

Effects of HIV Antiretroviral Therapy on Sexual and Injecting Risk-Taking Behavior: A Systematic Review and Meta-analysis

Joseph S. Doyle,^{1,2,3} Louisa Degenhardt,^{4,5} Alisa E. Pedrana,^{1,3} Emma S. McBryde,^{1,6} Rebecca J. Guy,⁷ Mark A. Stoové,^{1,3} Emma R. Weaver,¹ Andrew E. Grulich,⁷ Ying-Ru Lo,⁸ and Margaret E. Hellard^{1,2,3}

¹Centre for Population Health, Burnet Institute, ²Department of Infectious Diseases, The Alfred Hospital, ³Department of Epidemiology and Preventative Medicine, Monash University, and ⁴Centre for Health Policy, Programs and Economics, School of Population Health, University of Melbourne, Victoria, ⁵National Drug and Alcohol Research Centre, University of New South Wales, Sydney, ⁶Department of Medicine, Royal Melbourne Hospital, University of Melbourne, Victoria, and ⁷The Kirby Institute, University of New South Wales, Sydney, Australia; and ⁸Department of HIV/AIDS, World Health Organization, Geneva, Switzerland

Background. Increased global access and use of antiretroviral therapy (ART) for human immunodeficiency virus (HIV) has been postulated to undermine HIV prevention efforts by changing individual risk-taking behavior. This review aims to determine whether ART use is associated with changes in sexual or injecting risk-taking behavior or diagnosis of sexually transmitted infections (STIs).

Methods. A systematic review and meta-analysis was conducted of HIV-seropositive participants receiving ART compared with no ART use in experimental or observational studies. Primary outcomes included (1) any unprotected sexual intercourse, (2) STI diagnoses, and (3) any unsafe injecting behavior.

Results. Fifty-eight studies met the selection criteria. Fifty-six studies containing 32 857 participants reported unprotected sex; 11 studies containing 16 138 participants reported STI diagnoses; and 4 studies containing 1600 participants reported unsafe injecting behavior. All included studies were observational. Unprotected sex was lower in participants receiving ART than in those not receiving ART (odds ratio [OR], 0.73; 95% confidence interval [CI], .64–.83; $P < .001$; heterogeneity $I^2 = 79%$) in both high-income ($n = 38$) and low-/middle-income country ($n = 18$) settings, without any evidence of publication bias. STI diagnoses were also lower among individuals on ART (OR, 0.58; 95% CI, .33–1.01; $P = .053$; $I^2 = 92%$); however, there was no difference in injecting risk-taking behavior with antiretroviral use (OR, 0.90; 95% CI, .60–1.35; $P = .6$; $I^2 = 0%$).

Conclusions. Despite concerns that use of ART might increase sexual or injecting risk-taking, available research suggests that unprotected sex is reduced among HIV-infected individuals on treatment. The reasons for this are not yet clear, although self-selection and mutually reinforcing effects of HIV treatment and prevention messages among people on ART are likely.

Keywords. human immunodeficiency virus; antiretroviral therapy; sexual behavior; injecting behavior; risk-taking.

Prevention of human immunodeficiency virus (HIV) remains a challenge worldwide. Behavioral, biomedical,

and structural prevention strategies exist or are under development, including circumcision [1–4], topical microbicides [5], opioid substitution therapy for opioid-dependent people [6, 7], needle and syringe programs for people who inject drugs (PWID) [6], vaccination [8], and pre-/postexposure prophylactic and antiretroviral therapy (ART) [9–13]. Antiretroviral use prevents horizontal HIV transmission as preexposure prophylaxis [11–13] or treatment (reducing risk of onward transmission to sexual partners) [6, 9, 14]. However, countries with easy access to ART have experienced

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Correspondence: Joseph S. Doyle, MD, MSc, FRACP, Centre for Population Health, Burnet Institute, 85 Commercial Road, Melbourne, VIC 3004, Australia (j.doyle@burnet.edu.au).

