JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for HIV Infection in Asymptomatic, Nonpregnant Adolescents and Adults

Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Roger Chou, MD; Tracy Dana, MLS; Sara Grusing, BA; Christina Bougatsos, MPH

IMPORTANCE Untreated HIV infection can result in significant morbidity, mortality, and HIV transmission. A 2012 review for the US Preventive Services Task Force (USPSTF) found antiretroviral therapy (ART) associated with improved clinical outcomes and decreased transmission risk in persons with CD4 cell counts less than 500/mm^3.

OBJECTIVE To update the 2012 review on HIV screening to inform the USPSTF.

DATA SOURCES Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from 2012 to June 2018, with surveillance through January 2019.

STUDY SELECTION Nonpregnant individuals 12 years and older; randomized clinical trials (RCTs) and controlled observational studies of screening vs no screening, alternative screening strategies, earlier vs later initiation of ART, and long-term harms of ART.

DATA EXTRACTION AND SYNTHESIS One investigator abstracted data; a second checked accuracy. Two investigators independently rated study quality.

MAIN OUTCOMES AND MEASURES Mortality, AIDS events, quality of life, function, and HIV transmission; harms of screening and long-term (≥2 years) harms of ART; screening yield.

RESULTS Eighteen new studies (5 RCTs, 11 cohort studies, and 2 systematic reviews; N = 266 563) were included, and 11 studies (2 RCTs and 9 cohort studies; N = 218 542) were carried forward from the prior USPSTF report. No study directly evaluated effects of HIV screening vs no screening on clinical outcomes or harms, or the yield of alternative screening strategies. Two newly identified RCTs conducted completely or partially in low-resource settings found ART initiation at CD4 cell counts greater than 500/mm^3 associated with lower risk of a composite outcome of mortality, AIDS-defining events, or serious non-AIDS events (relative risk [RR], 0.44 [95% CI, 0.31-0.63] and RR, 0.57 [95% CI, 0.35-0.95]); results were consistent with those from a large observational study. Early ART was not associated with increased risk of cardiovascular events. Early ART initiation was associated with sustained reduction in risk of HIV transmission at 5.5 years (RR, 0.07 [95% CI, 0.02-0.22] for linked transmission). New evidence regarding the association between abacavir use and risk of cardiovascular events was inconsistent. Certain antiretroviral regimens were associated with increased risk of long-term neuropsychiatric, renal, hepatic, and bone adverse events.

CONCLUSIONS AND RELEVANCE In nonpregnant adolescents and adults there was no direct evidence on the clinical benefits and harms of screening for HIV infections vs no screening, or the yield of repeat or alternative screening strategies. New evidence extends effectiveness of ART to asymptomatic individuals with CD4 cell counts greater than 500/mm^3 and shows sustained reduction in risk of HIV transmission at longer-term follow-up, although certain ART regimens may be associated with increased risk of long-term harms.

JAMA. doi:10.1001/jama.2019.2592
Published online June 11, 2019.

Editorial
Author Audio Interview
Related articles and JAMA Patient Page
Supplemental content
Related articles at jamainternalmedicine.com jamanetworkopen.com

Author Affiliations: Pacific Northwest Evidence-based Practice Center, Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland (Chou, Dana, Grusing, Bougatsos); Division of General Internal Medicine and Geriatrics, Oregon Health & Science University, Portland (Chou).

Corresponding Author: Roger Chou, MD, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Mail Code BICC, Portland, OR 97239 (chour@ohsu.edu).

Approximately 990 000 people in the United States were living with HIV infection in 2016.[1] Among infected individuals, it was estimated that approximately 15% were unaware of their status.[2] The incidence of HIV infection in the United States decreased from about 42 000 in 2011 to 40 000 each year from 2013 to 2016.[3] Screening could identify HIV infection in asymptomatic patients, who could benefit from interventions to reduce risk of AIDS-related clinical events and transmission.

In 2013, the US Preventive Services Task Force (USPSTF) recommended that clinicians screen all adolescents and adults aged 15 to 65 years for HIV infection, as well as younger adolescents and older adults at increased risk (A recommendation).[4] This recommendation, which expanded on a previous USPSTF recommendation for risk-based HIV screening,[5] was based on new evidence supporting the effectiveness of earlier vs delayed antiretroviral therapy (ART) for HIV infection and the effectiveness of ART for decreasing transmission risk.[6,7]

This evidence report updates the previous USPSTF HIV screening review in nonpregnant adolescents and adults[6,7] to inform an updated USPSTF recommendation. It targets gaps identified in the prior review, including direct evidence on the benefits and harms of screening, the yield of screening at different intervals, and long-term harms of currently recommended ART regimens. This review also addresses effects of earlier vs later initiation of ART, focusing on patients with baseline CD4 cell counts greater than 350/mm^3, given expanded treatment indications for ART.[8] Prenatal HIV screening is addressed in a separate report.[9]

Methods

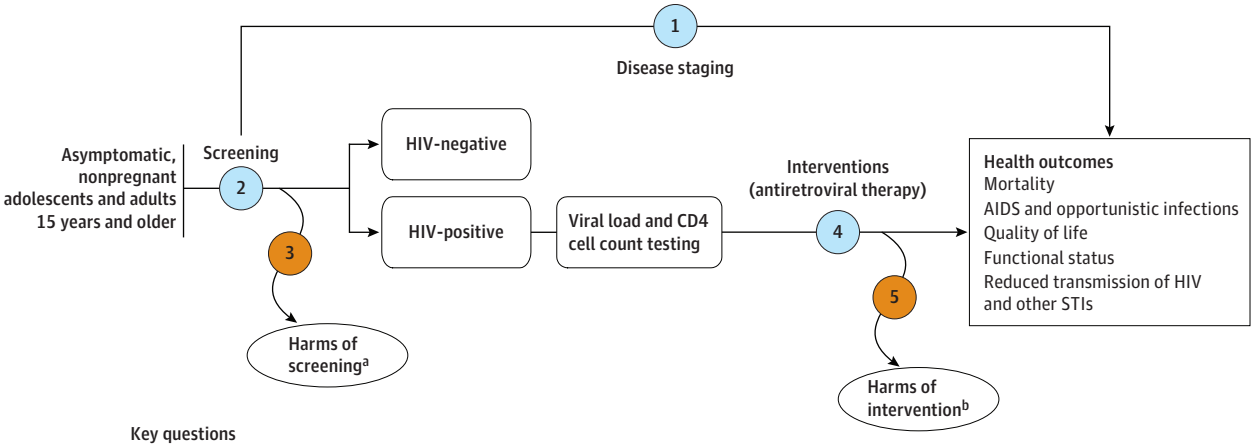
Scope of the Review

Detailed methods and additional study details are available in the full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/human-immunodeficiency-virus-hiv-infection-screening1. **Figure 1** shows the analytic framework and key questions (KQs) that guided the review.

