outcome.

Donnell-Fink LA, Arbelaez C, Collins JE, et al. Acceptability of fingerstick versus oral fluid rapid HIV testing: results from the universal screening for HIV infection in the emergency room (USHER Phase II) randomized controlled trial. J Acquir Immune Defic Syndr. 2012 Dec 15;61(5):588-92. doi: 10.1097/QAI.0b013e31826a6d67. PMID: 23183149. Excluded: Wrong outcome.

Doshi RK, Milberg J, Isenberg D, et al. High rates of retention and viral suppression in the US HIV safety net system: HIV care continuum in the Ryan White HIV/AIDS Program, 2011. Clin Infect Dis. 2015 Jan 1;60(1):117-25. doi: 10.1093/cid/ciu722. PMID: 25225233. Excluded: Wrong outcome.

Druyts E, Dybul M, Kanters S, et al. Male sex and the risk of mortality among individuals enrolled in antiretroviral therapy programs in Africa: a systematic review and meta-analysis. AIDS. 2013 Jan 28;27(3):417-25. doi: 10.1097/QAD.0b013e328359b89b. PMID: 22948271. Excluded: Wrong country.

Ekouevi DK, Tchounga BK, Coffie PA, et al. Antiretroviral therapy response among HIV-2 infected patients: a systematic review. BMC Infect Dis. 2014;14:461. doi: 10.1186/1471-2334-14-461. PMID: 25154616. Excluded: Wrong country.

Eluwa GI, Badru T, Agu KA, et al. Adverse drug reactions to antiretroviral therapy (ARVs): incidence, type and risk factors in Nigeria.[Erratum appears in BMC Clin Pharmacol. 2012;12:14 Note: Agu, Kenneth A [added]; Chabikuli, Otto [added]; Hamelmann, Christoph [added]]. BMC Clin Pharml. 2012;12:7. doi: 10.1186/1472-6904-12-7. PMID: 22369677. Excluded: Wrong country.

Elvstam O, Medstrand P, Yilmaz A, et al. Virological failure and all-cause mortality in HIV-positive adults with low-level viremia during antiretroviral treatment. PLoS One. 2017;12(7):e0180761. doi: 10.1371/journal.pone.0180761. PMID: 28683128. Excluded: Wrong comparator.

Elzi L, Battegay M. [When to start antiretroviral therapy]. Ther Umsch. 2014 Jan;71(1):23-9. doi: 10.1024/0040-5930/a000478. PMID: 24394206. Excluded: Not English language but possibly relevant.

Emerson B, Plough K. Detection of acute HIV-1 infections utilizing NAAT technology in Dallas, Texas. J Clin Virol. 2013 Dec;58 Suppl 1:e48-53. doi: 10.1016/j.jcv.2013.08.005. PMID: 23999031. Excluded: Wrong study design for Key Question.

ENCORE1 Study Group, R P, J A, et al. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. Lancet. 2014;383(9927):1474-82. PMID: 24522178. Excluded: Inadequate duration.

Encore Study Group, Carey D, Puls R, et al. Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1 study.[Erratum appears in Lancet Infect Dis. 2015 Jul;15(7):761; PMID: 26122437]. Lancet Infect Dis. 2015 Jul;15(7):793-802. doi: 10.1016/S1473-3099(15)70060-5. PMID: 25877963. Excluded: Inadequate duration.

Escarcega RO, Franco JJ, Mani BC, et al. Cardiovascular disease in patients with chronic human immunodeficiency virus infection. Int J Cardiol. 2014 Jul 15;175(1):1-7. doi: 10.1016/j.ijcard.2014.04.155. PMID: 24798779. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Ewald H, Santini-Oliveira M, Buhler JE, et al. Comparative effectiveness of tenofovir in HIV-infected treatment-experienced patients: systematic review and meta-analysis. HIV Clin Trials. 2017 Jan;18(1):17-27. doi: 10.1080/15284336.2016.1261073. PMID: 27951755. Excluded: Systematic review or meta- analysis used as a source document only to identify individual studies.

Ewings FM, Ford D, Walker AS, et al. Optimal CD4 count for initiating HIV treatment: impact of CD4 observation frequency and grace periods, and performance of dynamic marginal structural models. Epidemiology. 2014 Mar;25(2):194-202. doi: 10.1097/EDE.0000000000000043. PMID: 24487204. Excluded: Wrong study design for Key Question.

Fafin C, Pugliese P, Durant J, et al. Increased time exposure to tenofovir is associated with a greater decrease in estimated glomerular filtration rate in HIV patients with kidney function of less than 60 ml/min/1.73 m2. Nephron Clin Pract. 2012;120(4):c205-14. doi: 10.1159/000342377. PMID: 23037894. Excluded: Wrong outcome.

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Feyissa GT, Lockwood C, Munn Z. The effectiveness of home-based HIV counseling and testing on reducing stigma and risky sexual behavior among adults and adolescents: A systematic review and meta-analyses. JBI Database System Rev Implement Rep. 2015;13(6):318-72. doi: 10.11124/jbisrir-2015-2235. PMID: 26455755. Excluded: Wrong outcome.

Fidler S, Porter K, Ewings F, et al. Short-course antiretroviral therapy in primary HIV infection. N Engl J Med. 2013;368(3):207-17. PMID: 23323897. Excluded: Wrong comparator.

Fontela C, Castilla J, Juanbeltz R, et al. Comorbidities and cardiovascular risk factors in an aged cohort of HIV-infected patients on antiretroviral treatment in a Spanish hospital in 2016. Postgrad Med. 2018 Apr;130(3):317-24. doi: 10.1080/00325481.2018.1446653. PMID: 29486621. Excluded: Wrong outcome.

Frampton JE. Crofelemer: a review of its use in the management of non-infectious diarrhoea in adult patients with HIV/AIDS on antiretroviral therapy. Drugs. 2013 Jul;73(10):1121-9. doi: 10.1007/s40265-013-0083-6. PMID: 23807722. Excluded: Wrong intervention.

Friis-Moller N, Ryom L, Smith C, et al. An updated prediction model of the global risk of cardiovascular disease in HIV-positive persons: The Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study. Eur J Prev Cardiolog. 2016 Jan;23(2):214-23. doi: 10.1177/2047487315579291. PMID: 25882821. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Fu TC, Westergaard RP, Lau B, et al. Changes in sexual and drug-related risk behavior following antiretroviral therapy initiation among HIV-infected injection drug users. AIDS. 2012 Nov 28;26(18):2383-91. doi: 10.1097/QAD.0b013e32835ad438. PMID: 23079804. Excluded: Wrong outcome.

Furtado J, Madruga JV, Bicudo EL, et al. Safety and immunovirologic outcomes with maraviroc combination regimens in patients with a history of past treatment failures and virologic resistance in Brazil: an open-label, multicenter phase 3b study. AIDS Res Hum Retroviruses. 2013 Sep;29(9):1203-10. doi: 10.1089/AID.2012.0330. PMID: 23731330. Excluded: Wrong population.

Gabillard D, Lewden C, Ndoye I, et al. Mortality, AIDS-morbidity, and loss to follow-up by current CD4 cell count among HIV-1-infected adults receiving antiretroviral therapy in Africa and Asia: data from the ANRS 12222 collaboration. J Acquir Immune Defic Syndr. 2013 Apr 15;62(5):555-61. doi: 10.1097/QAI.0b013e3182821821. PMID: 23274931. Excluded: Wrong country.

Gagliardo C, Brozovich A, Birnbaum J, et al. A multicenter study of initiation of antiretroviral therapy and transmitted drug resistance in antiretroviral-naive adolescents and young adults with HIV in New York City. Clin Infect Dis. 2014 Mar;58(6):865-72. doi: 10.1093/cid/ciu003. PMID: 24429431. Excluded: Wrong outcome.

Galizzi N, Galli L, Poli A, et al. Long-term efficacy and safety of rilpivirine plus abacavir and lamivudine in HIV-1 infected patients with undetectable viral load. PLoS ONE. 2018;13(2):e0191300. doi: 10.1371/journal.pone.0191300. PMID: 29451870. Excluded: Wrong outcome.

Gallien S, Flandre P, Nguyen N, et al. Safety and efficacy of coformulated efavirenz/emtricitabine/tenofovir single-tablet regimen in treatment-naive patients infected with HIV-1. J Med Virol. 2015 Feb;87(2):187-91. doi: 10.1002/jmv.24023. PMID: 25070158. Excluded: Inadequate duration.

Geng EH, Odeny TA, Lyamuya RE, et al. Estimation of mortality among HIV-infected people on antiretroviral treatment in East Africa: a sampling based approach in an observational, multisite, cohort study. Lancet HIV. 2015 Mar;2(3):e107-16. doi: 10.1016/S2352-3018(15)00002-8. PMID: 26424542. Excluded: Wrong country.

Ghislain M, Bastard JP, Meyer L, et al. Late antiretroviral therapy (ART) initiation is associated with long-term persistence of systemic inflammation and metabolic abnormalities. PLoS One. 2015;10(12):e0144317. doi: 10.1371/journal.pone.0144317. PMID: 26636578. Excluded: Wrong outcome.

Giaquinto C, Anabwani G, Feiterna-Sperling C, et al. Steady-state pharmacokinetics of nevirapine extended-release tablets in HIV-1-infected children and adolescents: an open-label, multiple-dose, cross-over study. Pediatr Infect Dis J. 2014 Jul;33(7):e173-9. doi: 10.1097/INF.0000000000000241. PMID: 24378938. Excluded: Wrong outcome.

Gordon MS, Kinlock TW, McKenzie M, et al. Rapid HIV testing for individuals on probation/parole: outcomes of an intervention trial. AIDS Behav. 2013 Jul;17(6):2022-30. doi: 10.1007/s10461-013-0456-6. PMID: 23536140. Excluded: Wrong comparator.

Gotti D, Danesi M, Calabresi A, et al. Clinical characteristics, incidence, and risk factors of HIV-related Hodgkin lymphoma in the era of combination antiretroviral therapy. AIDS Patient Care STDS. 2013 May;27(5):259-65. doi: 10.1089/apc.2012.0424. PMID: 23600703. Excluded: Wrong study design for Key Question.

Gotuzzo E, Markowitz M, Ratanasuwan W, et al. Sustained efficacy and safety of raltegravir after 5 years of combination antiretroviral therapy as initial treatment of HIV-1 infection: final results of a randomized, controlled, phase II study (Protocol 004). J Acquir Immune Defic Syndr. 2012 Sep 1;61(1):73-7. PMID: 22743596. Excluded: Sample size too small.

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Goujard C, Emilie D, Roussillon C, et al. Continuous versus intermittent treatment strategies during primary HIV-1 infection: the randomized ANRS INTERPRIM Trial. AIDS. 2012 Sep 24;26(15):1895-905. PMID: 22842994. Excluded: Wrong comparator.

Gous N, Scott L, Potgieter J, et al. Feasibility of performing multiple point of care testing for HIV anti-retroviral treatment initiation and monitoring from multiple or single fingersticks. PLoS One. 2013;8(12):e85265. doi: 10.1371/journal.pone.0085265. PMID: 24376873. Excluded: Wrong country.

Grabarczyk P, van Drimmelen H, Kopacz A, et al. Head-to-head comparison of two transcription-mediated amplification assay versions for detection of hepatitis B virus, hepatitis C virus, and human immunodeficiency virus Type 1 in blood donors. Transfusion. 2013 Oct;53(10 Pt 2):2512-24. doi: 10.1111/trf.12190. PMID: 23590145. Excluded: Wrong outcome.

Grant PM, Zolopa AR. When to start ART in the setting of acute AIDS-related opportunistic infections: the time is now! Curr HIV/AIDS Rep. 2012 Sep;9(3):251-8. doi: 10.1007/s11904-012-0126-8. PMID: 22733609. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Gray RT, Prestage GP, Down I, et al. Increased HIV testing will modestly reduce HIV incidence among gay men in NSW and would be acceptable if HIV testing becomes convenient. PLoS One. 2013;8(2):e55449. doi: 10.1371/journal.pone.0055449. PMID: 23457470. Excluded: Wrong outcome.

Green N, Hoenigl M, Morris S, et al. Risk behavior and sexually transmitted infections among transgender women and men undergoing community-based screening for acute and early HIV infection in San Diego. Medicine (Baltimore). 2015 Oct;94(41):e1830. doi: 10.1097/MD.0000000000001830. PMID: 26469928. Excluded: Wrong outcome.

Greenwald JL, Bursetin GR, Pincus J, et al. A rapid review of rapid HIV antibody tests. Curr Infect Dis Rep. 2006;8:125-31. PMID: 16524549. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

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).

Greig SL, Deeks ED. Abacavir/dolutegravir/lamivudine single-tablet regimen: a review of its use in HIV-1 infection. Drugs. 2015 Apr;75(5):503-14. doi: 10.1007/s40265-015-0361-6. PMID: 25698454. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Guehi C, Badje A, Gabillard D, et al. High prevalence of being overweight and obese HIV-infected persons, before and after 24 months on early ART in the ANRS 12136 Temprano Trial. AIDS Res Ther. 2016;13:12. doi: 10.1186/s12981-016-0094-y. PMID: 26925155. Excluded: Wrong country.

Guest JL, Weintrob AC, Rimland D, et al. A comparison of HAART outcomes between the US military HIV Natural History Study (NHS) and HIV Atlanta Veterans Affairs Cohort Study (HAVACS). PLoS One. 2013;8(5):e62273. doi: 10.1371/journal.pone.0062273. PMID: 23658717. Excluded: Wrong comparator.

Gupta SK, McComsey GA, Lombaard J, et al. Efficacy, safety, bone and metabolic effects of HIV nucleoside reverse transcriptase inhibitor BMS-986001 (AI467003): a phase 2b randomised, controlled, partly blinded trial. Lancet HIV. 2016 Jan;3(1):e13-22. doi: 10.1016/S2352-3018(15)00231-3. PMID: 26762988. Excluded: Wrong intervention.

Gupta SK, Shen C, Moe SM, et al. Worsening endothelial function with efavirenz compared to protease inhibitors: a 12-month prospective study. PLoS One. 2012;7(9):e45716. doi: 10.1371/journal.pone.0045716. PMID: 23029197. Excluded: Wrong outcome.

Gwadz M, Cleland CM, Applegate E, et al. Behavioral intervention improves treatment outcomes among HIV-infected individuals who have delayed, declined, or discontinued antiretroviral therapy: a randomized controlled trial of a novel intervention. AIDS Behav. 2015 Oct;19(10):1801-17. doi: 10.1007/s10461-015-1054-6. PMID: 25835462. Excluded: Wrong intervention.

Hack CM, Scarfi CA, Sivitz AB, et al. Implementing routine HIV screening in an urban pediatric emergency department. Pediatr Emerg Care. 2013 Mar;29(3):319-23. doi: 10.1097/PEC.0b013e3182850910. PMID: 23426243. Excluded: Wrong study design for Key Question.

Han N, Wright ST, O'Connor CC, et al. HIV and aging: insights from the Asia Pacific HIV Observational Database (APHOD). HIV Med. 2015 Mar;16(3):152-60. doi: 10.1111/hiv.12188. PMID: 25407085. Excluded: Wrong study design for Key Question.