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increases in new HIV infections [15, 16], unprotected sex [17, 18], and sexually transmitted infections (STIs) [19, 20].

Antiretroviral use may modify risk perception, leading to increases in risk-taking behavior and HIV transmission [21–23]. Some HIV-positive people taking ART and some in the HIV-uninfected community may now perceive HIV as not life-threatening [24–27]. Optimistic beliefs have been associated with risk-taking behavior in some studies [28, 29], but others have rejected the role of “HIV optimism” in altering behavior and therefore HIV exposure at the population level [30, 31].

Any effect of ART on risk behaviors has important implications for HIV prevention, and foreshadows public health challenges in low- and middle-income countries (LMICs), where antiretroviral access and use is rapidly increasing and were most of the global HIV burden lies [32]. A quantitative review of 16 observational studies conducted prior to 2002 found no association between unprotected sex and ART use [29], but used only data from high-income countries (HICs), did not consider substance use and injecting risk, and did not fully explore sources of high heterogeneity. Another qualitative review of 3 studies from developing countries similarly concluded that ART was not associated with increased sexual risk-taking behavior among HIV-infected individuals, yet highlighted significant weaknesses in the individual studies [33]. Antiretroviral access and the medical literature have expanded substantially, particularly outside of HIC settings, since this hypothesis was last formally evaluated. Accordingly, our review aimed to determine whether use of ART among HIV-seropositive individuals is associated with increased unprotected sex, STI diagnosis, or unsafe injecting behavior.

METHODS

A systematic review and meta-analysis was undertaken using Cochrane guidelines for the conduct of and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) [34] and MOOSE (Meta-analysis of Observational Studies in Epidemiology) [35] guidelines for the reporting of systematic reviews. The review protocol was registered prospectively (PROSPERO registration number 2011:CRD42011001563).

Inclusion Criteria

Studies involving HIV-infected individuals were included if participants used any oral combination ART to treat HIV infection and were compared with participants not using ART (Table 1). Three outcome measures of risk-taking were used:

1. The proportion of unprotected anal or vaginal sexual intercourse, defined as inconsistent condom use (“unprotected sex”);
2. Newly diagnosed STIs, defined as new microbiologically confirmed chlamydia, gonorrhoea, or early syphilis infection; and

Table 1. Study Inclusion Criteria

Category	Criteria
Population	All HIV-seropositive participants
Intervention	Any HIV combination ART agents used for treatment
Comparison	Individuals not using or prior to starting ART
Outcomes	Within last 6 months, (1) any unprotected sexual intercourse measured by inconsistent condom use; (2) sexually transmitted infection diagnoses measured by new laboratory-detected chlamydia, new gonorrhoea, or early syphilis; (3) injecting risk measured by any needle/syringe lending, borrowing, or reuse
Study design and limitations	Any trial, cohort, or cross-sectional study in English language up to 1 April 2012

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus.

3. The proportion of unsafe injecting behavior, defined as any needle, syringe or injecting equipment lending, borrowing, or reuse.

Behavioral and STI outcomes were assessed in the preceding 6 months for cross-sectional studies. Among cohort studies, where individuals were assessed before and after ART initiation, outcomes were assessed as close to 6 months after ART commencement as possible. Cohort studies lacking individual before-and-after ART initiation comparisons, comparing with an untreated group instead, were treated as cross-sectional analyses. Studies were excluded if they measured beliefs about antiretroviral use rather than actual use, perceived risk or predicted behavioral change rather than actual self-reported behavior, or prophylactic antiretroviral use.