Data Sources and Searches

Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews were searched

Figure 1. Analytic Framework: Screening for HIV Infection in Asymptomatic, Nonpregnant Adolescents and Adults



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 vs lower CD4 cell 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?

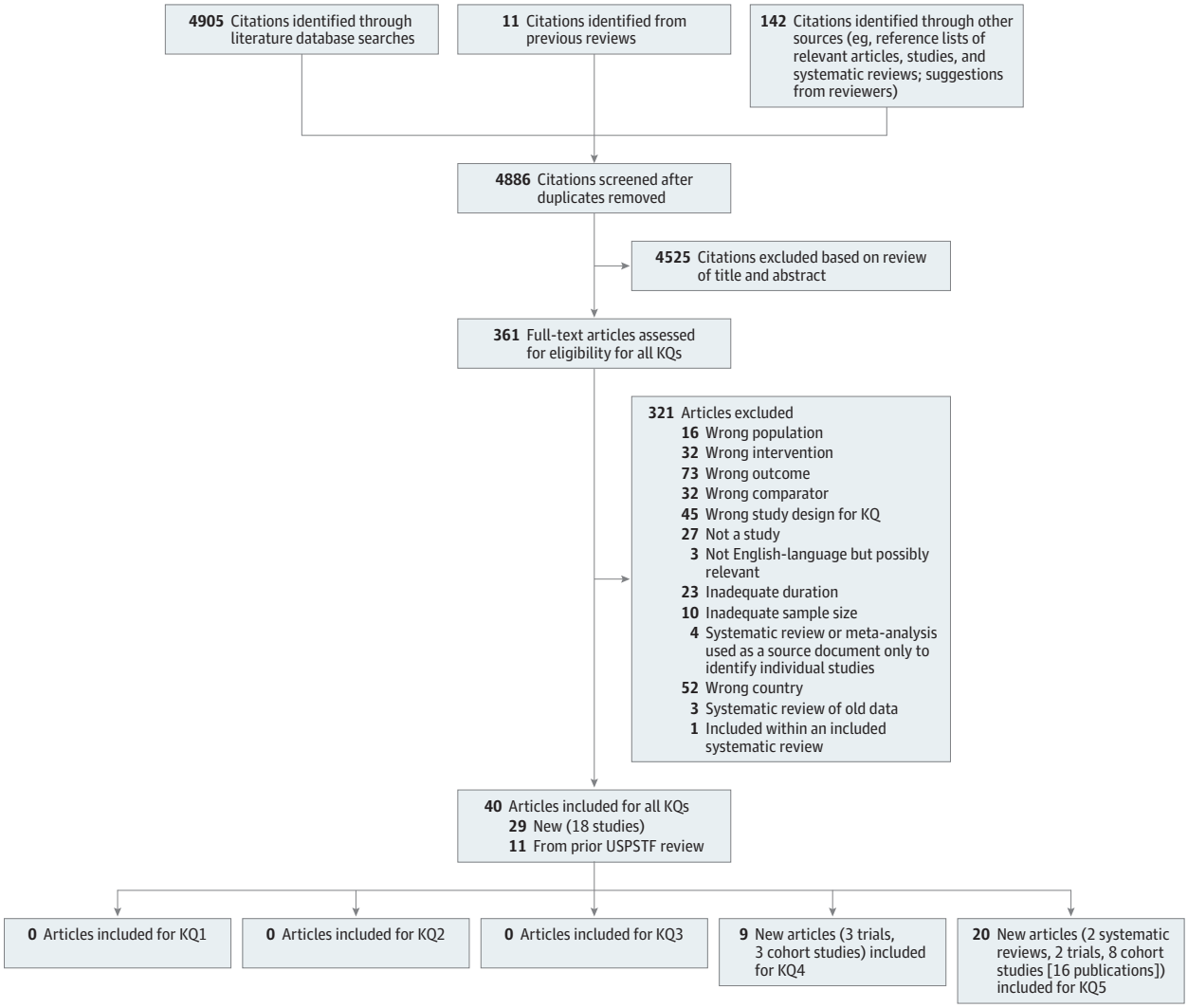
Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. Refer to the USPSTF Procedure Manual for further details.[10]

STI indicates sexually transmitted infection.

[a] Includes false-positive results; anxiety and effects of labeling; and partner discord, abuse, or violence.

[b] Includes adverse effects associated with antiretroviral therapy, including cardiometabolic outcomes.

Figure 2. Literature Search Flow Diagram: Screening for HIV Infection in Asymptomatic, Nonpregnant Adolescents and Adults



Additional articles are indicated for the included studies where relevant. KQ indicates key question; USPSTF, US Preventive Services Task Force.

for English-language articles published from 2012 through June 2018 (eMethods 1 in the Supplement). Searches were supplemented by review of reference lists from relevant systematic reviews and prior USPSTF reports. Since June 2018, ongoing surveillance was conducted through article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on January 25, 2019, and identified no eligible studies.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using predefined eligibility criteria. Randomized clinical trials (RCTs), cohort studies, and case-control studies of adolescents (13 to <18 years) and adults were eligible for all KQs. Studies that directly evaluated the effects of HIV screening vs no screening in asymptomatic individuals on clinical outcomes (mortality, AIDS and opportunistic infections, quality of life, function, HIV transmission, and harms) were eligible for KQ1 and KQ3. Studies that evaluated the yield (number of new diagnoses per tests performed) of screening for HIV infection at different intervals or in different risk groups were eligible for KQ2. Studies that compared effects of initiating ART at higher vs lower CD4 cell count on clinical outcomes were eligible for KQ4; observational studies had to enroll at least 1000 patients. Studies that evaluated longer-term (≥2 years) harms associated with currently recommended ART regimens were eligible for KQ5. This update focused on studies conducted in the United States and other settings with similar prevalence and management of HIV infection, unless such studies were not available.

Data Abstraction and Quality Rating

For each study, one investigator abstracted information on populations, interventions or screening instruments, comparators, adherence, outcomes, study designs, and settings. A second investigator reviewed abstracted information for accuracy. Randomized trials of early vs delayed ART primarily reported outcomes using hazard

Table 1. Randomized Clinical Trials of Immediate vs Delayed Antiretroviral Therapy