Handford CD, Rackal JM, Tynan AM, et al. The association of hospital, clinic and provider volume with HIV/AIDS care and mortality: systematic review and meta-analysis. AIDS Care. 2012;24(3):267-82. doi: 10.1080/09540121.2011.608419. PMID: 22007914. Excluded: Wrong comparator.

Hankin A, Freiman H, Copeland B, et al. A comparison of parallel and integrated models for implementation of routine HIV screening in a large, urban emergency department. Public Health Rep. 2016 Jan-Feb;131 Suppl 1:90-5. PMID: 26862234. Excluded: Wrong comparator.

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Hemkens LG, Bucher HC. HIV infection and cardiovascular disease. Eur Heart J. 2014 Jun 1;35(21):1373-81. doi: 10.1093/eurheartj/eht528. PMID: 24408888. Excluded: Wrong study design for Key Question.

Hemkens LG, Ewald H, Santini-Oliveira M, et al. Comparative effectiveness of tenofovir in treatment-naive HIV-infected patients: systematic review and meta-analysis. HIV Clin Trials. 2015 Oct;16(5):178-89. doi: 10.1179/1945577115Y.0000000004. PMID: 26395328. Excluded: Wrong outcome.

Hermans SM, van Leth F, Manabe YC, et al. Earlier initiation of antiretroviral therapy, increased tuberculosis case finding and reduced mortality in a setting of improved HIV care: a retrospective cohort study. HIV Med. 2012 Jul;13(6):337-44. doi: 10.1111/j.1468-1293.2011.00980.x. PMID: 22296211. Excluded: Wrong country.

Hirsch AA, Compan A, Lawrence RH, et al. Pilot study to assess subjective and objective reporting of potential adverse drug reactions in older versus younger HIV-infected patients using antiretroviral therapy. J Assoc Nurses AIDS Care. 2012 Sep-Oct;23(5):397-408. doi: 10.1016/j.jana.2011.09.005. PMID: 22137548. Excluded: Wrong comparator.

Hirschhorn LR, Kaaya SF, Garrity PS, et al. Cancer and the 'other' noncommunicable chronic diseases in older people living with HIV/AIDS in resource-limited settings: a challenge to success. AIDS. 2012 Jul 31;26 Suppl 1:S65-75. PMID: 22781178. Excluded: Wrong country.

Ho JE, Scherzer R, Hecht FM, et al. The association of CD4+ T-cell counts and cardiovascular risk in treated HIV disease. AIDS. 2012 Jun 1;26(9):1115-20. doi: 10.1097/QAD.0b013e328352ce54. PMID: 22382147. Excluded: Wrong outcome.

Hocqueloux L, Avettand-Fenoel V, Jacquot S, et al. Long-term antiretroviral therapy initiated during primary HIV-1 infection is key to achieving both low HIV reservoirs and normal T cell counts. J Antimicrob Chemother. 2013 May;68(5):1169-78. doi: 10.1093/jac/dks533. PMID: 23335199. Excluded: Wrong study design for Key Question.

Hoffmann C, Welz T, Sabranski M, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med. 2017 Jan;18(1):56-63. doi: 10.1111/hiv.12468. PMID: 27860104. Excluded: Sample size too small.

Hogan CM, Degruttola V, Sun X, et al. The setpoint study (ACTG A5217): effect of immediate versus deferred antiretroviral therapy on virologic set point in recently HIV-1-infected individuals. J Infect Dis. 2012 Jan 1;205(1):87-96. doi: 10.1093/infdis/jir699. PMID: 22180621. Excluded: Sample size too small.

Hoover JB, Tao G, Heffelfinger JD. Monitoring HIV testing at visits to emergency departments in the United States: very-low rate of HIV testing. J Acquir Immune Defic Syndr. 2013 Jan 1;62(1):90-4. doi: 10.1097/QAI.0b013e3182742933. PMID: 23018376. Excluded: Wrong study design for Key Question.

IeDea and A. R. T. Cohort Collaborations, Avila D, Althoff KN, et al. Immunodeficiency at the start of combination antiretroviral therapy in low-, middle-, and high-income countries. J Acquir Immune Defic Syndr. 2014 Jan 1;65(1):e8-16. doi: 10.1097/QAI.0b013e3182a39979. PMID: 24419071. Excluded: Wrong country.

Islam FM, Wu J, Jansson J, et al. Relative risk of cardiovascular disease among people living with HIV: a systematic review and meta-analysis. HIV Med. 2012 Sep;13(8):453-68. doi: 10.1111/j.1468-1293.2012.00996.x. PMID: 22413967. Excluded: Systematic review of old data.

Jain V, Hartogensis W, Bacchetti P, et al. Antiretroviral therapy initiated within 6 months of HIV infection is associated with lower T-cell activation and smaller HIV reservoir size. J Infect Dis. 2013 Oct 15;208(8):1202-11. doi: 10.1093/infdis/jit311. PMID: 23852127. Excluded: Wrong outcome.

Jamil MS, Prestage G, Fairley CK, et al. Rationale and design of FORTH: a randomised controlled trial assessing the effectiveness of HIV self-testing in increasing HIV testing frequency among gay and bisexual men. BMC Infect Dis. 2015;15:561. doi: 10.1186/s12879-015-1300-6. PMID: 26653203. Excluded: Wrong study design for Key Question.

Jose S, Quinn K, Hill T, et al. Laboratory adverse events and discontinuation of therapy according to CD4(+) cell count at the start of antiretroviral therapy. AIDS. 2014 Jun 1;28(9):1333-9. doi: 10.1097/QAD.0000000000000242. PMID: 24583670. Excluded: Wrong outcome.

Joyce VR, Barnett PG, Chow A, et al. Effect of treatment interruption and intensification of antiretroviral therapy on health-related quality of life in patients with advanced HIV: a randomized, controlled trial. Med Decis Making. 2012 Jan-Feb;32(1):70-82. doi: 10.1177/0272989X10397615. PMID: 21383086. Excluded: Wrong comparator.

Kahouadji Y, Dumurgier J, Sellier P, et al. Cognitive function after several years of antiretroviral therapy with stable central nervous system penetration score. HIV Med. 2013 May;14(5):311-5. doi: 10.1111/j.1468-1293.2012.01052.x. PMID: 23035982. Excluded: Wrong outcome.

Kakaire O, Byamugisha JK, Tumwesigye NM, et al. Clinical versus laboratory screening for sexually transmitted infections prior to insertion of intrauterine contraception among women living with HIV/AIDS: a randomized controlled trial. Hum Reprod. 2015 Jul;30(7):1573-9. doi: 10.1093/humrep/dev109. PMID: 25979373. Excluded: Wrong intervention.

Appendix A5. Excluded Studies List

Kalayjian RC, Lau B, Mechekano RN, et al. Risk factors for chronic kidney disease in a large cohort of HIV-1 infected individuals initiating antiretroviral therapy in routine care. AIDS. 2012 Sep 24;26(15):1907-15. PMID: 22824630. Excluded: Sample size too small.

Kanters S, Mills EJ, Thorlund K, et al. Antiretroviral therapy for initial human immunodeficiency virus/AIDS treatment: critical appraisal of the evidence from over 100 randomized trials and 400 systematic reviews and meta-analyses. Clin Microbiol Infect. 2014 Feb;20(2):114-22. doi: 10.1111/1469-0691.12475. PMID: 24274661. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Karim R, Mack WJ, Kono N, et al. T-cell activation, both pre- and post-HAART levels, correlates with carotid artery stiffness over 6.5 years among HIV-infected women in the WIHS. J Acquir Immune Defic Syndr. 2014 Nov 1;67(3):349-56. doi: 10.1097/QAI.0000000000000311. PMID: 25314253. Excluded: Wrong outcome.

Karris MY, Kao YT, Patel D, et al. Predictors of virologic response in persons who start antiretroviral therapy during recent HIV infection. AIDS. 2014 Mar 27;28(6):841-9. doi: 10.1097/QAD.0000000000000149. PMID: 24401640. Excluded: Wrong outcome.

Kiertiburanakul S, Boettiger D, Lee MP, et al. Trends of CD4 cell count levels at the initiation of antiretroviral therapy over time and factors associated with late initiation of antiretroviral therapy among Asian HIV-positive patients. J Int AIDS Soc. 2014;17:18804. doi: 10.7448/IAS.17.1.18804. PMID: 24598459. Excluded: Wrong population.

Kiertiburanakul S, Luengroongroj P, Sungkanuparph S. Clinical characteristics of HIV-infected patients who survive after the diagnosis of HIV infection for more than 10 years in a resource-limited setting. J Int Assoc Physicians AIDS Care. 2012 Nov-Dec;11(6):361-5. doi: 10.1177/1545109712449191. PMID: 22745182. Excluded: Wrong country.

Kim EK, Thorpe L, Myers JE, et al. Healthcare-related correlates of recent HIV testing in New York City. Prev Med. 2012 Jun;54(6):440-3. doi: 10.1016/j.ypmed.2012.03.006. PMID: 22449481. Excluded: Wrong study design for Key Question.

Kityo C, Gibb DM, Gilks CF, et al. High level of viral suppression and low switch rate to second-line antiretroviral therapy among HIV-infected adult patients followed over five years: retrospective analysis of the DART trial. PLoS One. 2014;9(3):e90772. doi: 10.1371/journal.pone.0090772. PMID: 24625508. Excluded: Wrong country.

Koethe JR, Grome H, Jenkins CA, et al. The metabolic and cardiovascular consequences of obesity in persons with HIV on long-term antiretroviral therapy. AIDS. 2016 Jan 2;30(1):83-91. doi: 10.1097/QAD.0000000000000893. PMID: 26418084. Excluded: Wrong comparator.

Koethe JR, Jenkins CA, Lau B, et al. Body mass index and early CD4 T-cell recovery among adults initiating antiretroviral therapy in North America, 1998-2010. HIV Med. 2015 Oct;16(9):572-7. doi: 10.1111/hiv.12259. PMID: 25960080. Excluded: Wrong study design for Key Question.

Koethe JR, Jenkins CA, Turner M, et al. Body mass index and the risk of incident noncommunicable diseases after starting antiretroviral therapy. HIV Med. 2015 Jan;16(1):67-72. doi: 10.1111/hiv.12178. PMID: 25230709. Excluded: Wrong study design for Key Question.

Krastinova E, Seng R, Lechenadec J, et al. Does transient cART started during primary HIV infection undermine the long-term immunologic and virologic response on cART resumption? BMC Infect Dis. 2015;15:178. doi: 10.1186/s12879-015-0892-1. PMID: 25888386. Excluded: Wrong outcome.

Krishnan S, Schouten JT, Atkinson B, et al. Metabolic syndrome before and after initiation of antiretroviral therapy in treatment-naive HIV-infected individuals. J Acquir Immune Defic Syndr. 2012 Nov 1;61(3):381-9. doi: 10.1097/QAI.0b013e3182690e3c. PMID: 22828718. Excluded: Wrong outcome.

Kryst J, Kawalec P, Pilc A. Efavirenz-based regimens in antiretroviral-naive HIV-infected patients: A systematic review and meta-analysis of randomized controlled trials. PLoS One. 2015;10(5):e0124279. doi: 10.1371/journal.pone.0124279. PMID: 25933004. Excluded: Wrong outcome.

Kunisaki KM, Niewoehner DE, Collins G, et al. Pulmonary function in an international sample of HIV-positive, treatment-naive adults with CD4 counts > 500 cells/muL: a substudy of the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med. 2015 Apr;16 Suppl 1:119-28. doi: 10.1111/hiv.12240. PMID: 25711330. Excluded: Wrong study design for Key Question.

Kurth AE, Severynen A, Spielberg F. Addressing unmet need for HIV testing in emergency care settings: a role for computer-facilitated rapid HIV testing? AIDS Educ Prev. 2013 Aug;25(4):287-301. doi: 10.1521/aeap.2013.25.4.287. PMID: 23837807. Excluded: Wrong intervention.

Kyle TL, Horigian VE, Tross S, et al. Uptake of HIV testing in substance use disorder treatment programs that offer on-site testing. AIDS Behav. 2015 Mar;19(3):536-42. doi: 10.1007/s10461-014-0864-2. PMID: 25074737. Excluded: Wrong outcome.

Appendix A5. Excluded Studies List

Laanani M, Ghosn J, Essat A, et al. Impact of the timing of initiation of antiretroviral therapy during primary HIV-1 infection on the decay of cell-associated HIV-DNA. Clin Infect Dis. 2015 Jun 1;60(11):1715-21. doi: 10.1093/cid/civ171. PMID: 25737374. Excluded: Wrong outcome.

Lacombe JM, Boue F, Grabar S, et al. Risk of Kaposi sarcoma during the first months on combination antiretroviral therapy. AIDS. 2013 Feb 20;27(4):635-43. doi: 10.1097/QAD.0b013e32835cba6c. PMID: 23196937. Excluded: Wrong outcome.

Lakey W, Yang LY, Yancy W, et al. Short communication: from wasting to obesity: initial antiretroviral therapy and weight gain in HIV-infected persons. AIDS Res Hum Retroviruses. 2013 Mar;29(3):435-40. doi: 10.1089/AID.2012.0234. PMID: 23072344. Excluded: Wrong outcome.

Langebeek N, Sprenger HG, Gisolf EH, et al. A simplified combination antiretroviral therapy regimen enhances adherence, treatment satisfaction and quality of life: results of a randomized clinical trial. HIV Med. 2014 May;15(5):286-90. doi: 10.1111/hiv.12112. PMID: 24215485. Excluded: Wrong intervention.

Laprise C, Baril JG, Dufresne S, et al. Atazanavir and other determinants of hyperbilirubinemia in a cohort of 1150 HIV-positive patients: results from 9 years of follow-up. AIDS Patient Care STDS. 2013 Jul;27(7):378-86. doi: 10.1089/apc.2013.0009. PMID: 23829329. Excluded: Wrong outcome.

Laureillard D, Marcy O, Madec Y, et al. Paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome after early initiation of antiretroviral therapy in a randomized clinical trial. AIDS. 2013 Oct 23;27(16):2577-86. doi: 10.1097/01.aids.0000432456.14099.c7. PMID: 24096631. Excluded: Wrong country.

Le T, Wright EJ, Smith DM, et al. Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. N Engl J Med. 2013 Jan 17;368(3):218-30. doi: 10.1056/NEJMoa1110187. PMID: 23323898. Excluded: Wrong outcome.

Legoupil C, Peltier A, Henry Kagan V, et al. Out-of-Hospital screening for HIV, HBV, HCV and Syphilis in a vulnerable population, a public health challenge. AIDS Care. 2017 Jun;29(6):686-8. doi: 10.1080/09540121.2016.1231886. PMID: 27626811. Excluded: Wrong outcome.

Lennox JL, Landovitz RJ, Ribaudo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: A randomized, controlled equivalence trial. Ann Intern Med. 2014;161(7):461-71. PMID: 25285539. Excluded: Wrong outcome.