Search Strategy for Identification of Studies

We searched electronic journal databases including Medline, Embase, the Cochrane Library, LILACS, and PsycINFO to 1 April 2012. Search terms and syntax were modified according to each database, but included combinations of free text and medical subject heading terms where available (see [Supplementary Appendix 1](#) for full description). Search terms reflected 3 categories:

1. Antiretroviral variables (ART, highly active ART, anti-HIV agents);
2. Disease variables (HIV, AIDS); and
3. Outcome variables:
 - (a) Sexual risk-taking (condom use, unsafe sex, unprotected sex, sexual risk-taking, sexual behavior);
 - (b) Injecting risk-taking (needle/syringe sharing, borrowing, or lending);
 - (c) STI diagnoses (incidence of chlamydia, gonorrhoea, syphilis, STIs, sexually transmitted diseases).

We searched the reference lists of all relevant articles and reviews and, given previously documented systematic differences between unpublished and published material, the International AIDS Society conference archive [36, 37]. If multiple publications reported data on a cohort, the more recent or complete study was included.

Conduct of the Review

Two reviewers assessed all search results and included studies that met at least 1 of the 3 outcome criteria. Full articles were then obtained and assessed to confirm eligibility and data were extracted to a standardized spreadsheet using 2 reviewers for each article; a third reviewer resolved differences between authors. Authors were contacted twice to solicit missing data.

Quality appraisal was conducted by the same reviewers prior to data synthesis. We used the Newcastle-Ottawa Scale [38] for nonrandomized and observational studies to score studies for potential selection, attrition, and performance biases [39, 40]. Subjectivity assessing quality in observational studies has been described [41], so subgroup analyses explored the effect of different quality score cutoffs and study type on the effect estimate and heterogeneity.

Statistical Analysis

Effect sizes for binary variables (ART vs no ART; risk behavior vs no risk behavior) were calculated using odds ratios (ORs) with 95% confidence intervals (CIs) using Stata software (version 11.2 for Windows; StataCorp, College Station Texas). We verified ORs and 95% CIs through calculations where possible, and otherwise used reported ORs. If a study reported multiple risk-taking comparisons (eg, insertive unprotected anal intercourse [UAI] vs any unprotected intercourse), only 1 outcome—the behavior with greatest risk of HIV transmission (defined a priori)—was used in the pooled analysis.

A quantitative meta-analysis was conducted with random-effects models, and heterogeneity was assessed by χ^2 and I^2 statistics [42, 43]. A χ^2 statistic with significance level of 0.10 and $I^2 > 50\%$ indicated moderate or high levels of heterogeneity [42]. Subgroup analysis and univariable meta-regression examined potential influences on outcomes and heterogeneity between studies. Where available, clinical variables included gender, sexual practices (eg, men who have sex with men [MSM] vs non-MSM), partnership status (casual vs regular), HIV RNA load, and unprotected sex with an HIV-negative partner or partner with unknown HIV status. Methodological variables included study location (HIC vs LMIC), study design (cross-sectional vs cohort), sample size, and study quality. Definitions of unprotected sex were stratified into receptive UAI, insertive UAI, and UAI position not specified. Insufficient data prevented multivariable meta-regression and stratifying by specific type of STI or specific injecting practices. The effect of outlying

studies and adjusted OR (vs unadjusted OR) on the pooled estimates and heterogeneity was assessed. Publication bias was assessed through a funnel plot [44].

RESULTS

We identified 136 full-text articles and excluded 78; the search results are presented in Figure 1. The included 58 studies contained 52 278 participants (range, 57 to 11 516; median, 365), were dated from 1999 to 2011, and included data collected between 1992 and 2011 (see [Supplementary Table 1](#)) [45–105].

Searching the articles' references failed to detect additional eligible studies, offering confidence in the sensitivity of the search process [106]. Included studies comprised 19 studies with longitudinal comparisons before and after ART initiation and 39 with cross-sectional comparisons. We classified 8 cohort studies that only provided data of interest at baseline as cross-sectional analyses. Only 1 relevant experimental study was found, but it was excluded as the behavioral outcome data needed for meta-analysis calculations were unavailable [9].