Source	Primary Composite Outcome	Mortality	AIDS-Related Events	Tuberculosis or Bacterial Infection	HIV Transmission
Baseline CD4 Cell Count >500/mm^3					
INSIGHT START Lungren et al,[13] 2015	All-cause mortality, serious AIDS-related events, and serious non-AIDS-related events: RR, 0.44 (95% CI, 0.31-0.63)	All-cause mortality: RR, 0.58 (95% CI, 0.29-1.18) Mortality due to AIDS-related event: RR, 0.25 (95% CI, 0.03-2.27)	Serious AIDS-related event: RR, 0.28 (95% CI, 0.16-0.51)	Tuberculosis: RR, 0.30 (95% CI, 0.12-0.76) Grade 4 bacterial infection: RR, 0.39 (95% CI, 0.21-0.73)	NR
TEMPRANO ANRS Daniel et al,[15] 2015	All-cause mortality, progression to AIDS, AIDS-defining cancer, or non-AIDS-defining invasive bacterial disease: RR, 0.57 (95% CI, 0.35-0.95)	All-cause mortality: RR, 0.79 (95% CI, 0.24-2.57)	Progression to AIDS: RR, 0.55 (95% CI, 0.29-1.05)	Tuberculosis: RR, 0.54 (95% CI, 0.27-1.09) Invasive bacterial disease: RR, 0.59 (95% CI, 0.20-1.80)	NR
Baseline CD4 Cell Count ≥350/mm^3 to 500/mm^3 or 550/mm^3 (Studies Included in Prior Report)					
HPTN 052, 2011 Grinsztejn et al,[12] 2014 Cohen et al,[40] 2011	All-cause mortality, serious AIDS-related events, and serious non-AIDS-related events: RR, 0.73 (95% 0.53-1.02)	All-cause mortality (1.7-y follow-up): RR, 0.76 (95% CI, 0.34-1.73) All-cause mortality (2.1-y follow-up): RR, 0.72 (95% CI, 0.33-1.57) Mortality due to AIDS-related event: RR, 0.25 (95% CI, 0.03-2.20)	Any AIDS-related event: RR, 0.65 (95% CI, 0.44-0.95)	Tuberculosis: RR, 0.49 (95% CI, 0.28-0.88) Serious bacterial infection: RR, 1.52 (95% CI, 0.76-3.04)	Any HIV transmission (1.7-y follow-up): RR, 0.11 (95% CI, 0.04-0.32) Any HIV transmission (5.5-y follow-up): RR, 0.32 (95% CI, 0.19-0.53) Linked HIV transmission (1.7-y follow-up): RR, 0.04 (95% CI, 0.005-0.27) Linked HIV transmission (5.5-y follow-up): RR, 0.07 (95% CI, 0.02-0.22)
SMART Emery et al,[41] 2008	All-cause mortality or opportunistic disease: RR, 0.31 (95% CI, 0.11-0.83)	All-cause mortality: RR, 0.26 (95% CI, 0.05-1.25)	Any opportunistic disease: RR, 0.33 (95% CI, 0.11-1.03)	Tuberculosis: RR, 0.46 (95% CI, 0.04-5.02)	NR

Abbreviations: HPTN, HIV Prevention Trials Network; NR, not reported; RR, relative risk; SMART, Strategies for Management of Anti-Retroviral Therapy; START, Strategic Initiatives in Global HIV Trials Strategic Timing of Antiretroviral Treatment.

ratios. Relative risks (RRs) were calculated based on reported event rates, to calculate absolute risk differences (ARDs). RRs and hazard ratios were very similar, and reported results are based on RRs. Two independent investigators assessed the quality of each study as good, fair, or poor using predefined criteria developed by the USPSTF (eMethods 2 in the Supplement). Individual study quality ratings are provided in eTables 1-6 in the Supplement.

Data Synthesis

Results were summarized qualitatively. Meta-analysis was not performed because of clinical and methodological heterogeneity among studies. For all KQs, the overall strength of the body of evidence was assessed as high, moderate, low, or insufficient using methods developed by the USPSTF, based on the overall quality of studies, consistency of results between studies, precision of findings, and risk of reporting bias.[10] The applicability of the findings to US primary care populations and settings was also assessed.

Results

Two reviewers independently assessed 4882 unique citations and 348 full-text articles for inclusion (**Figure 2**). Eighteen new studies (5 RCTs,[11-17] 11 cohort studies,[18-37] and 2 systematic reviews[38,39]; 29 articles; N = 266 563) were included, and 11 studies (2 RCTs[40,41] and 9 cohort studies[42-50]; N =218 542) were carried forward from the prior USPSTF report.

Screening

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 sexually transmitted infections?

No study met inclusion criteria for KQ1.

Key Question 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?

No study met inclusion criteria for KQ2.

Key Question 3. What are the harms of screening for HIV infection in asymptomatic, nonpregnant adolescents and adults?

No study met inclusion criteria for KQ3.

Treatment Initiation at Higher vs Lower CD4 Cell Count

Key Question 4. What are the effects of initiating ART in adolescents and adults with chronic HIV infection at a higher vs lower CD4 cell count on mortality, AIDS and opportunistic infections, quality of life, function, reduced transmission of HIV and other sexually transmitted infections, and harms?

Effects of ART in reducing risk of mortality and AIDS-associated events in people with advanced immunodeficiency (eg, CD4 cell count <200/mm^3) are well established.[51-53] The prior USPSTF review[6] included consistent evidence from 2 RCTs[40,41] (n = 2240) (**Table 1**) and 4 observational studies[42-45] (n = 110 111)

Table 2. Cohort Studies of Early vs Delayed Antiretroviral Therapy

Source	CD4 Cell Count at ART Initiation, /mm^3	All-Cause Mortality, HR/RR (95% CI)	AIDS-Related Events	
			Event	HR/RR (95% CI)
Studies Included in Prior Report				
CASCADE Collaboration et al,[45] 2011	≥350 to <500 vs no treatment initiation	HR, 0.51 (0.33-0.80)	Progression to AIDS or death	HR, 0.75 (0.49-1.14)
	≥500 vs no treatment initiation	HR, 1.02 (0.49-2.12)		HR, 1.10 (0.67-1.79)
Kitahata et al,[42] 2009	≥350 to 500 vs <350	RR, 0.61 (0.46-0.83)	NR	NR
	>500 vs ≤500	RR, 0.54 (0.35-0.83)		
May et al,[43] 2007	≥350 vs <250	HR, 0.34 (0.27-0.44)	Progression to AIDS or death	HR, 0.23 (0.19-0.27)
Ray et al,[44] 2010	500 vs 350	HR, 0.99 (0.82-1.19)	Progression to AIDS or death	HR, 0.72 (0.64-0.81)
	350 vs 200	HR, 0.85 (0.68-1.05)		HR, 0.73 (0.64-0.83)
Sterne et al,[46] 2009	>450 to 550 vs ≥350 to 450	HR, 0.93 (0.6-1.40)	Progression to AIDS or death	HR, 0.90 (0.76-1.29)
New Studies				
Edwards et al,[21] 2015	<500 vs <350	5-y follow-up: RR, 0.87 (0.79-0.95) Ages 18-34 y: RR, 0.95 (0.79-1.15) Ages 35-44 y: RR, 0.93 (0.82-1.05) Ages 45-65 y: RR, 0.81 (0.71-0.93) 10-y follow-up: RR, 0.93 (0.86-1.00) Ages 18-34 y: RR, 1.00 (0.87-1.15) Ages 35-44 y: RR, 0.92 (0.83-1.01) Ages 45-65 y: RR, 0.89 (0.80-0.99)	NR	NR
Lima et al,[20] 2015	<350 (2007-2012)	Probability, 0.05 (IQR, 0.03-0.08)	AIDS-defining illness	Probability, 0.05 (IQR, 0.03-0.08)
	≥350 (2007-2012)	Probability, 0.02 (IQR, 0.01-0.04)		Probability, 0.03 (IQR, 0.01-0.05)
	<500 (2007-2012)	Probability, 0.05 (IQR, 0.03-0.02)		Probability, 0.03 (IQR, 0.01-0.04)
	≥500 (2007-2012)	Probability, 0.01 (IQR, 0.01-0.02)		Probability, 0.01 (IQR, 0.00-0.01)
Lodi et al,[19] 2015	≥500 vs <500	RR, 0.98 (0.97-0.99)	Progression to AIDS or death	RR, 0.94 (0.93-0.94)
	≥500 vs <350	RR, 0.94 (0.91-0.97)	Progression to AIDS or death	RR, 0.83 (0.81-0.85) Subgroup of patients with baseline CD4 cell count >500/mm^3 vs entire sample: 7.1% vs 4.9%; RR, 1.52 (1.34-1.77)
Lodi et al,[18] 2017	≥500 vs <500	General HIV population: RR, 0.97 (0.94-0.99) General HIV population patients with CD4 cell count ≥500/mm^3: RR, 0.76 (0.58-0.97) VA population: RR, 0.95 (0.93-0.98)	NR	NR
	≥500 vs <350	General HIV population: RR, 0.93 (0.87-0.98) General HIV population patients with CD4 cell count ≥500/mm^3: RR, 0.64 (0.41-0.95) VA population: RR, 0.90 (0.85-0.95)		