Lenzi L, Wiens A, Pontarolo R. Evaluation of adverse events associated with antiretroviral therapy and the relationship to treatment adherence. Int J Clin Pharmacol Ther. 2013 Feb;51(2):141-6. doi: 10.5414/CP201818. PMID: 23253950. Excluded: Wrong outcome.

Leon N, Mathews C, Lewin S, et al. A comparison of linkage to HIV care after provider-initiated HIV testing and counselling (PITC) versus voluntary HIV counselling and testing (VCT) for patients with sexually transmitted infections in Cape Town, South Africa. BMC Health Serv Res. 2014;14:350. doi: 10.1186/1472-6963-14-350. PMID: 25134822. Excluded: Wrong country.

Leonard NR, Rajan S, Gwadz MV, et al. HIV testing patterns among urban YMSM of color. Health Educ Behav. 2014 Dec;41(6):673-81. doi: 10.1177/1090198114537064. PMID: 24973260. Excluded: Wrong study design for Key Question.

Leung V, Gillis J, Raboud J, et al. Predictors of CD4:CD8 ratio normalization and its effect on health outcomes in the era of combination antiretroviral therapy. PLoS One. 2013;8(10):e77665. doi: 10.1371/journal.pone.0077665. PMID: 24204912. Excluded: Wrong outcome.

Leutscher PD, Stecher C, Storgaard M, et al. Discontinuation of efavirenz therapy in HIV patients due to neuropsychiatric adverse effects. Scand J Infect Dis. 2013 Aug;45(8):645-51. doi: 10.3109/00365548.2013.773067. PMID: 23427878. Excluded: Wrong outcome.

Li L, Tian JH, Yang K, et al. Humanized PA14 (a monoclonal CCR5 antibody) for treatment of people with HIV infection. Cochrane Database Syst Rev. 2014;7:CD008439. doi: 10.1002/14651858.CD008439.pub3. PMID: 25063928. Excluded: Wrong intervention.

Li SL, Xu P, Zhang L, et al. Effectiveness and safety of rilpivirine, a non-nucleoside reverse transcriptase inhibitor, in treatment-naive adults infected with HIV-1: a meta-analysis. HIV Clin Trials. 2014 Nov-Dec;15(6):261-8. doi: 10.1310/hct1506-261. PMID: 25433665. Excluded: Inadequate duration.

Libois A, Feoli F, Nkuize M, et al. Prolonged antiretroviral therapy is associated with fewer anal high-grade squamous intraepithelial lesions in HIV-positive MSM in a cross-sectional study. Sex Transm Infect. 2017 Feb;93(1):15-7. doi: 10.1136/sextrans-2015-052444. PMID: 27030607. Excluded: Wrong comparator.

Lifson AR, Grandits GA, Gardner EM, et al. Quality of life assessment among HIV-positive persons entering the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med. 2015 Apr;16 Suppl 1:88-96. doi: 10.1111/hiv.12237. PMID: 25711327. Excluded: Wrong study design for Key Question.

Appendix A5. Excluded Studies List

Lin D, Li W, Rieder MJ. Cotrimoxazole for prophylaxis or treatment of opportunistic infections of HIV/AIDS in patients with previous history of hypersensitivity to cotrimoxazole. Cochrane Database Syst Rev. 2009(1)doi: 10.1002/14651858.CD005646.pub2. PMID: 17443608. Excluded: Wrong intervention.

Lin D, Rieder MJ. Interventions for the treatment of decreased bone mineral density associated with HIV infection. Cochrane Database Syst Rev. 2009(1)doi: 10.1002/14651858.CD005645.pub2. PMID: 17443607. Excluded: Wrong intervention.

Lipshultz SE, Mas CM, Henkel JM, et al. HAART to heart: highly active antiretroviral therapy and the risk of cardiovascular disease in HIV-infected or exposed children and adults. Expert Rev Anti Infect Ther. 2012 Jun;10(6):661-74. doi: 10.1586/eri.12.53. PMID: 22734956. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Lodi S, Fisher M, Phillips A, et al. Symptomatic illness and low CD4 cell count at HIV seroconversion as markers of severe primary HIV infection. PLoS One. 2013;8(11):e78642. doi: 10.1371/journal.pone.0078642. PMID: 24244330. Excluded: Wrong study design for Key Question.

Lodi S, Phillips A, Fidler S, et al. Role of HIV infection duration and CD4 cell level at initiation of combination anti-retroviral therapy on risk of failure. PLoS One. 2013;8(9):e75608. doi: 10.1371/journal.pone.0075608. PMID: 24086588. Excluded: Wrong outcome.

Longenecker CT, Triant VA. Initiation of antiretroviral therapy at high CD4 cell counts: does it reduce the risk of cardiovascular disease? Curr Opin HIV AIDS. 2014 Jan;9(1):54-62. doi: 10.1097/COH.0000000000000015. PMID: 24275676. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Lopez-Cortes LF, Gutierrez-Valencia A, Ben-Marzouk-Hidalgo OJ. Antiretroviral therapy in early HIV infection [Comment on "Initiation of antiretroviral therapy in early asymptomatic HIV infection"]. N Engl J Med. 2016 Jan 28;374(4):393. doi: 10.1056/NEJMc1513311#SA1. PMID: 26816020. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Lopez-Cortes LF, Viciana P, Giron-Gonzalez JA, et al. Clinical and virological efficacy of etravirine plus two active Nucleos(t)ide analogs in an heterogeneous HIV-infected population. PLoS One. 2014;9(5):e97262. doi: 10.1371/journal.pone.0097262. PMID: 24836963. Excluded: Wrong intervention.

Loutfy MR, Sherr L, Sonnenberg-Schwan U, et al. Caring for women living with HIV: gaps in the evidence. J Int AIDS Soc. 2013;16:18509. doi: 10.7448/IAS.16.1.18509. PMID: 24088395. Excluded: Wrong outcome.

Loutfy MR, Wu W, Letchumanan M, et al. Systematic review of HIV transmission between heterosexual serodiscordant couples where the HIV-positive partner is fully suppressed on antiretroviral therapy. PLoS One. 2013;8(2):e55747. doi: 10.1371/journal.pone.0055747. PMID: 23418455. Excluded: Wrong outcome.

Lu CL, Chang SY, Sun HY, et al. Impact of vaccination with seven-valent pneumococcal conjugate vaccine on virologic and immunologic outcomes among HIV-infected adult patients in the era of highly active antiretroviral therapy. J Formos Med Assoc. 2012 Aug;111(8):445-51. doi: 10.1016/j.jfma.2011.06.027. PMID: 22939663. Excluded: Wrong intervention.

Lucas KD, Eckert V, Behrends CN, et al. Evaluation of routine HIV opt-out screening and continuum of care services following entry into eight prison reception centers--California, 2012. MMWR Morb Mortal Wkly Rep. 2016 Feb 26;65(7):178-81. doi: 10.15585/mmwr.mm6507a3. PMID: 26914322. Excluded: Wrong study design for Key Question.

Lundgren J, Babiker AG, Neaton JD. Antiretroviral therapy in early HIV infection [Authors' reply]. N Engl J Med. 2016 Jan 28;374(4):394. doi: 10.1056/NEJMc1513311. PMID: 26816019. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Lundgren JD, Babiker AG, Gordin FM, et al. When to start antiretroviral therapy: the need for an evidence base during early HIV infection. BMC Med. 2013;11:148. doi: 10.1186/1741-7015-11-148. PMID: 23767777. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Luz PM, Grinsztejn B, Velasque L, et al. Long-term CD4+ cell count in response to combination antiretroviral therapy. PLoS One. 2014;9(4):e93039. doi: 10.1371/journal.pone.0093039. PMID: 24695533. Excluded: Wrong outcome.

Lyons MS, Lindsell CJ, Ruffner AH, et al. Randomized comparison of universal and targeted HIV screening in the emergency department. J Acquir Immune Defic Syndr. 2013 Nov 1;64(3):315-23. doi: 10.1097/QAI.0b013e3182a21611. PMID: 23846569. Excluded: Wrong comparator.

MacArthur RD, DuPont HL. Etiology and pharmacologic management of noninfectious diarrhea in HIV-infected individuals in the highly active antiretroviral therapy era. Clin Infect Dis. 2012 Sep;55(6):860-7. doi: 10.1093/cid/cis544. PMID: 22700829. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Madeddu G, Mameli G, Capobianco G, et al. HPV infection in HIV-positive females: the need for cervical cancer screening including HPV-DNA detection despite successful HAART. Eur Rev Med Pharmacol Sci. 2014;18(8):1277-85. PMID: 24817305. Excluded: Wrong intervention.

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Maggi P, Bartolozzi D, Bonfanti P, et al. Renal complications in HIV disease: between present and future. AIDS Rev. 2012 Jan-Mar;14(1):37-53. PMID: 22297503. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Maggi P, Di Biagio A, Rusconi S, et al. Cardiovascular risk and dyslipidemia among persons living with HIV: a review. BMC Infect Dis. 2017 Aug 09;17(1):551. doi: 10.1186/s12879-017-2626-z. PMID: 28793863. Excluded: Systematic review or meta-analysis used as a source document only to identify individual studies.

Mahajan AP, Kinsler JJ, Cunningham WE, et al. Does the Centers for Disease Control and Prevention's recommendation of opt-out HIV screening impact the effect of stigma on HIV test acceptance? AIDS Behav. 2016 Jan;20(1):107-14. PMID: 26462670. Excluded: Wrong outcome.

Maina EK, Bonney EY, Bukusi EA, et al. CD4+ T cell counts in initiation of antiretroviral therapy in HIV infected asymptomatic individuals; controversies and inconsistencies. Immunol Lett. 2015 Dec;168(2):279-84. doi: 10.1016/j.imlet.2015.10.005. PMID: 26475399. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Maman D, Pujades-Rodriguez M, Nicholas S, et al. Response to antiretroviral therapy: improved survival associated with CD4 above 500 cells/mul. AIDS. 2012 Jul 17;26(11):1393-8. doi: 10.1097/QAD.0b013e328352d054. PMID: 22441247. Excluded: Wrong country.

Manzardo C, Esteve A, Ortega N, et al. Optimal timing for initiation of highly active antiretroviral therapy in treatment-naive human immunodeficiency virus-1-infected individuals presenting with AIDS-defining diseases: the experience of the PISCIS Cohort. Clin Microbiol Infect. 2013 Jul;19(7):646-53. doi: 10.1111/j.1469-0691.2012.03991.x. PMID: 22967234. Excluded: Sample size too small.

Marco Mourino A, Gallego Castellvi C, Garcia de Olalla P, et al. Late diagnosis of HIV infection among prisoners. AIDS Rev. 2013 Jul-Sep;15(3):146-51. PMID: 24002198. Excluded: Wrong study design for Key Question.

Margolick JB, Apuzzo L, Singer J, et al. A randomized trial of time-limited antiretroviral therapy in acute/early HIV infection. PLoS One. 2015;10(11):e0143259. doi: 10.1371/journal.pone.0143259. PMID: 26600459. Excluded: Inadequate duration.

Margolis DA, Brinson CC, Smith GH, et al. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial. Lancet Infect Dis. 2015 Oct;15(10):1145-55. doi: 10.1016/S1473-3099(15)00152-8. PMID: 26201299. Excluded: Wrong intervention.

Margolis DA, Eron JJ, DeJesus E, et al. Unexpected finding of delayed-onset seizures in HIV-positive, treatment-experienced subjects in the Phase IIb evaluation of fosdevirine (GSK2248761). Antiviral Ther. 2014;19(1):69-78. doi: 10.3851/IMP2689. PMID: 24158593. Excluded: Wrong intervention.

Markowitz M, Zolopa A, Squires K, et al. Phase I/II study of the pharmacokinetics, safety and antiretroviral activity of tenofovir alafenamide, a new prodrug of the HIV reverse transcriptase inhibitor tenofovir, in HIV-infected adults. J Antimicrob Chemother. 2014 May;69(5):1362-9. doi: 10.1093/jac/dkt532. PMID: 24508897. Excluded: Wrong intervention.

Markowitz N, Lopardo G, Wentworth D, et al. Long-term effects of intermittent IL-2 in HIV infection: extended follow-up of the INSIGHT STALWART Study. PLoS One. 2012;7(10):e47506. doi: 10.1371/journal.pone.0047506. PMID: 23082173. Excluded: Wrong intervention.

Martin-Echevarria E, Serrano-Villar S, Sainz T, et al. Development of tuberculosis in human immunodeficiency virus infected patients receiving antiretroviral therapy. Int J Tuberc Lung Dis. 2014 Sep;18(9):1080-4. doi: 10.5588/ijtld.13.0757. PMID: 25189556. Excluded: Inadequate duration.

Maskew M, Fox MP, van Cutsem G, et al. Treatment response and mortality among patients starting antiretroviral therapy with and without Kaposi sarcoma: a cohort study. PLoS One. 2013;8(6):e64392. doi: 10.1371/journal.pone.0064392. PMID: 23755122. Excluded: Wrong country.

Matthews GV, Neuhaus J, Bhagani S, et al. Baseline prevalence and predictors of liver fibrosis among HIV-positive individuals: a substudy of the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med. 2015 Apr;16 Suppl 1:129-36. doi: 10.1111/hiv.12241. PMID: 25711331. Excluded: Wrong study design for Key Question.

May MT, Hogg RS, Justice AC, et al. Heterogeneity in outcomes of treated HIV-positive patients in Europe and North America: relation with patient and cohort characteristics. Int J Epidemiol. 2012 Dec;41(6):1807-20. doi: 10.1093/ije/dys164. PMID: 23148105. Excluded: Wrong outcome.

Mayer KH, Safren SA, Elsesser SA, et al. Optimizing pre-exposure antiretroviral prophylaxis adherence in men who have sex with men: Results of a pilot randomized controlled trial of "Life-Steps for PrEP". AIDS Behav. 2016 Nov 15doi: 10.1007/s10461-016-1606-4. PMID: 27848089. Excluded: Wrong intervention.

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McNicholl IR. Does once-daily etravirine have a role in the management of HIV-1 infection? Drugs. 2013 Mar;73(3):207-12. doi: 10.1007/s40265-013-0022-6. PMID: 23420097. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Merchant RC, Baird JR, Liu T, et al. Does a brief intervention increase HIV/HCV screening among drug-using emergency department patients? Acad Emerg Med. 2014 START: 2014 May 13 CONFERENCE END: 2014 May 17, 2014 Annual Meeting of the Society for Academic Emergency Medicine, SAEM 2014 Dallas, TX United States;21(5 SUPPL. 1):S305-S6. Excluded: Wrong outcome.

Metsch LR, Feaster DJ, Gooden L. Effect of risk-reduction counseling with rapid HIV testing on risk of acquiring sexually transmitted infections: The AWARE randomized clinical trial. JAMA. 2013;310(16):1701-10. PMID: 24150466. Excluded: Wrong comparator.