Forty studies (69%) were conducted in HICs, of which 24 (60%) were in the United States. Twelve studies (21%) only sampled MSM, 7 (12%) sampled PWID, and the remainder had mixed or unspecified groups ([Supplementary Table 1](#)). Unprotected sex was recorded in 56 studies, containing 58 measures of unprotected sex (47 any unprotected sexual intercourse; 2 receptive UAI; 3 insertive UAI; 6 UAI). STI diagnosis was measured in 11 studies (10 measured any new STI [47, 53, 57, 75, 79, 81, 88, 90, 91, 93] and 1 reported differences by chlamydia, gonorrhoea, and early syphilis diagnosis [64]). Four studies reported unsafe injecting, defined variably as sharing [49], borrowing [53, 96], or lending [74] needles or syringes.

Unprotected Sex

Fifty-six studies contained 32 857 participants (median, 287) who self-reported unprotected sex; the pooled OR was 0.73 (95% CI, .64–.83; $P < .001$)—that is, using ART is associated with a 27% reduction in the odds of unprotected sex (Figure 2). There was no evidence of publication bias (see funnel plot in [Supplementary Figure 1](#)). Twenty-one studies found decreased unprotected sex among those on ART (OR < 1 ; $P < .05$), and 32 studies found no clear difference (95% CI including OR = 1). Only 3 studies found that antiretroviral use was associated with increased unprotected sex (OR > 1 ; $P < .05$) [70, 80, 95]. Statistical ($\chi^2 P < .001$; $I^2 = 79\%$) and qualitative heterogeneity existed across studies. Notably, in subgroup analyses of at-risk populations including MSM and injecting drug users, and among both males and females, there was no increase in unprotected sex among people using ART (Table 2). This association