Abbreviations: ART, antiretroviral therapy; CASCADE, Concerted Action on SeroConversion to AIDS and Death in Europe; HR, hazard ratio; IQR, interquartile range; NR, not reported; RR, relative risk; VA, US Department of Veterans Affairs.

(**Table 2**) that initiation of ART at CD4 cell counts greater than 350/mm^3 to 500/mm^3 or 550/mm^3 was associated with decreased risk of death or AIDS events compared with initiation at lower CD4 cell counts; 1 trial[40] also found early ART associated with substantially decreased risk of HIV transmission. Observational evidence on initiation of ART at CD4 cell counts greater than 500/mm^3 did not consistently demonstrate beneficial associations with clinical outcomes (Table 2).[42,44-46] Neither the prior report nor this update found evidence on the effects of early vs later ART initiation on quality of life or function.

New evidence on initiation of ART in people with CD4 cell counts of 350/mm^3 to 500/mm^3 or 550/mm^3 vs delayed initiation was

available from longer-term (up to 5.5 years) follow-up of a trial included in the prior USPSTF report (the HIV Prevention Trials Network [HPTN] 052 study [n = 1701]),[11,12] 2 new RCTs (n = 6529),[13-15] and 3 large (≥1000 participants [total n = 63 478]), fair-quality cohort studies (reported in 4 articles) conducted in the United States, Europe, and Canada[18-21] (Table 1 and Table 2; eTables 7-10 in the Supplement).

The new International Network for Strategic Initiatives in Global HIV Trials Strategic Timing of Antiretroviral Treatment (INSIGHT START, or START) trial (n = 4473) randomized ART-naive, HIV-positive participants with CD4 cell counts greater than 500/mm^3 at baseline (median, 651/mm^3) to immediate ART vs deferred initiation at CD4 cell counts less than 350/mm^3. About half of participants were from high-income geographic regions (United States, Europe, and Australia). Mean follow-up duration was 3 years. The other new RCT, the African Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-Infected Adults (TEMPRANO ANRS 12136) trial (n = 2056), enrolled people with baseline CD4 cell counts less than 800/mm^3 without an indication for ART, based on then-current World Health Organization guidelines.[15] Follow-up was 2.5 years. A prespecified subgroup analysis was conducted in people with a CD4 cell count of 500/mm^3 or greater at baseline (≈40% of trial population). Treatment initiation thresholds for delayed ART varied according to changing World Health Organization guidance. Both trials evaluated a composite primary outcome consisting of mortality, AIDS-defining events, and serious non-AIDS events; neither trial evaluated effects on risk of HIV transmission or other sexually transmitted infections. The START trial was rated good quality and TEMPRANO ANRS 12136 fair quality because of open-label design and changing criteria for initiation of ART. The HPTN 052 trial was previously rated good quality.[6]

Three new, fair-quality cohort studies enrolled a total of 63 478 participants (Table 2; eTables 9-10 in the Supplement).[18-21] Two articles were based on the large HIV Cohorts Analyzed Using Structural Approaches to Longitudinal (HIV-CAUSAL) Collaboration (n = 55 826)[18,19] of 12 US and European cohort studies (mean age, 35 years). Three-year data from the HIV CAUSAL Collaboration were included in the prior USPSTF report[44]; new articles report 7-year outcomes[19] and subgroup analyses of adults older than 50 years.[18] The other 2 studies evaluated cohorts from Canada (n = 4120)[20] and the United States (n = 3532).[21] 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 vs Delayed ART in People With Baseline CD4 Cell Count Greater Than 500/mm^3

Two new RCTs found initiation of ART at baseline CD4 cell counts greater than 500/mm^3 more beneficial than delayed initiation (Table 1; eTables 7-8 in the Supplement).[13,15] In START, early ART 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]; ARD, −2.3% [95% CI, −3.2% to −1.3%]), compared with initiation at CD4 cell counts less than 350/mm^3.[13] When outcomes were disaggregated, immediate ART was associated with reduced risk of serious AIDS-related events, tuberculosis, and serious bacterial infection. Associations with all-cause mortality and AIDS-related mortality favored immediate ART but were not statistically significant; there were only 5 cases of AIDS-related mortality.[13] Results for the primary outcome were similar when analyses were stratified by geographic region (high or low income, P = .55 for interaction), age (>35 years, ≤35 years), sex, race, baseline HIV viral load, smoking status, and cardiovascular risk. In TEMPRANO ANRS 12136, in a prespecified subgroup analysis of patients with CD4 cell counts of 500/mm^3 or greater at baseline, immediate 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%]).[15] Associations with all-cause mortality, progression to AIDS, tuberculosis, and invasive bacterial disease also favored immediate ART but were not statistically significant (Table 1). Results were similar when adjusted for study center and concomitant isoniazid use.