Mfinanga SG, Kirenga BJ, Chanda DM, et al. Early versus delayed initiation of highly active antiretroviral therapy for HIV-positive adults with newly diagnosed pulmonary tuberculosis (TB-HAART): a prospective, international, randomised, placebo-controlled trial.[Erratum appears in Lancet Infect Dis. 2014 Jul;14(7):548]. Lancet Infect Dis. 2014 Jul;14(7):563-71. doi: 10.1016/S1473-3099(14)70733-9. PMID: 24810491. Excluded: Wrong population.

Miller CJ, Baker JV, Bormann AM, et al. Adjudicated morbidity and mortality outcomes by age among individuals with HIV infection on suppressive antiretroviral therapy. PLoS One. 2014;9(4):e95061. doi: 10.1371/journal.pone.0095061. PMID: 24728071. Excluded: Wrong comparator.

Ming Z, Prybylski D, Cheng F, et al. Two-year prospective cohort study on quality of life outcomes among people living with HIV after initiation of antiretroviral therapy in Guangxi, China. J Assoc Nurses AIDS Care. 2014 Nov-Dec;25(6):603-13. doi: 10.1016/j.jana.2014.04.003. PMID: 24950656. Excluded: Wrong outcome.

Mitchell SG, Schwartz RP, Kirk AS, et al. SBIRT implementation for adolescents in urban federally qualified health centers. J Subst Abuse Treat. 2016 Jan;60:81-90. doi: 10.1016/j.jsat.2015.06.011. PMID: 26297321. Excluded: Wrong outcome.

Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study.[Erratum appears in Lancet HIV. 2015 Apr;2(4):e126]. Lancet HIV. 2015 Apr;2(4):e127-36. doi: 10.1016/S2352-3018(15)00027-2. PMID: 26424673. Excluded: Inadequate duration.

Molina JM, Clumeck N, Orkin C, et al. Week 96 analysis of rilpivirine or efavirenz in HIV-1-infected patients with baseline viral load < 100 000 copies/mL in the pooled ECHO and THRIVE phase 3, randomized, double-blind trials. HIV Med. 2014 Jan;15(1):57-62. doi: 10.1111/hiv.12071. PMID: 23980523. Excluded: Inadequate duration.

Molina JM, Clumeck N, Redant K, et al. Rilpivirine vs. efavirenz in HIV-1 patients with baseline viral load 100,000 copies/ml or less: week 48 phase III analysis. AIDS. 2013 Mar 27;27(6):889-97. doi: 10.1097/QAD.0b013e32835e1554. PMID: 23276806. Excluded: Inadequate duration.

Molina JM, Lamarca A, Andrade-Villanueva J, et al. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study. Lancet Infect Dis. 2012 Jan;12(1):27-35. doi: 10.1016/S1473-3099(11)70249-3. PMID: 22015077. Excluded: Wrong population.

Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: An analysis of trial data. Ann Intern Med. 2014;161(1):1-10. PMID: 24979445. Excluded: included within an included systematic review.

Montoy JC, Chan GK, Mahadevan SV. Opt-in versus opt-out HIV screening in emergency departments: A randomized trial. Ann Emerg Med. 2012 START: 2012 Oct 8 CONFERENCE END: 2012 Oct 9, American College of Emergency Physicians, ACEP Research Forum 2012 Denver, CO United States;60(4 SUPPL. 1):S103. Excluded: Wrong intervention.

Montoy JC, Dow WH, Kaplan BC. Patient choice in opt-in, active choice, and opt-out HIV screening: randomized clinical trial. BMJ. 2016;532:h6895. doi: 10.1136/bmj.h6895. PMID: 26786744. Excluded: Wrong intervention.

Mudiope PK, Kim S, Wabwire D, et al. Long-term clinical and immunologic outcomes of HIV-infected women with and without previous exposure to nevirapine. Trop Med Int Health. 2013 Mar;18(3):344-51. doi: 10.1111/tmi.12054. PMID: 23289497. Excluded: Wrong country.

Mudzviti T, Sibanda M, Gavi S, et al. Implementing a pharmacovigilance program to evaluate cutaneous adverse drug reactions in an antiretroviral access program. J Infect Dev Ctries. 2012;6(11):806-8. doi: 10.3855/jidc.1908. PMID: 23277506. Excluded: Wrong country.

Mugo NR, Hong T, Celum C, et al. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. Jama. 2014 Jul 23-30;312(4):362-71. doi: 10.1001/jama.2014.8735. PMID: 25038355. Excluded: Wrong intervention.

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Mugusi SF, Ngaimisi E, Janabi MY, et al. Risk factors for mortality among HIV-positive patients with and without active tuberculosis in Dar es Salaam, Tanzania. Antiviral Ther. 2012;17(2):265-74. doi: 10.3851/IMP1956. PMID: 22293579. Excluded: Wrong country.

Munene E, Ekman B. Does duration on antiretroviral therapy determine health-related quality of life in people living with HIV? A cross-sectional study in a regional referral hospital in Kenya. Glob Health Action. 2014;7:23554. doi: 10.3402/gha.v7.23554. PMID: 24713353. Excluded: Wrong country.

Murphy K, Hoover DR, Shi Q, et al. Association of self-reported race with AIDS death in continuous HAART users in a cohort of HIV-infected women in the United States. AIDS. 2013 Sep 24;27(15):2413-23. doi: 10.1097/01.aids.0000432537.92958.73. PMID: 24037210. Excluded: Wrong study design for Key Question.

Murray M, Hogg RS, Lima VD, et al. The effect of injecting drug use history on disease progression and death among HIV-positive individuals initiating combination antiretroviral therapy: collaborative cohort analysis. HIV Med. 2012 Feb;13(2):89-97. doi: 10.1111/j.1468-1293.2011.00940.x. PMID: 21819529. Excluded: Wrong comparator.

Mussini C, Galli L, Lepri AC, et al. Incidence, timing, and determinants of bacterial pneumonia among HIV-infected patients: data from the ICONA Foundation Cohort. J Acquir Immune Defic Syndr. 2013 Jul 1;63(3):339-45. doi: 10.1097/QAI.0b013e318295ab85. PMID: 23591636. Excluded: Wrong outcome.

Mwesigire DM, Martin F, Seeley J, et al. Relationship between CD4 count and quality of life over time among HIV patients in Uganda: a cohort study. Health Qual Life Outcomes. 2015;13:144. doi: 10.1186/s12955-015-0332-3. PMID: 26370702. Excluded: Wrong country.

Nabatanzi R, Bayigga L, Ssinabulya I, et al. Low antigen-specific CD4 T-cell immune responses despite normal absolute CD4 counts after long-term antiretroviral therapy an African cohort. Immunol Lett. 2014 Dec;162(2 Pt B):264-72. doi: 10.1016/j.imlet.2014.09.016. PMID: 25263953. Excluded: Wrong country.

Naidoo K, Hassan-Moosa R, Yende-Zuma N, et al. High mortality rates in men initiated on anti-retroviral treatment in KwaZulu-Natal, South Africa. PLoS One. 2017;12(9):e0184124. doi: 10.1371/journal.pone.0184124. PMID: 28902869. Excluded: Wrong comparator.

Nan C, Shaefer M, Urbaityte R, et al. Abacavir use and risk for myocardial infarction and cardiovascular events: Pooled analysis of data from clinical trials. Open Forum Infect Dis. 2018 May;5(5):ofy086. doi: 10.1093/ofid/ofy086. PMID: 29766019. Excluded: Inadequate duration.

Ndagije H, Nambasa V, Namagala E, et al. Targeted spontaneous reporting of suspected renal toxicity in patients undergoing highly active anti-retroviral therapy in two public health facilities in Uganda. Drug Saf. 2015 Apr;38(4):395-408. doi: 10.1007/s40264-015-0277-9. PMID: 25749663. Excluded: Wrong country.

Nduka C, Sarki A, Uthman O, et al. Impact of antiretroviral therapy on serum lipoprotein levels and dyslipidemias: a systematic review and meta-analysis. Int J Cardiol. 2015 Nov 15;199:307-18. doi: 10.1016/j.ijcard.2015.07.052. PMID: 26241636. Excluded: Wrong outcome.

Nguyen KA, Peer N, Mills EJ, et al. A meta-analysis of the metabolic syndrome prevalence in the global HIV-infected population. PLoS One. 2016;11(3):e0150970. doi: 10.1371/journal.pone.0150970. PMID: 27008536. Excluded: Wrong outcome.

Nishijima T, Komatsu H, Teruya K, et al. Once-daily darunavir/ritonavir and abacavir/lamivudine versus tenofovir/emtricitabine for treatment-naive patients with a baseline viral load of more than 100 000 copies/ml. AIDS. 2013 Mar 13;27(5):839-42. doi: 10.1097/QAD.0b013e32835cadb7. PMID: 23719354. Excluded: Wrong comparator.

Nishijima T, Takano M, Ishisaka M, et al. Abacavir/lamivudine versus tenofovir/emtricitabine with atazanavir/ritonavir for treatment-naive Japanese patients with HIV-1 infection: a randomized multicenter trial. Intern Med. 2013;52(7):735-44. PMID: 23545667. Excluded: Wrong outcome.

Nsanzimana S, Remera E, Kanters S, et al. Effect of baseline CD4 cell count at linkage to HIV care and at initiation of antiretroviral therapy on mortality in HIV-positive adult patients in Rwanda: a nationwide cohort study.[Erratum appears in Lancet HIV. 2015 Sep;2(9):e364]. Lancet HIV. 2015 Sep;2(9):e376-84. doi: 10.1016/S2352-3018(15)00112-5. PMID: 26423551. Excluded: Wrong country.

Nunn A, Towey C, Chan PA, et al. Routine HIV screening in an urban community health center: Results from a geographically focused implementation science program. Public Health Rep. 2016 Jan-Feb;131 Suppl 1:30-40. PMID: 26862228. Excluded: Wrong study design for Key Question.

Nyaku AN, Williams LM, Galvin SR. Comparison of HIV testing uptake in an urban academic emergency department using different testing assays and support systems. AIDS Patient Care STDS. 2016 Apr;30(4):166-9. doi: 10.1089/apc.2015.0297. PMID: 26982908. Excluded: Wrong study design for Key Question.

Appendix A5. Excluded Studies List

Obiabo YO, Ogunrin OA, Ogun AS. Effects of highly active antiretroviral therapy on cognitive functions in severely immune-compromised HIV-seropositive patients. J Neurol Sci. 2012 Feb 15;313(1-2):115-22. doi: 10.1016/j.jns.2011.09.011. PMID: 21996271. Excluded: Wrong country.

O'Brien D, Spelman T, Greig J, et al. Risk factors for mortality during antiretroviral therapy in older populations in resource-limited settings. J Int AIDS Soc. 2016;19(1):20665. doi: 10.7448/IAS.19.1.20665. PMID: 26782169. Excluded: Wrong country.

Odafe S, Idoko O, Badru T, et al. Patients' demographic and clinical characteristics and level of care associated with lost to follow-up and mortality in adult patients on first-line ART in Nigerian hospitals. J Int AIDS Soc. 2012;15(2):17424. doi: 10.7448/IAS.15.2.17424. PMID: 23010378. Excluded: Wrong country.

Olsen CM, Knight LL, Green AC. Risk of melanoma in people with HIV/AIDS in the pre- and post-HAART eras: a systematic review and meta-analysis of cohort studies. PLoS One. 2014;9(4):e95096. doi: 10.1371/journal.pone.0095096. PMID: 24740329. Excluded: Wrong outcome.

O'Neill TJ, Nguemo JD, Tynan AM, et al. Risk of colorectal cancer and associated mortality in HIV: A systematic review and meta-analysis. J Acquir Immune Defic Syndr. 2017 Aug 01;75(4):439-47. doi: 10.1097/QAI.0000000000001433. PMID: 28471838. Excluded: Wrong comparator.

Orkin C, DeJesus E, Khanlou H, et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naive patients in the ARTEMIS trial. HIV Med. 2013 Jan;14(1):49-59. doi: 10.1111/j.1468-1293.2012.01060.x. PMID: 23088336. Excluded: Wrong comparator.

Otwombe KN, Laher F, Tutu-Gxashe T, et al. The effect of a maturing antiretroviral program on early mortality for patients with advanced immune-suppression in Soweto, South Africa. PLoS One. 2013;8(11):e81538. doi: 10.1371/journal.pone.0081538. PMID: 24312317. Excluded: Wrong country.

Pacheco YM, Jarrin I, Rosado I, et al. Increased risk of non-AIDS-related events in HIV subjects with persistent low CD4 counts despite cART in the CoRIS cohort. Antiviral Res. 2015 May;117:69-74. doi: 10.1016/j.antiviral.2015.03.002. PMID: 25766861. Excluded: Wrong outcome.

Pammi M, Arumainayagam J, Kumari B, et al. Safety and efficacy of tenofovir/emtricitabine or abacavir/lamivudine in combination with efavirenz in treatment naive HIV patients: a 5 year retrospective observational cohort study. (the TOKEN Study). Int J Clin Pract. 2013 Sep;67(9):922-3. doi: 10.1111/ijcp.12233. PMID: 23952469. Excluded: Wrong country.

Pantazis N, Psichogiou M, Paparizos V, et al. Treatment modifications and treatment-limiting toxicities or side effects: Risk factors and temporal trends. AIDS Res Hum Retroviruses. 2015 Jul;31(7):707-17. doi: 10.1089/AID.2015.0018. PMID: 25950848. Excluded: Wrong study design for Key Question.

Patel P, Bennett B, Sullivan T, et al. Rapid HIV screening: missed opportunities for HIV diagnosis and prevention. J Clin Virol. 2012 May;54(1):42-7. doi: 10.1016/j.jcv.2012.01.022. PMID: 22381919. Excluded: Wrong comparator.

Patterson S, Cescon A, Samji H, et al. Cohort profile: HAART Observational Medical Evaluation and Research (HOMER) cohort. Int J Epidemiol. 2015 Feb;44(1):58-67. doi: 10.1093/ije/dyu046. PMID: 24639444. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Pedrol E, Llibre JM, Tasias M, et al. Outcome of neuropsychiatric symptoms related to an antiretroviral drug following its substitution by nevirapine: the RELAX study. HIV Med. 2015 Nov;16(10):628-34. doi: 10.1111/hiv.12298. PMID: 26238151. Excluded: Wrong intervention.

Perez-Molina JA, Diaz-Menendez M, Plana MN, et al. Very late initiation of HAART impairs treatment response at 48 and 96 weeks: results from a meta-analysis of randomized clinical trials. J Antimicrob Chemother. 2012 Feb;67(2):312-21. doi: 10.1093/jac/dkr478. PMID: 22127587. Excluded: Wrong population.

Perez-Molina JA, Mora Rillo M, Suarez-Lozano I, et al. Response to combined antiretroviral therapy according to gender and origin in a cohort of naive HIV-infected patients: GESIDA-5808 study. HIV Clin Trials. 2012 May-Jun;13(3):131-41. doi: 10.1310/hct1303-131. PMID: 22592093. Excluded: Wrong comparator.

Peters PJ, Westheimer E, Cohen S, et al. Screening yield of HIV antigen/antibody combination and pooled HIV RNA testing for acute HIV infection in a high-prevalence population. JAMA. 2016 Feb 16;315(7):682-90. doi: 10.1001/jama.2016.0286. PMID: 26881371. Excluded: Wrong comparator.