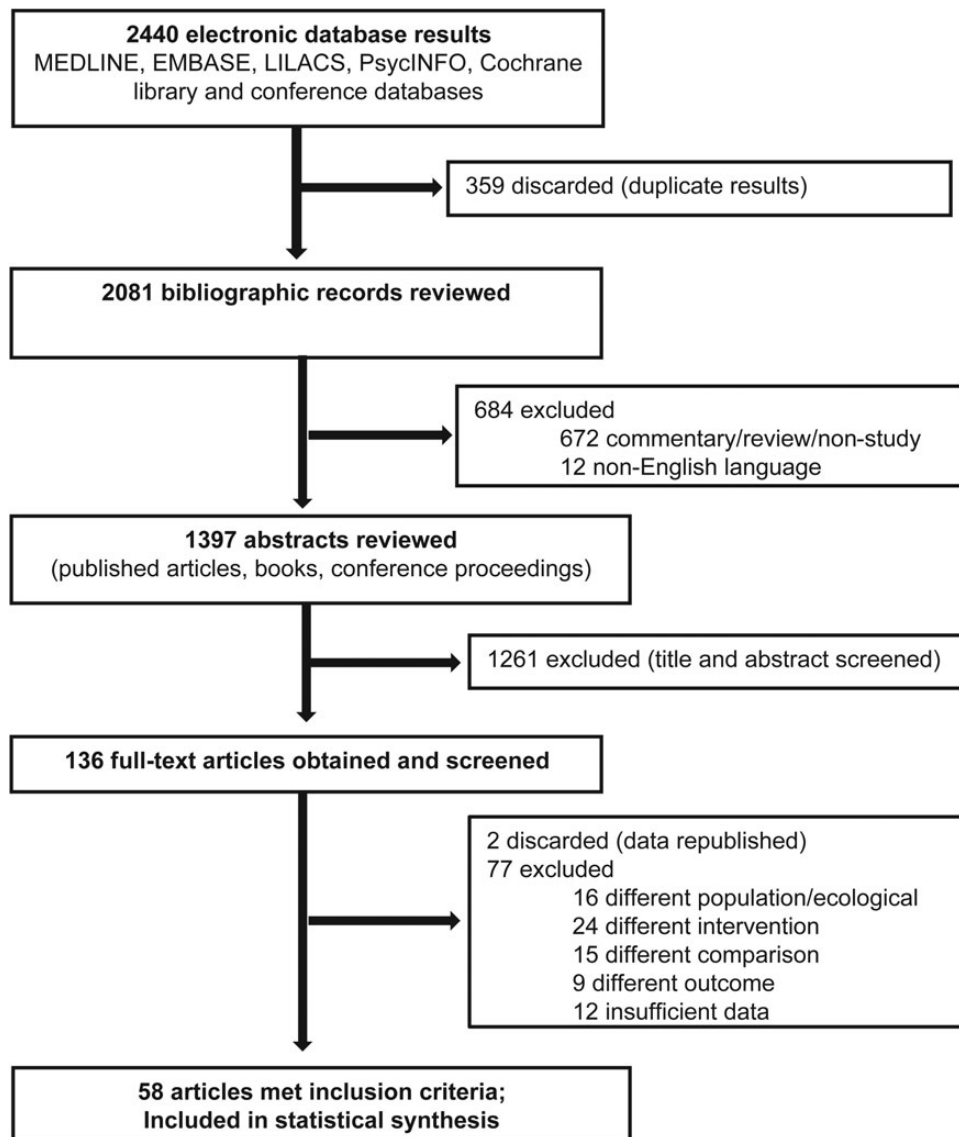


Figure 1. Schematic diagram of study selection and inclusion process.

was also present within 38 studies in HIC settings (OR, 0.85 [95% CI, .73–.99]; $P = .036$) and 18 in LMIC settings (OR, 0.57 [95% CI, .46–.72]; $P < .001$).

The direction of effect did not change significantly after stratification (Table 2), but insufficient information precluded stratifying for differential effects of antiretroviral adherence, scheduled treatment interruptions, or duration of ART on unprotected sex as per our protocol. Eight cohorts measured sexual behavior at multiple time points after ART initiation, yet provided similar estimates of effect to sexual behavior measured closest to 6 months after ART initiation. Heterogeneity was not readily accounted for by any study design factors, but decreased with similar effect estimate following stratification by important

clinical factors among the 11 studies describing risk with HIV-seronegative/status unknown partners [46, 50–52, 64, 70, 75, 81, 88, 97, 105], 3 reporting heterosexual behavior [45, 51, 62], and 3 reporting behavior among PWID [49, 62, 77]. Unprotected sex with an HIV-negative partner or partner with unknown HIV status might be the most accurate indicator of HIV transmission risk, and in this group using ART and less sexual risk-taking were associated (OR, 0.64 [95% CI, .46–.88]; $P < .001$; heterogeneity $I^2 = 61\%$).

Meta-regression analyses examining the effect of clinical predictors on risk-taking and heterogeneity were conducted (Supplementary Table 2). Only 1 variable—undetectable HIV RNA load—significantly modified the relationship between ART and