The new cohort studies also found initiation of ART at CD4 cell counts greater than 500/mm^3 associated with beneficial effects on clinical outcomes. An analysis of the HIV-CAUSAL Collaboration (n = 55 826; median baseline CD4 cell count, 376/mm^3) found ART initiation at CD4 cell counts less than 350/mm^3 associated with increased risk of the composite end point 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 immediate initiation (Table 2).[19] Associations with immediate ART were stronger in the subgroup of patients with baseline CD4 cell count greater than 500/mm^3 (7.1% vs 4.9%; RR, 1.52 [95% CI, 1.34 to 1.77]). Initiation of ART at CD4 cell counts less than 350/mm^3 was also associated with slightly increased risk of all-cause mortality compared with immediate initiation in the whole sample (4.2% vs 4.0%; RR, 1.06 [95% CI, 1.03 to 1.10]). Findings were similar in an HIV-CAUSAL analysis that focused on patients older than 50 years (n = 9599).[18] Another cohort study (n = 4120) found that in 2007 to 2012, ART initiation at CD4 cell counts of 500/mm^3 or greater was associated with lower probability of mortality (0.01 [interquartile range {IQR}, 0.01-0.02]) and AIDS-related morbidity (0.01 [IQR, 0.00-0.01]) than initiation at CD4 cell counts less than 500/mm^3 (0.05 [IQR, 0.03-0.08] and 0.03 [IQR, 0.01-0.04], respectively) or less than 350/mm^3 (0.05 [IQR, 0.03-0.08] and 0.05 [IQR, 0.03-0.08], respectively) (Table 2).

Immediate vs Delayed ART in People With Baseline CD4 Cell Count of 350/mm^3 to 500/mm^3 or 550/mm^3

The prior USPSTF report[6,7] included 1.7-year results from the HPTN 052 trial (n = 1763), which enrolled persons with baseline CD4 cell count 350/mm^3 to 550/mm^3.[40] Longer follow-up from HPTN 052 is now available. At mean 2.1 years follow-up, initiation of ART at CD4 cell counts of 350/mm^3 to 550/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]), mostly due to tuberculosis events (1.9% vs 3.9%; RR, 0.49 [95% CI, 0.28 to 0.88]), vs initiation at CD4 cell counts less than 250/mm^3. 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, and AIDS-related mortality favored early ART (Table 1) but were not statistically significant. HPTN 052 also found that at 5 years (n = 1701), early 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 effect was attributable to fewer virologically linked cases (Table 1).[11]

A new US-based cohort study (n = 3532) found that relative to initiation of ART at CD4 cell counts less than 500/mm^3, initiation at counts less than 200/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 counts less than 350/mm^3 (RR, 1.08 [95% CI, 1.00 to 1.16]) (Table 2).[21] However, the confidence intervals for the risk estimates overlapped and there was no test for statistical significance for the difference.

Harms of Immediate vs Delayed ART

Two RCTs (n = 4950) found no evidence of an increased risk of cardiovascular events with early vs delayed ART, although data were limited by small numbers of events (eTable 8 in the Supplement).[13,41] The START, HPTN 052, and TEMPRANO ANRS 12136 trials also found no significant differences between early vs delayed initiation of ART and risk of other harms, such as liver disease, renal disease, and new-onset diabetes.[12,13,15] Few adverse events were reported and some risk estimates were imprecise.

Longer-Term Harms of Treatment

Key Question 5. What are the longer-term harms (≥2 years) associated with currently recommended ART regimens?

The prior USPSTF report focused on longer-term cardiovascular harms of ART.[6,7] Details on evidence reviewed for this update on longer-term cardiovascular and additional harms are reported in eTables 11-13 in the Supplement.

Cardiovascular Events

The prior USPSTF report found mixed evidence on the risk of long-term cardiovascular events with abacavir use based on 4 cohort studies, including the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) observational study,[47-50] and evidence of no increased cardiovascular risk associated with efavirenz use.[47] A meta-analysis of 26 trials (total n = 9868) published since the prior report found no association between ART containing abacavir vs ART without abacavir and risk of myocardial infarction (risk difference, 0.008% [95% CI, −0.26% to 0.27%]).[38] This conflicts with longer-term (median, 7.0 years) follow-up from the large (n = 49 717) D:A:D study, which found abacavir use associated with increased risk of myocardial infarction (RR, 1.98 [95% CI, 1.72 to 2.29]),[23] and another cohort study (n = 24 510), which found abacavir use associated with increased risk of cardiovascular events (odds ratio, 1.50 [95% CI, 1.26 to 1.79]).[25] The D:A:D study (n = 49 734) found no significant 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]).[24] Another cohort study (n = 24 510) found efavirenz, lamivudine, and zidovudine each associated with increased risk of cardiovascular events (odds ratios ranged from 1.40 to 1.53).[25]

Neuropsychiatric Events

A systematic review of 42 randomized and quasi-randomized trials (n = 8466 exposed to efavirenz; mean duration, 78 weeks) found efavirenz associated with an increased risk of severe neuropsychiatric adverse events vs 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]).[39] Three observational studies (n = 75 548), including D:A:D, found no significant association between use of efavirenz and death from suicide or suicidal ideation.[32,34,35]

Cancer

Analysis of D:A:D data (n = 41 762) found longer exposure to ART associated with lower risk of AIDS-defining cancers (rate ratio, 0.88/y [95% CI, 0.85/y to 0.92/y]).[26] Use of protease inhibitors, but not nonnucleoside reverse transcriptase inhibitors, was associated with higher risk of non–AIDS-defining cancers (rate ratio, 1.03/y [95% CI, 1.01/y to 1.05/y]).

Hepatic and Renal Adverse Events

Analysis of data from the D:A:D study (n = 45 544) found long-term tenofovir use associated with increased risk of end-stage liver disease or hepatocellular carcinoma (relative rate, 1.46 [95% CI, 1.11 to 1.93]) and emtricitabine use associated with decreased risk (relative rate, 0.51 [95% CI, 0.32 to 0.83]).[27] Another D:A:D analysis (n = 23 905) found an association between use of tenofovir (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.[30] Other observational studies (n = 34 487) also found tenofovir and protease inhibitors associated with increased risk of renal adverse events.[29,31,33]

Fracture

A cohort study (n = 11 820) found ever using tenofovir associated with increased risk of fracture (incidence rate ratio, 1.40 [95% CI, 1.15 to 1.70]) but no association between cumulative exposure to tenofovir and risk of fracture (incidence rate ratio per 5 years of exposure, 1.08 [95% CI, 0.94 to 1.25]).[36]

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 deaths after a median of 5.4 years.[22]

Discussion

As in previous USPSTF reviews on this topic,[7,52] there remains no direct evidence on clinical benefits and harms of screening for HIV infection vs no screening or the yield of repeat or alternative screening strategies. **Table 3** summarizes the other evidence reviewed in this update.