Petersen ML, Tran L, Geng EH, et al. Delayed switch of antiretroviral therapy after virologic failure associated with elevated mortality among HIV-infected adults in Africa. AIDS. 2014 Sep 10;28(14):2097-107. PMID: 24977440. Excluded: Wrong country.

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Petoumenos K, Reiss P, Ryom L, et al. Increased risk of cardiovascular disease (CVD) with age in HIV-positive men: a comparison of the D:A:D CVD risk equation and general population CVD risk equations. HIV Med. 2014 Nov;15(10):595-603. doi: 10.1111/hiv.12162. PMID: 24840675. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Phanuphak N, Ananworanich J, Teeratakulpisarn N, et al. A 72-week randomized study of the safety and efficacy of a stavudine to zidovudine switch at 24 weeks compared to zidovudine or tenofovir disoproxil fumarate when given with lamivudine and nevirapine. Antiviral Ther. 2012;17(8):1521-31. doi: 10.3851/IMP2497. PMID: 23220732. Excluded: Inadequate duration.

Phusanti S, Manosudprasit K, Sungkanuparph S. Long-term liver diseases after initiation of antiretroviral therapy in HIV-infected patients with and without HBV or HCV coinfection. J Int Assoc Provid AIDS Care. 2017 Mar/Apr;16(2):194-200. doi: 10.1177/2325957416686838. PMID: 28071205. Excluded: Wrong intervention.

Piwowar-Manning E, Fogel JM, Laeyendecker O, et al. Failure to identify HIV-infected individuals in a clinical trial using a single HIV rapid test for screening. HIV Clin Trials. 2014 Mar-Apr;15(2):62-8. doi: 10.1310/hct1502-62. PMID: 24710920. Excluded: Wrong study design for Key Question.

Podzamczer D, Imaz A, Perez I, et al. Abacavir/lamivudine plus darunavir/ritonavir in routine clinical practice: a multicentre experience in antiretroviral therapy-naive and -experienced patients. J Antimicrob Chemother. 2014 Sep;69(9):2536-40. doi: 10.1093/jac/dku157. PMID: 24833755. Excluded: Inadequate duration.

Pottie K, Medu O, Welch V, et al. Effect of rapid HIV testing on HIV incidence and services in populations at high risk for HIV exposure: an equity-focused systematic review. BMJ Open. 2014;4(12):e006859. doi: 10.1136/bmjopen-2014-006859. PMID: 25510889. Excluded: Wrong comparator.

Prekker ME, Gary BM, Patel R, et al. A comparison of routine, opt-out HIV screening with the expected yield from physician-directed HIV testing in the ED. Am J Emerg Med. 2015 Apr;33(4):506-11. doi: 10.1016/j.ajem.2014.12.057. PMID: 25727169. Excluded: Wrong study design for Key Question.

Prosperi MC, Fabbiani M, Fanti I, et al. Predictors of first-line antiretroviral therapy discontinuation due to drug-related adverse events in HIV-infected patients: a retrospective cohort study. BMC Infect Dis. 2012;12:296. doi: 10.1186/1471-2334-12-296. PMID: 23145925. Excluded: Wrong outcome.

Protopopescu C, Raffi F, Spire B, et al. Twelve-year mortality in HIV-infected patients receiving antiretroviral therapy: the role of social vulnerability. The ANRS CO8 APROCO-COPILOTE cohort. Antiviral Ther. 2015;20(7):763-72. doi: 10.3851/IMP2960. PMID: 25859625. Excluded: Wrong outcome.

Pujari SN, Smith C, Makane A, et al. Higher risk of renal impairment associated with tenofovir use amongst people living with HIV in India: a comparative cohort analysis between Western India and United Kingdom. BMC Infect Dis. 2014;14:173. doi: 10.1186/1471-2334-14-173. PMID: 24679159. Excluded: Wrong comparator.

Raffi F, Babiker AG, Richert L, et al. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. Lancet. 2014;384(9958):1942-51. PMID: 25103176. Excluded: Wrong intervention.

Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2013 Nov;13(11):927-35. doi: 10.1016/S1473-3099(13)70257-3. PMID: 24074642. Excluded: Inadequate duration.

Rajesh R, Vidyasagar S, Varma DM, et al. A prospective study of highly active antiretroviral therapy in Indian human immunodeficiency virus positive patients. Int J Risk Saf Med. 2013 Jan 1;25(1):53-65. doi: 10.3233/JRS-130580. PMID: 23442298. Excluded: Wrong country.

Rasmussen LD, Kronborg G, Larsen CS, et al. Statin therapy and mortality in HIV-infected individuals; a Danish nationwide population-based cohort study. PLoS One. 2013;8(3):e52828. doi: 10.1371/journal.pone.0052828. PMID: 23469159. Excluded: Wrong intervention.

Read TR, Hocking JS, Bradshaw CS, et al. Provision of rapid HIV tests within a health service and frequency of HIV testing among men who have sex with men: randomised controlled trial. BMJ. 2013;347:f5086. doi: 10.1136/bmj.f5086. PMID: 24004988. Excluded: Wrong outcome.

Reniers G, Slaymaker E, Nakiyingi-Miiro J, et al. Mortality trends in the era of antiretroviral therapy: evidence from the Network for Analysing Longitudinal Population based HIV/AIDS data on Africa (ALPHA). Aids. 2014 Nov;28 Suppl 4:S533-42. doi: 10.1097/qad.0000000000000496. PMID: 25406756. Excluded: Wrong country.

Reynes J, Trinh R, Pulido F, et al. Lopinavir/ritonavir combined with raltegravir or tenofovir/emtricitabine in antiretroviral-naive subjects: 96-week results of the PROGRESS study. AIDS Res Hum Retroviruses. 2013 Feb;29(2):256-65. doi: 10.1089/AID.2011.0275. PMID: 22730929. Excluded: Wrong comparator.

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Riveiro-Barciela M, Falco V, Burgos J, et al. Neurological opportunistic infections and neurological immune reconstitution syndrome: impact of one decade of highly active antiretroviral treatment in a tertiary hospital. HIV Med. 2013 Jan;14(1):21-30. doi: 10.1111/j.1468-1293.2012.01033.x. PMID: 22726389. Excluded: Wrong population.

Rockstroh JK, DeJesus E, Henry K, et al. A randomized, double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus coformulated emtricitabine and tenofovir DF for initial treatment of HIV-1 infection: analysis of week 96 results. J Acquir Immune Defic Syndr. 2013 Apr 15;62(5):483-6. doi: 10.1097/QAI.0b013e318286415c. PMID: 23337366. Excluded: Wrong outcome.

Rokx C, Fibriani A, van de Vijver DA, et al. Increased virological failure in naive HIV-1-infected patients taking lamivudine compared with emtricitabine in combination with tenofovir and efavirenz or nevirapine in the Dutch nationwide ATHENA cohort. Clin Infect Dis. 2015 Jan 1;60(1):143-53. doi: 10.1093/cid/ciu763. PMID: 25273080. Excluded: Inadequate duration.

Roy A, Anaraki S, Hardelid P, et al. Universal HIV testing in London tuberculosis clinics: a cluster randomised controlled trial. Eur Respir J. 2013 Mar;41(3):627-34. doi: 10.1183/09031936.00034912. PMID: 22700845. Excluded: Wrong population.

Rutstein RM, Samson P, Fenton T, et al. Long-term safety and efficacy of atazanavir-based therapy in HIV-infected infants, children and adolescents: the Pediatric AIDS Clinical Trials Group Protocol 1020A. Pediatr Infect Dis J. 2015 Feb;34(2):162-7. doi: 10.1097/INF.0000000000000538. PMID: 25232777. Excluded: Inadequate duration.

Ryan R, Dayaram YK, Schaible D, et al. Outcomes in older versus younger patients over 96 weeks in HIV-1- infected patients treated with rilpivirine or efavirenz in ECHO and THRIVE. Curr HIV Res. 2013 Oct;11(7):570-5. PMID: 24467642. Excluded: Wrong comparator.

Ryom L, Mocroft A, Lundgren JD. Antiretroviral therapy, immune suppression and renal impairment in HIV-positive persons. Curr Opin HIV AIDS. 2014 Jan;9(1):41-7. doi: 10.1097/COH.0000000000000023. PMID: 24225381. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Sarfo FS, Sarfo MA, Kasim A, et al. Long-term effectiveness of first-line non-nucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral therapy in Ghana. J Antimicrob Chemother. 2014 Jan;69(1):254-61. doi: 10.1093/jac/dkt336. PMID: 24003181. Excluded: Wrong country.

Schnall R, Liu N, Sperling J, et al. An electronic alert for HIV screening in the emergency department increases screening but not the diagnosis of HIV. Appl Clin Inform. 2014;5(1):299-312. doi: 10.4338/ACI-2013-09-RA-0075. PMID: 24734140. Excluded: Wrong intervention.

Second-Line Study Group, Boyd MA, Kumarasamy N, et al. Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study. Lancet. 2013 Jun 15;381(9883):2091-9. doi: 10.1016/S0140-6736(13)61164-2. PMID: 23769235. Excluded: Wrong population.

Sendagire I, Cobelens F, Kambugu A, et al. Frequency and predictors for late start of antiretroviral therapy in primary care clinics, Kampala, Uganda. J Acquir Immune Defic Syndr. 2012 Nov 1;61(3):e33-9. doi: 10.1097/QAI.0b013e318265aad7. PMID: 22820807. Excluded: Wrong country.

Seng R, Goujard C, Krastinova E, et al. Influence of lifelong cumulative HIV viremia on long-term recovery of CD4+ cell count and CD4+/CD8+ ratio among patients on combination antiretroviral therapy. AIDS. 2015 Mar 13;29(5):595-607. doi: 10.1097/QAD.0000000000000571. PMID: 25715104. Excluded: Wrong outcome.

Sengayi M, Babb C, Egger M, et al. HIV testing and burden of HIV infection in black cancer patients in Johannesburg, South Africa: a cross-sectional study. BMC Cancer. 2015;15:144. doi: 10.1186/s12885-015-1171-7. PMID: 25884599. Excluded: Wrong country.

Sepako E, Glennie SJ, Jambo KC, et al. Incomplete recovery of pneumococcal CD4 T cell immunity after initiation of antiretroviral therapy in HIV-infected malawian adults. PLoS One. 2014;9(6):e100640. doi: 10.1371/journal.pone.0100640. PMID: 24959834. Excluded: Wrong country.

Serrano Vicente MC, Navarro Aznarez H, Carrera Lasfuentes P, et al. [Safety and effectiveness of salvage therapy in HIV patients]. Farm Hosp. 2012 Jul-Aug;36(4):187-93. PMID: 22099741. Excluded: Not English language but possibly relevant.

Serrano-Villar S, Perez-Elias MJ, Dronda F, et al. Increased risk of serious non-AIDS-related events in HIV-infected subjects on antiretroviral therapy associated with a low CD4/CD8 ratio. PLoS One. 2014;9(1):e85798. doi: 10.1371/journal.pone.0085798. PMID: 24497929. Excluded: Wrong outcome.

Serrano-Villar S, Sainz T, Lee SA, et al. HIV-infected individuals with low CD4/CD8 ratio despite effective antiretroviral therapy exhibit altered T cell subsets, heightened CD8+ T cell activation, and increased risk of non-AIDS morbidity and mortality. PLoS Pathog. 2014 May;10(5):e1004078. doi: 10.1371/journal.ppat.1004078. PMID: 24831517. Excluded: Wrong outcome.

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Serrano-Villar S, Sainz T, Ma ZM, et al. Effects of combined CCR5/integrase inhibitors-based regimen on mucosal immunity in HIV-infected patients naive to antiretroviral therapy: A pilot randomized trial.[Erratum appears in PLoS Pathog. 2016 Mar;12(3):e1005540; PMID: 27015639]. PLoS Pathog. 2016 Jan;12(1):e1005381. doi: 10.1371/journal.ppat.1005381. PMID: 26795282. Excluded: Wrong outcome.

Seth P, Figueroa A, Wang G, et al. HIV testing, HIV positivity, and linkage and referral services in correctional facilities in the United States, 2009-2013. Sex Transm Dis. 2015 Nov;42(11):643-9. doi: 10.1097/OLQ.0000000000000353. PMID: 26462190. Excluded: Wrong study design for Key Question.

Seth P, Wang G, Sizemore E, et al. HIV testing and HIV service delivery to populations at high risk attending sexually transmitted disease clinics in the United States, 2011-2013. Am J Public Health. 2015 Nov;105(11):2374-81. doi: 10.2105/AJPH.2015.302778. PMID: 26378854. Excluded: Wrong study design for Key Question.

Setkina S, Dotsenko M, Bondar S, et al. Safety and effectiveness of highly active antiretroviral therapy in treatment-naive HIV patients: Preliminary findings of a cohort event monitoring study in Belarus. Drug Saf. 2015 Apr;38(4):365-72. doi: 10.1007/s40264-015-0279-7. PMID: 25808626. Excluded: Inadequate duration.

Shaffer D, Hughes MD, Sawe F, et al. Cardiovascular disease risk factors in HIV-infected women after initiation of lopinavir/ritonavir- and nevirapine-based antiretroviral therapy in Sub-Saharan Africa: A5208 (OCTANE). J Acquir Immune Defic Syndr. 2014 Jun 1;66(2):155-63. doi: 10.1097/QAI.0000000000000131. PMID: 24562349. Excluded: Wrong country.

Sharma A, Hoover DR, Shi Q, et al. Relationship between body mass index and mortality in HIV-infected HAART users in the Women's Interagency HIV Study. PLoS One. 2015;10(12):e0143740. doi: 10.1371/journal.pone.0143740. PMID: 26699870. Excluded: Wrong study design for Key Question.

Shih HI, Ko NY, Hsu HC, et al. Rapid human immunodeficiency virus screening in an emergency department in a region with low HIV seroprevalence. Jpn J Infect Dis. 2015;68(4):305-11. doi: 10.7883/yoken.JJID.2014.088. PMID: 25720638. Excluded: Wrong study design for Key Question.

Shubber Z, Calmy A, Andrieux-Meyer I, et al. Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. AIDS. 2013 Jun 1;27(9):1403-12. doi: 10.1097/QAD.0b013e32835f1db0. PMID: 23343913. Excluded: Wrong intervention.

Singano V, Amberbir A, Garone D, et al. The burden of gynecomastia among men on antiretroviral therapy in Zomba, Malawi. PLoS One. 2017;12(11):e0188379. doi: 10.1371/journal.pone.0188379. PMID: 29155891. Excluded: Wrong outcome.

Sloan DJ, van Oosterhout JJ, Malisita K, et al. Evidence of improving antiretroviral therapy treatment delays: an analysis of eight years of programmatic outcomes in Blantyre, Malawi. BMC Public Health. 2013;13:490. doi: 10.1186/1471-2458-13-490. PMID: 23687946. Excluded: Wrong country.

Soliman EZ, Sharma S, Arasteh K, et al. Baseline cardiovascular risk in the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med. 2015 Apr;16 Suppl 1:46-54. doi: 10.1111/hiv.12233. PMID: 25711323. Excluded: Wrong study design for Key Question.

Surgers L, Valin N, Viala C, et al. Evaluation of the efficacy and safety of switching to tenofovir, emtricitabine, and rilpivirine in treatment-experienced patients. J Acquir Immune Defic Syndr. 2015 Jan 1;68(1):e10-2. doi: 10.1097/QAI.0000000000000401. PMID: 25321178. Excluded: Inadequate duration.

Suthar AB, Ford N, Bachanas PJ, et al. Towards universal voluntary HIV testing and counselling: a systematic review and meta-analysis of community-based approaches. PLoS Med. 2013 Aug;10(8):e1001496. doi: 10.1371/journal.pmed.1001496. PMID: 23966838. Excluded: Wrong study design for Key Question.

Swartz JE, Vandekerckhove L, Ammerlaan H, et al. Efficacy of tenofovir and efavirenz in combination with lamivudine or emtricitabine in antiretroviral-naive patients in Europe. J Antimicrob Chemother. 2015;70(6):1850-7. doi: 10.1093/jac/dkv033. PMID: 25740950. Excluded: Inadequate duration.

Tanaka H, Arai M, Tomoda Y, et al. Evaluation of renal adverse effects of combination anti-retroviral therapy including tenofovir in HIV-infected patients. J Pharm Pharm Sci. 2013;16(3):405-13. PMID: 24021289. Excluded: Inadequate duration.

Tanuma J, Lee KH, Haneuse S, et al. Incidence of AIDS-defining opportunistic infections and mortality during antiretroviral therapy in a cohort of adult HIV-infected individuals in Hanoi, 2007-2014. PLoS One. 2016;11(3):e0150781. doi: 10.1371/journal.pone.0150781. PMID: 26939050. Excluded: Inadequate duration.

Teofilo E, Rocha-Pereira N, Kuhlmann B, et al. Long-term efficacy, tolerability, and renal safety of atazanavir/ritonavir-based antiretroviral therapy in a cohort of treatment-naive patients with HIV-1 infection: the REMAIN study. HIV Clin Trials. 2016 Feb;17(1):17-28. doi: 10.1080/15284336.2015.1112494. PMID: 26899539. Excluded: Wrong outcome.

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Todd JV, Cole SR, Pence BW, et al. Effects of antiretroviral therapy and depressive symptoms on all-cause mortality among HIV-infected women. Am J Epidemiol. 2017 May 15;185(10):869-78. doi: 10.1093/aje/kww192. PMID: 28430844. Excluded: Wrong outcome.

U.S. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Accessed January 11, 2019. Excluded: Not a study.

Uthman OA, Okwundu C, Gbenga K, et al. Optimal timing of antiretroviral therapy initiation for HIV-infected adults with newly diagnosed pulmonary tuberculosis: A systematic review and meta-analysis. Ann Intern Med. 2015 Jul 7;163(1):32-9. doi: 10.7326/M14-2979. PMID: 26148280. Excluded: Wrong population.

Vendruscolo O, Majdalani M, Mota R, et al. Frequency of adverse events associated to antiretroviral drugs in patients starting therapy in Salvador, Brazil. Braz J Infect Dis. 2015 Jan-Feb;19(1):108-9. doi: 10.1016/j.bjid.2014.09.008. PMID: 25527110. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Wada N, Jacobson LP, Cohen M, et al. Cause-specific mortality among HIV-infected individuals, by CD4(+) cell count at HAART initiation, compared with HIV-uninfected individuals. AIDS. 2014 Jan 14;28(2):257-65. doi: 10.1097/QAD.0000000000000078. PMID: 24105030. Excluded: Wrong study design for Key Question.

Wolff MJ, Giganti MJ, Cortes CP, et al. A decade of HAART in Latin America: Long term outcomes among the first wave of HIV patients to receive combination therapy. PLoS One. 2017;12(6):e0179769. doi: 10.1371/journal.pone.0179769. PMID: 28651014. Excluded: Wrong intervention.

Wu PY, Cheng CY, Liu CE, et al. Multicenter study of skin rashes and hepatotoxicity in antiretroviral-naive HIV-positive patients receiving non-nucleoside reverse-transcriptase inhibitor plus nucleoside reverse-transcriptase inhibitors in Taiwan. PLoS One. 2017;12(2):e0171596. doi: 10.1371/journal.pone.0171596. PMID: 28222098. Excluded: Inadequate duration.

Zhyvytsia D. Mortality and its predictors among highly active antiretroviral therapy naive hiv-infected individuals: data from prospective cohort study in Ukraine. Georgian Med. 2014 Jul-Aug(232-233):69-74. PMID: 25214276. Excluded: Wrong population.

Zolopa A, Sax PE, DeJesus E, et al. A randomized double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: analysis of week 96 results. J Acquir Immune Defic Syndr. 2013 May 1;63(1):96-100. doi: 10.1097/QAI.0b013e318289545c. PMID: 23392460. Excluded: Inadequate duration.

Preferred Regimens

Integrase strand transfer inhibitor + two nucleoside reverse transcriptase inhibitors:

- Bictegravir/tenofovir alafenamide/emtricitabine
- Dolutegravir/abacavir/lamivudine*
- Dolutegravir + tenofovir†/emtricitabine*
- Raltegravir + tenofovir†/emtricitabine*

Secondary Regimens (Based on Clinical Considerations)

Integrase strand transfer inhibitor + two nucleoside reverse transcriptase inhibitors:

- Elvitegravir/tenofovir†/emtricitabine
- Raltegravir + abacavir/lamivudine*

Boosted protease inhibitor + two nucleoside reverse transcriptase inhibitors:

- Darunavir/cobicistat or darunavir/ritonavir + tenofovir†/emtricitabine*
- Atazanavir/cobicistat or atazanavir/ritonavir + tenofovir†/emtricitabine*
- Darunavir/cobicistat or darunavir/ritonavir + abacavir/lamivudine*

Nonnucleoside reverse transcriptase inhibitor + two nucleoside reverse transcriptase inhibitors:

- Doravirine/tenofovir disoproxil fumarate†/lamivudine or doravirine + tenofovir alafenamide†/emtricitabine
- Efavirenz + tenofovir disoproxil fumarate†/emtricitabine*
- Rilpivirine/tenofovir†/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.
†Tenofovir alafenamide and tenofovir disoproxil fumarate are two forms of tenofovir approved by the U.S. Food and Drug Administration.

Source: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. October 25, 2018. Available at https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.

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

- 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

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

Source: U.S. Preventive Services Task Force Procedure Manual. Accessed at https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes.

Appendix A8. Expert Reviewers of the Draft Report

- 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

Study name Author, Year	Study design	Setting	Duration of followup	Treatment groups	Inclusion criteria	Population characteristics	Screened Eligible Enrolled Analyzed Lost to followup	Funding source	Quality rating
START Lundgren, 2015[85]	RCT	Africa, Europe, Israel, North America, South America, Mexico, Australia	3 years (mean)	A. Immediate ART: CD4 >500 cells/mm^3 (n=2,326) B. Deferred ART: CD4 <350 cells/mm^3 (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/mm^3 at least 2 weeks apart within 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 Analyzed: 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

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Study name Author, Year	Study design	Setting	Duration of followup	Treatment groups	Inclusion criteria	Population characteristics	Screened Eligible Enrolled Analyzed Lost to followup	Funding source	Quality rating
START O'Connor, 2017[94]	Same as Lundgren, 2015	Same as Lundgren, 2015	Same as Lundgren, 2015	Same as Lundgren, 2015	Same as Lundgren, 2015	Same as Lundgren, 2015	Same as Lundgren, 2015	Same as Lundgren, 2015	Same as Lundgren, 2015
HPTN 052 Grinsztejn, 2014[90]	RCT	Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, U.S., Zimbabwe	Median 2.1 years	A. Immediate ART: CD4 ≥350 to <550 cells/mm^3 (n=886) B. Delayed ART: CD4 ≤250 cells/mm^3 (n=877)	HIV-positive member of serodiscordant couple with CD4 ≥350 to <550 cells/mm^3 and no previous long-term ART	A vs. B Median age 33 years (IQR, 27 to 39 years) Mean age <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, 3.8 to 4.9) vs. 4.4 (IQR, 3.9 to 4.9) $\log_{10}$ copies/mL (4.4 $\log_{10}$ copies/mL = 24,119 copies/mL) Note: Only two couples enrolled from the U.S., both were subsequently excluded from the study	Screened: 5,419 couples Eligible: 1,763 HIV-1 infected partners Enrolled: 1,763 Analyzed: 1,701 Lost to followup: 2% (34/176)	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.	Good
HPTN 052 Cohen 2016[93]	Same as Grinsztejn, 2014	Same as Grinsztejn, 2014	Median 5.5 years	Same as Grinsztejn, 2014; HIV uninfected partner: A. Immediate ART (n=901) B. Delayed ART (n=888)	HIV uninfected member of serodiscordant couple	Same as Grinsztejn, 2014; demographic and clinical characteristics of uninfected partners NR	Same as Grinsztejn, 2014	Same as Grinsztejn, 2014	Same as Grinsztejn, 2014
TEMPRANO	RCT	Ivory Coast	30 months	A. Early ART:	Age ≥18 years,	A vs. B	Screened:	French National Agency for	Fair

Appendix B Table 1. Key Question 4: Evidence Table of Trials of Initiating Antiretroviral Therapy at Different CD4 Counts on Clinical Outcomes—Study Characteristics

Study name Author, Year	Study design	Setting	Duration of followup	Treatment groups	Inclusion criteria	Population characteristics	Screened Eligible Enrolled Analyzed Lost to followup	Funding source	Quality rating
ANRS 12136 Study TEMPRANO ANRS Study Group, 2015[86]				immediate ART initiation upon study enrollment (n=1,033) B. Delayed ART ART initiation according to criteria described below (n=1,023) 1. From March 1, 2008 to November 30, 2009, criteria for ART initiation were: 1 CD4 count <200 cells/mm^3 or WHO clinical stage 4; or 1 CD4 count 200 to 350 cells/mm^3 and WHO clinical stage 2 or 3 2. From December 1, 2009 to July 31, 2013, criteria for ART initiation were: 2 consecutive CD4 counts <350 cells/mm^3 regardless of WHO clinical stage; or WHO clinical stage 3 or 4	HIV-1 infection or dual infection with HIV-1 and HIV-2, CD4 count <800 cells/mm^3, met no criteria for starting ART according to the most recent WHO guidelines	Median age 35 vs. 35 years 80% vs. 77% female Race NR; study conducted in Africa CD4 459 (IQR, 359 to 575) vs. 466 cells/mm^3 (IQR, 369 to 584) HIV-RNA 4.6 (IQR, 4.0 to 5.2) vs. 4.7 (IQR, 4.0 to 5.3) $\log_{10}$ copies/mL (39,811 vs. 50,119)	2,962 Eligible: 2,560 Enrolled: 2,076 Analyzed: 2,056 Lost to followup: 3% (58/2076)	Research on AIDS and Viral Hepatitis	

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Study name Author, Year	Study design	Setting	Duration of followup	Treatment groups	Inclusion criteria	Population characteristics	Screened Eligible Enrolled Analyzed Lost to followup	Funding source	Quality rating
TEMPRANO ANRS 12136 Study TEMPRANO ANRS Study Group, 2015[86] Cont'd	See above	See above	See above	3. From August 1, 2013 to study cessation, 2 consecutive CD4 counts <350 cells/mm^3, 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	See above	See above	See above	See above	See above

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

Study name Author, Year	Treatment groups	Clinical outcomes*	Adverse events
START Lundgren, 2015[85]	A. Immediate ART: CD4 >500 cells/mm^3 (n=2,326) B. Deferred ART: CD4 <350 cells/mm^3 (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)
START O'Connor, 2017[94]	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

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Study name Author, Year	Treatment groups	Clinical outcomes*	Adverse events
HPTN 052 Grinsztejn, 2014[90]	A. Immediate ART: CD4 ≥350 to <550 cells/mm^3 (n=886) B. Delayed ART: CD4 ≤250 cells/mm^3 (n=877)	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)	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)
HPTN 052 Cohen 2016[93]	Same as Grinsztejn, 2014; HIV uninfected partner: A. Immediate ART (n=901) B. Delayed ART (n=888)	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)	NR

Appendix B Table 2. Key Question 4: Evidence Table of Trials of Initiating Antiretroviral Therapy at Different CD4 Counts on Clinical Outcomes—Results

Study name Author, Year	Treatment groups	Clinical outcomes*	Adverse events
TEMPRANO ANRS 12136 Study TEMPRANO ANRS Study Group, 2015[86]	A. Early ART: immediate ART initiation upon study enrollment (n=1,033) B. Delayed ART: ART initiation according to criteria described below (n=1,023): 1. From March 1, 2008 to November 30, 2009, the criteria for ART initiation were: 1 CD4 count <200 cells/mm^3 or WHO clinical stage 4; or 1 CD4 count 200 to 350 cells/mm^3 and WHO clinical stage 2 or 3 2. From December 1, 2009 to July 31, 2013, the criteria for ART initiation were: 2 consecutive CD4 counts <350 cells/mm^3 regardless of WHO clinical stage; or WHO clinical stage 3 or 4 3. From August 1, 2013 to study cessation, 2 consecutive CD4 counts <350 cells/mm^3, 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 Patients with baseline CD4 ≥500 cells/mm^3: 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) All-cause mortality: 1.1% (5/436) vs. 1.5% (6/413); RR, 0.79 (95% CI, 0.24 to 2.57) 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) Progression to AIDS: 3.2% (14/436) vs 5.8% (24/413); aHR, 0.55 (95% CI, 0.28 to 1.06); RR, 0.55 (95% CI, 0.29 to 1.05) 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) 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) Patients with baseline CD4 <500 cells/mm^3: 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) 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) 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) 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) 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) All patients: 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) 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) 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) 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) 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) 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)	A vs. B Patients with CD4 ≥500 cells/mm^3 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) Patients with CD4 <500 cells/mm^3 at baseline: Any Grade 3 or 4 adverse event: 7.2% (43/597) vs. 7.2% (44/610); RR, 1.00 (95% CI, 0.67 to 1.50) 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) 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) 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) 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

Study name Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential (>10%)/high (>20%)?	Analyze persons in the groups in which they were randomized?	Quality
START[85]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Good
HPTN 052[90]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Good
TEMPRANO ANRS, 2015[86]	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Fair