New data extend evidence on effectiveness of ART to people with CD4 cell counts greater than 500/mm,[3,13,15,19] expanding on previous findings[7] of a strong association between initiation of ART at CD4 cell counts of 350/mm^3 to 500/mm^3 or 550/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 cell counts. New data also found effects of ART initiation at CD4 cell counts greater than 350/mm^3 were sustained.[11,12] Other systematic reviews on timing of ART found insufficient evidence to determine effects of initiation of ART at CD4 cell counts greater than 500/mm^3

Table 3. Summary of Evidence

No. of Studies, No. of Participants, Study Design	Summary of Findings by Outcome	Consistency/ Precision, Reporting Bias	Overall Risk of Bias/ Quality	Other Limitations	Strength of Evidence	Applicability
KQ1: Benefits of HIV Screening vs No Screening						
No studies	NA	NA	NA	NA	NA	NA
KQ2: Yield of Repeat vs 1-Time HIV Screening or of HIV Screening at Different Intervals						
No studies	NA	NA	NA	NA	NA	NA
KQ3: Harms of HIV Screening vs No Screening						
No studies	NA	NA	NA	NA	NA	NA
KQ4: Effects of Immediate vs Delayed ART						
CD4 cell count ≥500/mm^3 2012 USPSTF review: 4 observational studies (n = 74 563) New evidence: 4 studies (2 RCTs [n = 6761] 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 cell counts >500/mm^3 vs delayed initiation Two new RCTs found initiation of ART in patients with CD4 cell counts >500/mm^3 associated with decreased risk of death, AIDS events, OR serious non-AIDS events (RR, 0.44 [95% CI, 0.31-0.63] and RR, 0.57 [95% CI, 0.35-0.95]) Two new observational studies also found initiation of ART at CD4 cell counts >500/mm^3 associated with lower risk of death and AIDS-related events vs delayed initiation, although 1 study reported effects smaller than those observed in the randomized trials In 1 RCT, there was no association between early ART and increased risk of cardiovascular events (RR, 0.87 [95% CI, 0.40-1.88])	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 and 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 cell counts >500 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 cell count was 651/mm^3 in one trial, and in the other trial baseline CD4 cell count ranged from 500/mm^3 to 800/mm^3 (average CD4 cell count not reported in the subgroup of patients with count ≥500/mm^3 at baseline) Patients were randomized between 2008 and 2013 in the RCTs Observational studies were conducted in US and European cohorts
CD4 cell count >350/mm^3 to 500/mm^3 or 550/mm^3 2012 USPSTF review: 6 studies (2 RCTs [n = 2012] and 4 observational studies [n = 71 460]) New evidence: 1 observational study (n = 3532) plus longer-term follow-up from RCT included in 2012 review	Two RCTs in the prior USPSTF review found initiation of ART at CD4 cell counts >350/mm^3 associated with decreased risk of death or AIDS events after ≈1.5 y compared with initiation at counts <250/mm^3 (RR, 0.30 [95% CI, 0.11-0.81] and RR, 0.61 [95% CI, 0.42-0.89]), and 1 of the RCTs found early ART associated with decreased risk of HIV transmission (RR, 0.04 [95% CI, 0.005-0.27] for virologically linked transmission) Four observational studies reported consistent findings on clinical outcomes One RCT found a potential protective effect of early ART on risk of cardiovascular events (RR, 0.07 [95% CI, 0.004-1.24]) Longer-term (2.1 y) follow-up from 1 RCT included in the prior review reported decreased risk of AIDS-related events (RR, 0.65 [95% CI, 0.44-0.95]); effects on the primary composite outcome (death, AIDS events, and non-AIDS events) favored early ART, but the effect was not statistically significant (RR, 0.73 [95% CI, 0.53-1.02]); beneficial effects on HIV transmission remained present at 5.5 y of follow-up (RR, 0.07 [95% CI, 0.02-0.22] 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 1 RCT One RCT included in the prior USPSTF review conducted a post hoc subgroup analysis of patients with CD4 cell counts >350/mm^3 at baseline	High	One trial primarily conducted in high-income settings and 1 primarily conducted in low-income settings Median CD4 cell counts at baseline in the RCTs were 430/mm^3-440/mm^3 Patients were randomized between years 2002 to 2006 in one trial and from 2007 to 2010 in the other

(continued)

Table 3. Summary of Evidence (continued)

No. of Studies, No. of Participants, Study Design	Summary of Findings by Outcome	Consistency/ Precision, Reporting Bias	Overall Risk of Bias/ Quality	Other Limitations	Strength of Evidence	Applicability
KQ5: Long-Term Harms of ART						
2012 USPSTF review: 4 observational studies (n >60 500[a]) New evidence: 11 studies (2 systematic reviews [n = 18 334], 2 trials [n = 2296], and 8 observational studies in 16 articles [n = approximately 134 225[a]] including longer-term follow-up from a large observational study included in the prior review)	Cardiovascular harms: a meta-analysis of 26 trials found no association between abacavir use and risk of myocardial infarction, but 2 observational studies found abacavir associated with increased risk (RR, 1.98 [95% CI, 1.72-2.29] and OR, 1.50 [95% CI, 1.26-1.79]) Neuropsychiatric harms: a systematic review of randomized and quasi-randomized trials found efavirenz associated with increased risk of neuropsychiatric adverse events vs other antiretroviral agents Three observational studies found no association between use of efavirenz 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 found emtricitabine associated with decreased risk Renal harms: 2 observational studies found tenofovir associated with increased risk of chronic kidney disease, and 2 observational studies found ritonavir-boosted atazanavir and protease inhibitors associated with renal adverse events Fracture: a cohort study found ever using tenofovir associated with increased risk of fracture (IRR, 1.40 [95% CI, 1.15-1.70]) but no association between cumulative exposure to tenofovir and risk of fracture (IRR per 5 y of exposure, 1.08 [95% CI, 0.94-1.25])	Some inconsistency between RCT and observational data regarding cardiovascular risks of abacavir; 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; 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 after antiretroviral agent discontinuation and availability of alternative ART regimens

Abbreviations: ART, antiretroviral therapy; IRR, incidence rate ratio; KQ, key question; NA, not applicable; OR, odds ratio; RCT, randomized clinical trial; RR, relative risk; USPSTF, US Preventive Services Task Force; WHO, World Health Organization.