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

Author, Year	Setting/ Data source	Cohorts	Duration of followup	Inclusion criteria	Number analyzed	Comparison groups	Population characteristics	Quality rating
Edwards, 2015[88]	U.S., Centers for AIDS Research Network of Integrated Clinical Systems	Centers for AIDS Research Network of Integrated Clinical Systems enrollees from 1 of 8 sites	10 years	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	3,532	A. Initiation of ART at <500 cells/mm^3 B. Initiation of ART at <350 cells/mm^3 C. Initiation of ART at <200 cells/mm^3	*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% CD4 count: 37% 500 to 600 cells/mm^3; 34% 601 to 750 cells/mm^3; 23% 751 to 1,000 cells/mm^3; 7% >1,000 cells/mm^3	Fair
Lima, 2015[96]	British Columbia (Canada) Centre for Excellence in HIV/AIDS Drug Treatment Programme	DTP enrollees between January 1 2000 and December 31 2012	Median 5 years	ART naïve, age ≥19 years enrolled in DTP during specified time frame	4,120	A. Initiation of ART at ≥500 cells/ mm^3 B. Intiation of ART at <500 cells/mm^3 C. Initiation of ART at ≥350 cells/mm^3 D. Initiation of ART at <350 cells/mm^3	*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: 44% <200 cells/mm^3; 32% 200 to 349 cells/mm^3; 14% 350 to 499 cells/mm^3; 10% ≥500 cells/mm^3	Fair
Lodi, 2015[87]	Pooled national health care data from 12 European cohorts	HIV-CAUSAL collaboration of cohorts in Europe and the U.S.	7 years	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	55,826	A. Initiation of ART at ≥500 cells/mm^3 B. Intiation of ART at <500 cells/mm^3 C. Initiation of ART at <350 cells/mm^3	A vs. B Mean age 35 (IQR, 28 to 44) vs. 38 (IQR, 31 to 46) 22% vs. 24% female Transmission group: 30% vs. 40% heterosexual; 56% vs. 44% homosexual or bisexual; 2 vs. 3% PWID; 11% vs. 14% other/unknown Geographic origin: 78% vs. 67% Western country; 11% vs. 20% sub-Saharan Africa; 8% vs. 9% rest of the world; 4% vs. 5% unknown	Fair

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

Author, Year	Setting/ Data source	Cohorts	Duration of followup	Inclusion criteria	Number analyzed	Comparison groups	Population characteristics	Quality rating
Lodi, 2017[95]	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/mm^3 B. Initiation of ART at <500 cells/mm^3 C. Initiation of ART at <350 cells/mm^3	*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/mm^3; 13% 100 to 200 cells/mm^3; 25% 200 to 349 cells/mm^3; 22% 350 to 499 cells/mm^3; 29% ≥500 cells/mm^3 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/mm^3; 16% 100 to 200 cells/mm^3; 23% 200 to 349 cells/mm^3; 19% 350 to 499 cells/mm^3; 22% ≥500 cells/mm^3 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

Author, Year	Comparison groups	Adjusted variables for statistical analysis	Clinical outcomes
Edwards, 2015[88]	A. Initiation of ART at <500 cells/mm^3 B. Initiation of ART at <350 cells/mm^3 C. Initiation of ART at <200 cells/mm^3	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[96]	A. Initiation of ART at ≥500 cells/mm^3 B. Intiation of ART at <500 cells/mm^3 C. Initiation of ART at ≥350 cells/mm^3 D. Initiation of ART at <350 cells/mm^3	Mortality: Age, sex, history of injection drug use, longitudinal adherence to cART, longitudinal viral load, followup 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^3, 2000–2006: 0.14 (0.08 to 0.22) CD4 ≥350 cells/mm^3, 2000–2006: 0.14 (0.09 to 0.22) CD4 <350 cells/mm^3, 2007–2012: 0.05 (0.03 to 0.08) CD4 ≥350 cells/mm^3, 2007–2012: 0.02 (0.01 to 0.04) CD4 <500 cells/mm^3, 2000–2006: 0.13 (0.08 to 0.22) CD4 ≥500 cells/mm^3, 2000–2006: 0.16 (0.10 to 0.24) CD4 <500 cells/mm^3, 2007–2012: 0.05 (0.03 to 0.02) CD4 ≥500 cells/mm^3, 2007–2012: 0.01 (0.01 to 0.02) AIDS-defining illness, probability (IQR): CD4 <350 cells/mm^3, 2000–2006: 0.14 (0.08 to 0.22) CD4 ≥350 cells/mm^3, 2000–2006: 0.13 (0.08 to 0.22) CD4 <350 cells/mm^3, 2007–2012: 0.05 (0.03 to 0.08) CD4 ≥350 cells/mm^3, 2007–2012: 0.03 (0.01 to 0.05) CD4 <500 cells/mm^3, 2000–2006: 0.04 (0.02 to 0.08) CD4 ≥500 cells/mm^3, 2000–2006: 0.02 (0.01 to 0.03) CD4 <500 cells/mm^3, 2007–2012: 0.03 (0.01 to 0.04) CD4 ≥500 cells/mm^3, 2007–2012: 0.01 (0.00 to 0.01)

Appendix B Table 5. Key Question 4: Evidence Table of Cohort Studies of Initiating Antiretroviral Therapy at Different CD4 Counts on Clinical Outcomes—Results

Author, Year	Comparison groups	Adjusted variables for statistical analysis	Clinical outcomes
Lodi, 2015[87]	A. Initiation of ART at ≥500 cells/mm^3 B. Intiation of ART at <500 cells/mm^3 C. Initiation of ART at <350 cells/mm^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[95]	A. Initiation of ART at ≥500 cells/mm^3 B. Initiation of ART at <500 cells/mm^3 C. Initiation of ART at <350 cells/mm^3	CD4 cell count, HIV-RNA level, age, sex, mode of acquisition, calendar year, geographical origin, cohort	<u>General HIV population</u> 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^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 2.82) <u>VA population</u> 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

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality rating
Lodi, 2015[96]	Yes	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Lodi, 2017[95]	Yes	Unclear	Yes	Unclear	Yes	Yes	No	Yes	Fair
Lima, 2015[96]	Yes	Unclear	Yes	Unclear	Yes	Yes	No	Yes	Fair
Edwards, 2015[88]	Yes	Unclear	Yes	Unclear	Yes	Yes	No	Yes	Fair

Appendix B Table 7. Key Question 5: Evidence Table of Systematic Reviews of Harms While Using Antiretroviral Therapy—Study Characteristics

Author, year	Databases and time period covered	Number of studies Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Funding	Quality rating
Ding, 2012[101] U.S. Food and Drug Administration	International Pharmaceutical Abstracts, Inteleos, Embase, Scopus (searches conducted by U.S. Food and Drug Administration and GlaxoSmithKline) Inception to 2009	26 RCTs included in meta-analysis N=9,868 (5,028 ABC vs. 4,840 non-ABC)	Trials, sample size >50 (Observational studies excluded)	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/mm^3 Log viral load: 4.38 vs. 4.38 log_{10} 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/mm^3 Log viral load: 4.72 vs. 4.7 log_{10} copies/mL *Other trials* N: 702 vs. 863 % Male: 82% vs. 66% Age: 42 vs. 42 years CD4 count: 255 vs. 250 cells/mm^3 Log viral load: 5.03 vs. 4.94 log_{10} copies/mL	ABC, randomized as part of a combined antiretroviral regimen, vs. non-ABC regimens	Reports no funding or conflicts of interest	Fair
Ford, 2015[105]	MEDLINE, Embase, LILACS, Cochrane Central Register of Controlled Trials Inception to 2014	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)	HIV+ adults and children (although no pediatric trials met inclusion criteria) No geographical restrictions	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	Fair

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

Author, year	Harms
Ding, 2012[101] 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[105]	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

Author Year	A priori design provided?	Duplicate study selection and data extraction? a. Study selection b. Data extraction	Comprehensive literature search performed?	Searched for more than published studies?	List of studies (included and excluded) provided?	Characteristics of the included studies provided?	Scientific quality of included studies assessed and documented?	Scientific quality of the included studies used appropriately in formulating conclusions?	Methods used to combine the findings of studies appropriate?	Likelihood of publication bias assessed?	Conflict of interest stated? a) Systematic Review b) Individual Studies	Quality Rating
Ding, 2012[101]	Yes	Unclear	Yes	Yes	Yes/No	Yes	No	Unclear	Yes	No	Yes/No	Fair
Ford, 2015[105]	Yes	Yes/Yes	Yes	No	Yes/No	Yes	Yes	Unclear	Yes	Yes	Yes/No	Fair

Appendix B Table 10. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

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
Multiple	Arribas 2017[115] 2 RCTs (GS-US-292-0104 and GS-US-292-0111)	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	2 years	A. TAF + EVG/ COBI/FTC (n=866) B. TDF + EVG/ COBI/FTC (n=867)	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.	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/mm^3 HIV-1 RNA >100,000 copies/mL: 23% vs. 22% Median eGFR (Cockcroft-Gault): 117 vs. 114 mL/min	1,733	Gilead Sciences, Inc.	Good
Multiple	Rockstroh 2013[116] STARTMRK Study RCT	67 centers Australia, Brazil, Canada, Columbia, Germany, India, Italy, Mexico, Peru, Spain, Thailand, U.S.	4.6 years	A. RAL + TDF-FTC (n=281) B. EFV + TDF-FTC (n=282)	Treatment-naive HIV-infected patients age ≥18 years were eligible if their viral load was >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 >5 xULN, patients with acute or decompensated chronic hepatitis excluded.	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	563	Merck	Good

Appendix B Table 10. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

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
Mortality	Kowalska, 2012[121] EuroSIDA Study Prospective cohort, single arm	103 centers Europe, Israel, Argentina	Followed from time of starting ART or study entry until death or 6 months after last followup visit Median followup: 5.4 years (70,613 person-years)	cART	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	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/mm^3 HIV RNA viral load: 2.84 log_{10} copies/mL Median time of exposure to cART: 4.4 years	12,069	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	Fair

Appendix B Table 10. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

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
Myocardial Infarction	Sabin 2016[102] D:A:D Study Prospective cohort	11 cohorts Europe, Australia, U.S.	Followed from study entry until MI, death, February 2013, or 6 months after last visit	ABC vs. not on ABC	HIV-1 positive patients followed prospectively during visits to outpatient clinics scheduled 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)	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 trigylcerides: 1.5 mmol/L Median CD4: 566 cells/mm^3 Median viral load: 1.7 log_{10} copies/mL	49,717	See table note	Good

Appendix B Table 10. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

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
Myocardial Infarction	Monforte, 2013[104] D:A:D Study Prospective cohort	Same as Sabin 2016	Followed from study entry until MI, stroke, death, February 2011, or 6 months after last visit	ATV, boosted or unboosted by RTV	Same as Sabin 2016	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. 6.5% 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%	49,734	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

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
Myocardial Infarction	Monforte, 2013[104] D:A:D Study Prospective cohort	See above	See above	See above	See above	Framingham score: Low (<10%) 60.3% vs. 50.3% vs. 49.1% Moderate (10%–20%) 19.8% vs. 14.0% vs. 8.9% High (>20%) 8.6% vs. 6.7% vs. 3.7% Unknown 11.3% vs. 29.0% vs. 38.3%	See above	See above	See above
Myocardial Infarction	Desai 2015[103] Retrospective cohort	Database analysis U.S.	Enrolled from 1996–2009 Mean followup varied according to study drug	Current ART exposure vs. no exposure	Patients with evidence of a positive HIV lab test on or after January 1, 1996, who also received subsequent medical care in the VA	Mean age: 46.5 years (SD, 10.1) % Male: 97.6% 33.8% 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	24,510	National Institutes of Health; Patient-Centered Outcomes Research Institute	Fair

Appendix B Table 10. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

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	Bruyand, 2015[109] D:A:D Study Prospective cohort	Same as Sabin 2016	Followed from study entry or January 2004 until cancer diagnosis, February 2012, or 6 months after last visit 241,556 Person-years (6.5 years per person)	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/mm^3 Median plasma HIV RNA: 2.3 log_{10} copies/mL HCV: positive 10.5%, negative 63.0%, unknown 26.5% HBV: positive 4.2%, negative 66.0%, 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

Appendix B Table 10. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

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, 2016[110] D:A:D Study Prospective cohort	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 Median followup: 8.4 years	cART	Same as Sabin 2016	White ethnicity: 49.6% % Male: 73.5% Median age: 40 years Mode of HIV acquisition: MSM 44.5%, PWID 14.0%, heterosexual 33.6%, other/unknown 7.8% Ethnicity: white 49.6%, black African 9.4%, other 2.8%, unknown 38.2% CD4 cell count: 434 cells/mm^3 HIV RNA: 2.3 log_{10} copies/mL HCV status: positive 18.1%, negative 63.7%, unknown 18.2% HBV status: positive 4.6%, negative 80.6%, unknown 14.8% Smoking status: current 38.7%, ex-smoker 17.0%, never 26.4%, unknown 17.9% Previous AIDS: 23.8%	45,544	See table note	Same as Sabin 2016
Cancer/Liver Disease	Kovari, 2013[117] D:A:D Study Prospective cohort	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	% Male: 73.1% Median age: 38 years Ethnicity: white 47.3%, black 7.7%, other 2.2%, unknown 42.9% Mode of HIV acquisition: MSM 49.9%, PWID 1.8%, heterosexual 41.3%, other/unknown 7.0% CD4 cell count: 410 cells/mm^3 Previous clinical AIDS: 22.6% Diabetes: 2.6% Smoking status: current 30.6%, former 20.6%, never 29.6%, unknown 19.2% Median cumulative exposure to treatment: ART 0.9 years, NRTI 0.8 years, PI 0.0 years, NNRTI 0.0 years Treatment status: naive 38.1%, interruption 4.7%, on ART 57.2%	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

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
Kidney Disease	Ryom, 2013[123] D:A:D Study Prospective cohort	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/mm^3 Mean HIV RNA load: 2.1 log_{10} 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

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
Kidney Disease	Mocroft, 2016[111] D:A:D Study Prospective cohort	Same as Sabin 2016	Followed from January 2004 until they had a confirmed eGFR of ≤60 mL/min per 1.73 m^2 or until last eGFR during followup or February 2014 Median followup duration of 7.2 years	cART (TDF, ATV/r, LPV/r, other RTV-boosted PIs, ABC)	Same as Sabin 2016 All participants with normal baseline renal function eGFR of ≥90 mL/min per 1.73 m^2	Median age: 39 years % Male: 73% Ethnicity: white 46%, black 8%, other 2%, unknown 44% Risk factor: MSM 45%, PWID 13%, heterosexual 36%, other 6% 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) Median CD4 cell count: 441 cells/mm^3 Median viral load <400 copies/mL: 56% Antiretrovirals: never used ART 27%, ever started ART 72% Smoking status: current 42%, previous 18%, never 28%, unknown 12% Family history of CVD: no 64%, yes 7%, unknown 29% Hypertension: 8% Previous CVD: 1% Diabetes: 3% AIDS: 22%	23,905	See table note	Same as Sabin 2016
Kidney Disease	Laprise 2013[118] Retrospective cohort	Single center Canada	Enrollment 2002–2012 Median followup 7.9 years	A. TDF exposure B. Nonexposure Other ART comparisons: NRTI, NNRTI, PI exposure vs. nonexposure	Enrolled after January 2002 with eGFR measures	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 m^2	1,043	None reported	Fair

Appendix B Table 10. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

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
Kidney Disease	Nkhoma 2016b[120] (see also **Fracture**) Retrospective cohort	Database analysis U.S.	Enrollment 2008–2014 Mean followup 2.5 years	A. EVF + TDF-FTC B. RPV + TDF-FTC C. EVG + COBI + TDF-FTC	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	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	9,876	Bristol-Myers Squibb, authors are employees of and own stock in Bristol-Myers Squibb	Fair
Kidney Disease	Scherzer 2012[119] Retrospective cohort	National database U.S.	Enrollment from 1997–2007 Median followup 3.9–5.5 years (varied according to outcome)	A. Tenofovir exposure (n=4,303) B. Nonexposure (n=6,538)	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	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 m^2 Proportion with eGFR <60 mL/min per 1.73 m^2: 4.7% vs. 7.3% Proteinuria: 19% vs. 21%	10,841	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	Fair
Suicidality	Chang 2018[108] Prospective cohort	Single center Uganda	Enrollment 2005–2015 2 years mean followup	A. EFV, any use (n=305) B. NVP only (n=389)	Age ≥18 years, ART-naive, and living within 60 km (about 37.3 miles) of the clinic	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	694	National Institutes of Health, Harvard and San Francisco Centers for AIDS Research, and Doris Duke Charitable Foundation	Fair

Appendix B Table 10. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

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
Suicidality	Smith, 2014[107] D:A:D Study (abstract only) Prospective cohort	Same as Sabin 2016	Followed from study entry until death, February 2013, or last study visit	cART, including efavirenz-containing regimens vs. other	Same as Sabin 2016	NR, but see above for patient characteristics from other D:A:D publications	49,717	See table note	Same as Sabin 2016
Suicidality	Nkhoma, 2016[106] Retrospective cohort	Unclear U.S.	Followed from study entry until death, end of exposure to anchor agent, disenrollment of insurance, or 2013 (end of study period)	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)	U.S. administrative claims data for commercially-insured (Truven Health MarketScan Commerical 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	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%	25,137	Bristol-Myers Squibb Authors are employees of Bristol-Myers Squibb and Truven Health Analytics	Fair

Appendix B Table 10. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Study Characteristics

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
Fracture	Borges 2017[112] EuroSIDA Study Prospective cohort	11 cohorts Europe, Australia, U.S.	Enrollment from 2004; mean followup unclear (total 86,118 person-years)	TDF exposure vs. no TDF exposure	Age >16 years with baseline data on CD4 counts and viral loads with prospective followup	Total population Mean age: 49 years % Male: 75% 86% white; 6% black; 2% Asian; 6% other 2% prior fracture 97% ART use (defined as ZDV, ddl, D4L, 3TC, FTC, TDF, ABC, NVP, EFV, SQV, RTV, LPV, IDV, NFV, ATV, LPV/r, and any other boosted PIs)	11,820	Bristol-Myers Squibb, European Union 7th Framework Programme; Gilead; Glaxo-Smith Kline; Janssen Research and Development; Merck; Pfizer; Swiss National Science Foundation; Danish National Research Foundation	Fair
Fracture	Nkhoma 2016b[120] (see also **Kidney Disease**) Retrospective cohort	Database analysis U.S.	Enrollment 2008–2014 Mean followup 2.5 years	A. EVF + TDF-FTC B. RPV + TDF-FTC C. EVG + COBI + TDF-FTC	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 regimens	A vs. B vs. C Fracture (defined as ICD-9-CM diagnosis codes for bone fracture) Mean age: 43 (10.6) vs. 42 (11.0) vs. 43 years (11.1) % Male: 87% vs. 84% vs. 89% Race/ethnicity NR	10,383	Bristol-Myers Squibb, authors are employees of and own stock in Bristol-Myers Squibb	Fair

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=nevriapine; 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., ViiV Healthcare, Merck & Co Inc., and Janssen

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

Harm category	Study author, year Study design	Intervention	Adverse events
Multiple	Arribas 2017[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, 019 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[116] STARTMRK Study 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)

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

Harm category	Study author, year Study design	Intervention	Adverse events
Mortality	Kowalska, 2012[121] EuroSIDA Study Prospective cohort, single arm	cART	Mortality overall 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) Specific causes of death AIDS-related: 32% (413/1,297); crude incidence rate, 5.85/1,000 person-years followup (95% CI, 5.28 to 6.14) Non–AIDS-related: 68% (884/1,297); crude incidence rate, 12.5/1,000 person-years followup (95% CI, 11.7 to 13.3) Non–AIDS-related infection: 9% (121/1,297) Liver-related: 14% (182/1,297) Non–AIDS-defining malignancies: 10% (125/1,297) Cardiovascular disease: 9% (122/1,297) Violent: 7% (90/1,297) Other: 7% (90/1,297) Unknown: 12% (153/1,297) 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. 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]) Non–AIDS-related: IRR, 0.97 (95% CI, 0.95 to 1.00) Non–AIDS-related infection: IRR, 0.97 (95% CI, 0.90 to 1.05) Liver-related: IRR, 0.94 (95% CI, 0.89 to 1.00) Non–AIDS-defining malignancies: IRR, 1.07 (95% CI, 1.00 to 1.04) Cardiovascular disease: IRR, 0.99 (95% CI, 0.93 to 1.06) Violent: IRR, 0.90 (95% CI, 0.81 to 0.99) Other: IRR, 1.01 (95% CI, 0.94 to 1.09) Unknown: IRR, 0.94 (95% CI, 0.86 to 1.01)

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

Harm category	Study author, year Study design	Intervention	Adverse events
Myocardial Infarction	Sabin, 2016[102] D:A:D Study Prospective cohort	ABC vs. not on ABC	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
Myocardial Infarction	Monforte, 2013[104] D:A:D Study Prospective cohort	ATV, boosted or unboosted by RTV	MI Overall events: 844/49,734 (incidence, 0.28/100 person-years followup [95% CI, 0.26 to 0.30]) >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]) >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)

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

Harm category	Study author, year Study design	Intervention	Adverse events
Myocardial Infarction	Desai 2015[103] Retrospective cohort	Current ART exposure vs. no exposure	Cardiovascular event (MI, stroke, or cardiovascular procedure) ABC: OR, 1.50 (95% CI, 1.26 to 1.79) EFV: OR, 1.40 (95% CI, 1.19 to 1.66) 3TC: OR, 1.53 (95% CI, 1.34 to 1.75) NVP: OR, 0.91 (95% CI, 0.70 to 1.18) D4L: OR, 1.14 (95% CI, 0.95 to 1.37) Tenofovir: OR, 1.10 (95% CI, 0.93 to 1.30) ZDV: OR, 1.41 (95% CI, 1.22 to 1.63) *Other drugs and ART combinations had <2 years mean followup*

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

Harm category	Study author, year Study design	Intervention	Adverse events
Cancer/ Liver Disease	Bruyand, 2015[109] 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]) Association between cART use (per year longer exposure) and cancer AIDS-defining cancer (n=718): Any cART: aRR, 0.88 (95% CI, 0.85 to 0.92) PI-based ART: aRR, 0.96 (95% CI, 0.92 to 1.00) NNRTI-based ART: aRR, 0.86 (95% CI, 0.81 to 0.91) Kaposi Sarcoma (n=341): Any cART: aRR, 0.84 (95% CI, 0.78 to 0.89) PI-based ART: aRR, 0.93 (95% CI, 0.87 to 1.00) NNRTI-based ART: aRR, 0.81 (95% CI, 0.74 to 0.90) Non-Hodgkin Lymphoma (n=321): Any cART: aRR, 0.90 (95% CI, 0.85 to 0.95) PI-based ART: aRR, 0.98 (95% CI, 0.93 to 1.04) NNRTI-based ART: aRR, 0.87 (95% CI, 0.80 to 0.94) Non–AIDS-defining cancer (n=1,114): Any cART: aRR, 1.02 (95% CI, 1.00 to 1.03) PI-based ART: aRR, 1.03 (95% CI, 1.01 to 1.05) NNRTI-based ART: aRR, 1.00 (95% CI, 0.98 to 1.02) Lung cancer (n=195): Any cART: aRR, 0.99 (95% CI, 0.95 to 1.03) PI-based ART: aRR, 1.01 (95% CI, 0.97 to 1.05) NNRTI-based ART: aRR, 0.97 (95% CI, 0.93 to 1.02) Anal cancer (n=131): Any cART: aRR, 1.06 (95% CI, 1.01 to 1.11) PI-based ART: aRR, 1.08 (95% CI, 1.04 to 1.13) NNRTI-based ART: aRR, 0.97 (95% CI, 0.97 to 1.09) Hodgkin Lymphoma (n=107): Any cART: aRR, 0.91 (95% CI, 0.85 to 0.97) PI-based ART: aRR, 0.99 (95% CI, 0.92 to 1.06) NNRTI-based ART: aRR, 0.90 (95% CI, 0.82 to 0.99) Head and neck cancer (n=97): Any cART: aRR, 1.01 (95% CI, 0.96 to 1.07) PI-based ART: aRR, 1.01 (95% CI, 0.96 to 1.07) NNRTI-based ART: aRR, 1.03 (95% CI, 0.97 to 1.10)

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

Harm category	Study author, year Study design	Intervention	Adverse events
Cancer/ Liver Disease	Ryom, 2016[110] 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) ddl: 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, 1.01 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[117] 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. Key Question 5: Evidence Table of Studies of Harms While Using Antiretroviral Therapy—Results

Harm category	Study author, year Study design	Intervention	Adverse events
Kidney Disease	Ryom, 2013[123] D:A:D Study Prospective cohort	cART	Renal impairment, median followup duration of 4.5 years: eGFR ≤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 ≤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 ≥90 mL/min: aIRR, 1.72 (95% CI, 1.38 to 2.14) After discontinuation, the treatment-associated incidence rates decreased
Kidney Disease	Mocroft, 2016[111] D:A:D Study Prospective cohort	cART (TDF, ATV/r, LPV/r, other PI/r, ABC)	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)

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

Harm category	Study author, year Study design	Intervention	Adverse events
Kidney Disease	Laprise 2013[118] 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 m^2): 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 m^2): 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 m^2): 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 m^2): 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)
Kidney Disease	Nkhoma 2016b[120] (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

Harm category	Study author, year Study design	Intervention	Adverse events
Kidney Disease	Scherzer 2012[119] 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^2): aHR, 1.36 (95% CI, 1.22 to 1.51) Rapid decline in kidney function (3 mL/min/1.73m^2 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[108] 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

Harm category	Study author, year Study design	Intervention	Adverse events
Suicidality	Smith, 2014[107] D:A:D Study (abstract only) Prospective cohort	cART, including EFV-containing regimens vs. other	Overall deaths: 4,420 over 371,333 person-years; rate, 11.9 per 1,000 person-years (95% CI, 11.6 to 12.3) Deaths with an underlying cause of suicide or psychiatric disease: Overall: 193 deaths/371,333 person-years; rate, 0.52 per 1,000 person years (95% CI, 0.45 to 0.59) EFV-containing regimen: 24 deaths/78,580 person-years; aRR, 0.59 (95% CI, 0.33 to 1.06) Other NNRTI-containing regimen: 31 deaths/64,288 person-years; aRR, 0.93 (95% CI, 0.53 to 1.62) Other ART: 66 deaths/157,664 person-years; aRR, 0.81 (95% CI, 0.49 to 1.32) No ART, naive: 21 deaths/40,454 person-years (reference) No ART, experienced: 51 deaths/30,348 person-years; aRR, 3.24 (95% CI, 1.95 to 5.38) Deaths with suicide or psychiatric disease "mentioned anywhere": Overall: 482 deaths/371,333 person-years; rate, 1.30 per 1,000-person years (95% CI, 1.18 to 1.41) Efavirenz-containing regimen: 60 deaths/78,580 person-years; aRR, 0.42 (95% CI, 0.28 to 0.63) Other NNRTI-containing regimen: 72 deaths/64,288 person-years; aRR, 0.68 (95% CI, 0.46 to 1.00) Other ART: 162 deaths/157,664 person-years; aRR, 0.52 (95% CI, 0.37 to 0.73) No ART, naive: 62 deaths/40,454 person-years (reference) No ART, experienced: 126 deaths/30,348 person-years; aRR, 2.29 (95% CI, 1.63 to 3.21)
Suicidality	Nkhoma, 2016[106] Retrospective cohort	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)	A vs. B vs. C vs. D Suicidality Events, n: 0.38% (42/11,187) vs. 2.0% (45/2,224) vs. 0.33% (29/8,796) vs. 2.5% (74/2,930) 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: Commercial: aHR, 1.029 (95% CI, 0.636 to 1.665) 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: Commercial: aHR, 1.122 (95% CI, 0.686 to 1.836) Medicaid: aHR, 0.935 (95% CI, 0.626 to 1.395) Suicide attempt Events: 7 vs. 1 vs. 1 vs. 12 Propensity score adjusted HR, EFV use vs. EFV-free regimen: Commercial: aHR, 5.697 (95% CI, 0.688 to 47.147) 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: Commercial: aHR, 1.000 (95% CI, 0.513 to 1.950) Medicaid: aHR, 0.710 (95% CI, 0.334 to 1.509)

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

Harm category	Study author, year Study design	Intervention	Adverse events
Fracture	Borges 2017[112] EuroSIDA Study Prospective cohort	TDF exposure vs. no TDF exposure	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)
Fracture	Nkhoma 2016b[120] (see also **Kidney Disease**) Retrospective cohort	A. EVF + TDF-FTC B. RPV + TDF-FTC C. EVG/COBI + TDF-FTC	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: IR, 3.4 (95% CI, 2.7 to 4.2) vs. 3.6 (95% CI, 1.9 to 6.9) vs. 7.2 (95% CI, 4.4 to 12.0); unadjusted IRD, A vs. B: -0.25 (95% CI, -1.02 to 0.44); IRD, A vs. C: -3.85 (95% CI, -5.02 to -2.78)

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=rilpivirine; RR=relative risk; RTV=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.

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Appendix B Table 12. Key Question 5: Quality Assessment of Randomized, Controlled Trials

Study name Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential (>10%)/ high (>20%)?	Analyze persons in the groups in which they were randomized?	Quality
Arribas 2017[115]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Rockstroh 2013[116]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good

Appendix B Table 13. Key Question 5: Quality Assessment of Single-Arm Cohort Studies

Study Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Is there high attrition?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality rating
D:A:D Study[102,104,107,109-111,117,123]	Yes	Yes	Yes	Yes	No	Yes	Good
Desai 2015[103]	Yes	Yes	No	No	Unclear	Yes	Fair
EuroSIDA Study Kowalska, 2012[121], Borges 2017[112]	Yes	Yes	Unclear	No	Unclear	Yes	Fair
Laprise 2013[118]	Yes	Yes	Unclear	No	Unclear	Yes	Fair
Scherzer 2012[119]	Yes	Yes	Unclear	No	Unclear	Yes	Fair

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

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality rating
Chang 2018[108]	Yes	No (some variables, such as pregnancy)	Yes	Yes	No	Yes	Yes	Differential: yes; high overall: yes, for NVP group	Yes	Fair
Nkhoma, 2016[106]	Yes	No, significant differences for some variables	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Nkhoma 2016b[120]	Yes	No; differences in baseline concomitant medications used	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair

Abbreviation: NVP=nevirapine.