[a] The number of participants in D:A:D cohort publications ranged from 23 905 to 49 717, depending on year of follow-up and outcome.

on clinical outcomes but were conducted before the publication of the recent trials.[54,55]

Understanding long-term harms of ART is important because patients are started on ART earlier and typically continue it indefinitely. As in the 2012 USPSTF report,[7] new evidence regarding abacavir and cardiovascular harms remains mixed, with a discrepancy between shorter-term randomized trials (no increased risk)[38] and longer-term observational studies (increased risk).[23,25] A recent systematic review also noted a discrepancy between randomized trials and observational studies.[56] A new analysis found no association between the currently used protease inhibitor atazanavir and risk of cardiovascular events.[24] Data from randomized trials found no association between early vs later initiation of ART and increased risk of cardiovascular events,[13,41] with 1 trial finding ART initiation at CD4 cell counts greater than 350/mm^3 associated with a potential protective effect. Because HIV infection is itself associated with increased cardiovascular risk, effects of ART on mitigating cardiovascular risk may be greater in people with more advanced disease.[57]

Data are also available on other long-term harms. Although a systematic review found efavirenz associated with an increased risk of severe neuropsychiatric adverse events compared with other antiretroviral medications,[39] other studies found no clear association between efavirenz use and suicidal ideation or death from suicide.[32,34,35] Long-term data on neuropsychiatric adverse events associated with integrase inhibitors is limited. Some new evidence also indicates that long-term hepatic, renal, and bone (fracture) adverse events are associated with certain antiretroviral medications.[28-31,33,36,37] The clinical effect of such adverse events depends on their reversibility, their severity, and the availability of effective alternative ART regimens. Abacavir and efavirenz are not recommended as part of initial ART in most people with HIV, although they are recommended in certain clinical situations.[8]

No clinical study evaluated the yield of repeat vs 1-time screening or 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 individuals, depending on testing

frequency, HIV incidence, HIV risk category, test assay, and other factors.[58-60] A recent Centers for Disease Control and Prevention 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 more frequent screening could prevent some new HIV infections and be cost-effective.[61]

Limitations

This review had several limitations. First, inclusion was restricted to English-language articles, although no non–English-language studies that would have met inclusion criteria were identified. Second, it was not possible to formally assess for publication bias with graphical or statistical methods because of small numbers of studies; however, eligible unpublished trials were not identified in searches on ClinicalTrials.gov. Third, observational studies, which are susceptible to bias and confounding, were included, although results focused on studies that performed statistical adjustment for potential confounding. Fourth, some studies were conducted in resource-poor and high-prevalence settings, which could reduce applicability to US practice. Fifth, studies of long-term harms of ART often did not specify the regimen used or analyze effects of specific antiretroviral drugs rather than the regimen as a whole, some evidence on long-term harms of ART apply to drugs not considered first-line options, and analyses have difficulty in accounting for ART regimen switches.

Conclusions

In nonpregnant adolescents and adults there was no direct evidence on the clinical benefits and harms of screening for HIV infections vs no screening, or the yield of repeat or alternative screening strategies. New evidence extends effectiveness of ART to asymptomatic individuals with CD4 cell counts greater than 500/mm^3 and shows sustained reduction in risk of HIV transmission at longer-term follow-up, although certain ART regimens may be associated with increased risk of long-term harms.

ARTICLE INFORMATION

Accepted for Publication: March 4, 2019.

Published Online: June 11, 2019. doi:10.1001/jama.2019.2592

Author Contributions: Dr Chou had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Chou.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: Chou.
Statistical analysis: Chou, Dana.
Obtained funding: Chou.
Administrative, technical, or material support: Dana, Grusing, Bougatsos.
Supervision: Chou, Bougatsos.

Conflict of Interest Disclosures: None reported.

Funding/Support: This research was funded under contract HHSA290201500009i, Task Order 7, from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services, under a contract to support the USPSTF.

Role of the Funder/Sponsor: Investigators worked with USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions for this review. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the report to ensure that the analysis met methodological standards, and distributed the draft for peer review. Otherwise, AHRQ had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript findings. The opinions expressed in this document are those of the authors and do not reflect the official position of AHRQ or the US Department of Health and Human Services.

Additional Contributions: We gratefully acknowledge the AHRQ Medical Officer (Howard Tracer, MD). We also acknowledge past and current USPSTF members who contributed to topic deliberations. The USPSTF members, external peer reviewers, and federal partner reviewers did not receive financial compensation for their contributions.

Additional Information: A draft version of this evidence report underwent external peer review from 2 content experts (Lisa Metsch, PhD, Columbia University; and Zelalem Temesgen, MD, Mayo Clinic Global HIV Education Initiative, Mayo Center for Tuberculosis) and 3 federal partner reviewers from the Centers for Disease Control and Prevention and the Department of Veterans Affairs. Comments from reviewers were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence review.

Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF Recommendation Statement. It did not undergo additional peer review after submission to *JAMA*.

REFERENCES

1. Centers for Disease Control and Prevention (CDC). HIV Surveillance Report, Volume 29: Diagnoses of HIV Infection in the United States and Dependent Areas, 2017. CDC website. https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2017-vol-29.pdf. Published 2017. Accessed January 31, 2019.

2. Dailey AF, Hoots BE, Hall HI, et al. Vital signs: human immunodeficiency virus testing and diagnosis delays—United States. *MMWR Morb Mortal Wkly Rep*. 2017;66(47):1300-1306. doi:10.15585/mmwr.mm6647e1

3. Centers for Disease Control and Prevention (CDC). HIV Surveillance Report, Volume 28: Diagnoses of HIV Infection in the United States and Dependent Areas, 2016. CDC website. https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2016-vol-28.pdf. Published 2016. Accessed December 8, 2017.

4. Moyer VA; US 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

5. US Preventive Services Task Force. Screening for HIV: recommendation statement. *Ann Intern Med*. 2005;143(1):32-37. doi:10.7326/0003-4819-143-1-200507050-00008

6. 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*. Rockville, MD: Agency for Healthcare Research and Quality; November 2012. AHRQ publication 12-05173-EF-1.

7. Chou R, Selph 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(10):706-718. doi:10.7326/0003-4819-157-10-201211200-00007

8. Panel on Antiretroviral Guidelines for Adults and Adolescents, US Department of Health and Human Services (HHS). Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. National Institutes of Health website. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Published 2018. Accessed November 9, 2018.

9. Selph S, 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*. Rockville, MD: Agency for Healthcare Research and Quality; 2019. AHRQ publication 18-05246-EF-2.

10. US Preventive Services Task Force. Procedure Manual. https://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual. Published 2018. Accessed December 8, 2018.

11. Cohen MS, Chen YQ, McCauley M, et al; HPTN 052 Study Team. Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med*. 2016;375(9):830-839. doi:10.1056/NEJMoa1600693

12. Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al; HPTN 052-ACTG Study Team. 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):281-290. doi:10.1016/S1473-3099(13)70692-3

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

14. O'Connor J, Vjecha MJ, Phillips AN, et al; INSIGHT START Study Group. 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 µL: secondary outcome results from a randomised controlled trial. *Lancet HIV*. 2017;4(3):e105-e112. doi:10.1016/S2352-3018(16)30216-8

15. Danel C, Moh R, Gabillard D, et al; TEMPRANO ANRS 12136 Study Group. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med*. 2015;373(9):808-822. doi:10.1056/NEJMoa1507198

16. 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 with elvitegravir, cobicistat, and emtricitabine (E/C/F) for initial HIV-1 treatment: week 144 results. *J Acquir Immune Defic Syndr*. 2017;75(2):211-218. doi:10.1097/QAI.0000000000001350

17. Rockstroh JK, DeJesus E, Lennox JL, et al; STARTMRK Investigators. 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

18. 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):311-318. doi:10.1097/QAI.0000000000001498

19. Lodi S, Phillips A, Logan R, et al; HIV-CAUSAL Collaboration. 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-e343. doi:10.1016/S2352-3018(15)00108-3

20. Lima VD, Reuter A, Harrigan PR, et al. Initiation of antiretroviral therapy at high CD4+ cell counts is associated with positive treatment outcomes [published correction appears in *AIDS*. 2016;30(4):677]. *AIDS*. 2015;29(14):1871-1882. doi:10.1097/QAD.0000000000000790

21. Edwards JK, Cole SR, Westreich D, et al; Centers for AIDS Research Network of Integrated Clinical Systems Investigators. 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):1189-1195. doi:10.1093/cid/civ463

22. Kowalska JD, Reekie J, Mocroft A, et al; EuroSIDA Study Group. 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):315-323. doi:10.1097/QAD.0b013e32834e8805

23. Sabin CA, Reiss P, Ryom L, et al; D:A:D Study Group. 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

24. Monforte Ad, Reiss P, Ryom L, et al. Atazanavir is not associated with an increased risk of cardio- or cerebrovascular disease events. *AIDS*. 2013;27(3):407-415. doi:10.1097/QAD.0b013e32835b2ef1

25. 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):445-452. doi:10.1093/cid/civ316

26. Bruyand M, Ryom L, Shepherd L, et al; D:A:D Study Group. 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):568-577. doi:10.1097/QAI.0000000000000523

27. Ryom L, Lundgren JD, De Wit S, et al; D:A:D Study Group. Use of antiretroviral therapy and risk of end-stage liver disease and hepatocellular carcinoma in HIV-positive persons. *AIDS*. 2016;30(11):1731-1743. doi:10.1097/QAD.0000000000001018

28. 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):870-879. doi:10.1093/cid/cis919

29. Ryom L, Mocroft A, Kirk O, et al; D:A:D Study Group. 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):1359-1369. doi:10.1093/infdis/jit043

30. Mocroft A, Lundgren JD, Ross M, et al; Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study. 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-e32. doi:10.1016/S2352-3018(15)00211-8

31. Laprise C, Baril J-G, Dufresne S, Trottier H. 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):567-575. doi:10.1093/cid/cis937

32. 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

33. Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. *AIDS*. 2012;26(7):867-875. doi:10.1097/QAD.0b013e328351f68f

34. 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;169(3):146-155. doi:10.7326/M17-2252

35. Smith C, Ryom L, Monforte Ad, 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

36. Borges AH, Hoy J, Florence E, et al; EuroSIDA. Antiretrovirals, fractures, and osteonecrosis in a large international HIV cohort. *Clin Infect Dis*. 2017;64(10):1413-1421. doi:10.1093/cid/cix167

37. Nkhoma ET, Rosenblatt L, Myers J, Villasis-Keever A, Coumbis J. 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

38. 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):441-447. doi:10.1097/QAI.0b013e31826f993c

39. 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):422-429. doi:10.1097/QAI.0000000000000606

40. Cohen MS, Chen YQ, McCauley M, et al; HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365(6):493-505. doi:10.1056/NEJMoa1105243

41. Emery S, Neuhaus JA, Phillips AN, et al; Strategies for Management of Antiretroviral Therapy (SMART) Study Group. 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):1133-1144. doi:10.1086/586713

42. Kitahata MM, Gange SJ, Abraham AG, et al; NA-ACCORD Investigators. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med*. 2009;360(18):1815-1826. doi:10.1056/NEJMoa0807252

43. May M, Sterne JA, Sabin C, et al; Antiretroviral Therapy (ART) Cohort Collaboration. Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies. *AIDS*. 2007;21(9):1185-1197. doi:10.1097/QAD.0b013e328133f285

44. Ray M, Logan R, Sterne JA, et al; HIV-CAUSAL Collaboration. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. *AIDS*. 2010;24(1):123-137. doi:10.1097/QAD.0b013e3283324283

45. Writing Committee for the CASCADE Collaboration. Timing of HAART initiation and clinical outcomes in human immunodeficiency virus type 1 seroconverters. *Arch Intern Med*. 2011;171(17):1560-1569. doi:10.1001/archinternmed.2011.401

46. Sterne JA, May M, Costagliola D, et al; When To Start Consortium. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet*. 2009;373(9672):1352-1363. doi:10.1016/S0140-6736(09)60612-7

47. 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;201(3):318-330. doi:10.1086/649897

48. Bedimo RJ, Westfall AO, Drechsler H, Vidiella G, Tebas P. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era. *Clin Infect Dis*. 2011;53(1):84-91. doi:10.1093/cid/cir269

49. 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;11(2):130-136. doi:10.1111/j.1468-1293.2009.00751.x

50. Ribaudo HJ, Benson CA, Zheng Y, et al; ACTG A5001/ALLRT Protocol Team. 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;52(7):929-940. doi:10.1093/cid/ciq244

51. Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med*. 2010;363(3):257-265. doi:10.1056/NEJMoa0910370

52. Chou R, Huffman LH, Fu R, Smits AK, Korthuis PT; US Preventive Services Task Force. Screening for HIV: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2005;143(1):55-73. doi:10.7326/0003-4819-143-1-200507050-00010

53. Chou R, Korthuis PT, Huffman LH, Smits AK. Screening for Human Immunodeficiency Virus in Adolescents and Adults: Evidence Summary: Human Immunodeficiency Virus (HIV) Infection: Screening. US Preventive Services Task Force website. https://www.uspreventiveservicestaskforce.org/Page/Document/screening-for-hiv-in-adolescents-and-adults-evidence-summary/human-immunodeficiency-virus-hiv-infection-screening. Published November 2012. Accessed October 31, 2016.

54. Siegfried N, Uthman OA, Rutherford GW. Optimal time for initiation of antiretroviral therapy in asymptomatic, HIV-infected, treatment-naive adults. *Cochrane Database Syst Rev*. 2010;(3):CD008272.

55. Anglemyer A, Rutherford GW, Easterbrook PJ, et al. Early initiation of antiretroviral therapy in HIV-infected adults and adolescents: a systematic review. *AIDS*. 2014;28(suppl 2):S105-S118. doi:10.1097/QAD.0000000000000232

56. 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

57. 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;3(1):ofw032. doi:10.1093/ofid/ofw032

58. Hutchinson AB, Farnham PG, Sansom SL, Yaylali E, Mermin JH. Cost-effectiveness of frequent HIV testing of high-risk populations in the United States. *J Acquir Immune Defic Syndr*. 2016;71(3):323-330. doi:10.1097/QAI.0000000000000838

59. Lucas A, Armbruster B. The cost-effectiveness of expanded HIV screening in the United States. *AIDS*. 2013;27(5):795-801. doi:10.1097/QAD.0b013e32835c54f9

60. 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

61. 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 Morb Mortal Wkly Rep*. 2017;66(31):830-832. doi:10.15585/mmwr.mm6631a3