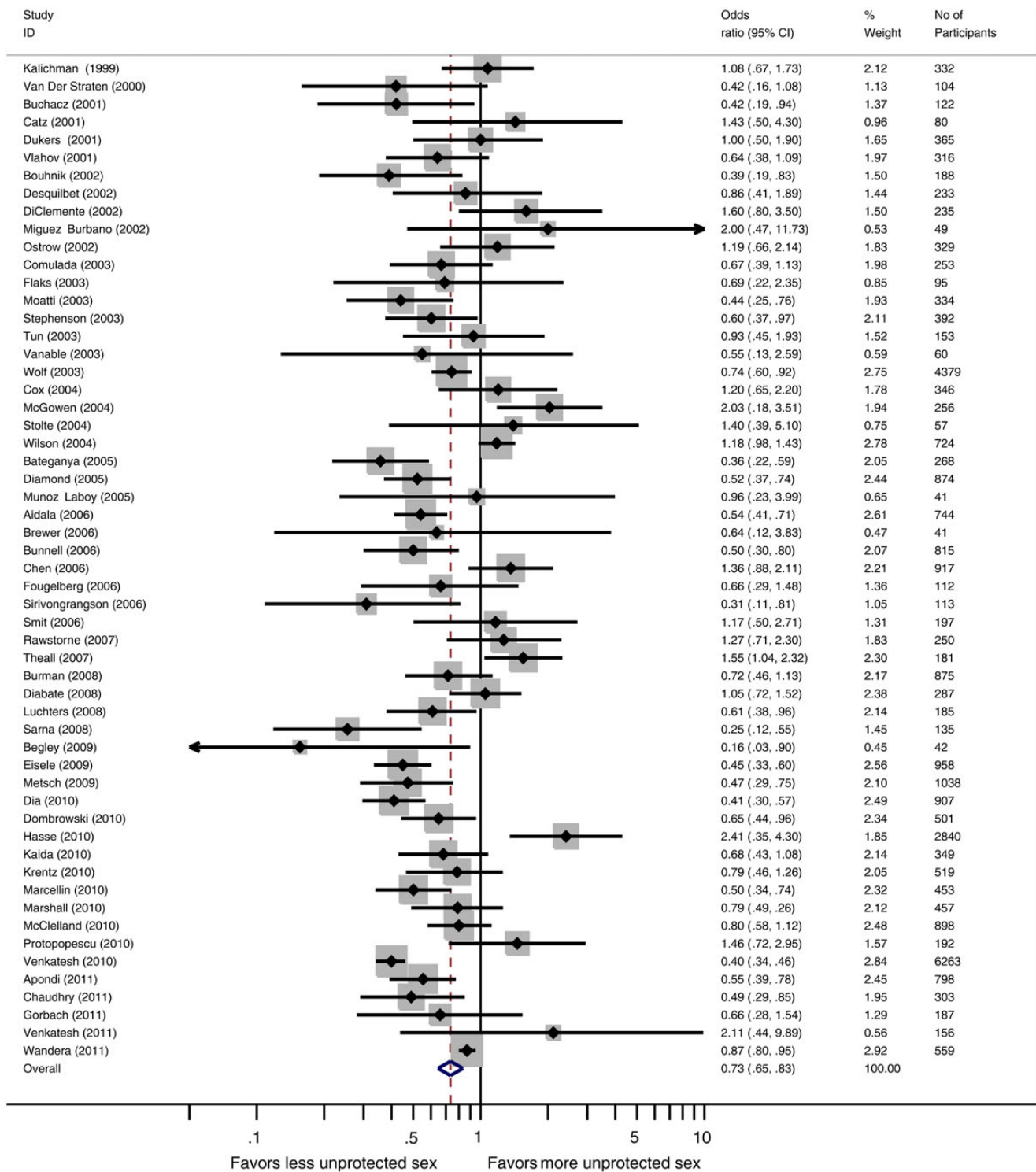


Figure 2. Random-effects meta-analysis of effects of antiretroviral therapy on unprotected sex. Abbreviation: CI, confidence interval.

sexual risk-taking. Odds of sexual risk-taking increased by 0.11 (95% CI, .03–.19; $P = .008$; $I^2 = 9\%$), as the proportion of participants who reported an undetectable HIV RNA load increased by 10% (Supplementary Figure 2).

STI Diagnosis

Eleven studies containing 16 138 participants (median, 439) reported the proportion of patients diagnosed with STIs, with a pooled OR of 0.58 (95% CI, .33–1.01; $P = .053$), indicating

Table 2. Effect of Antiretroviral Therapy (ART) Versus No ART Use on Unprotected Sex

Variable	No. of Studies	Odds Ratio (95% CI)	P Value	Heterogeneity χ^2 Test (I^2 %)
Overall	56	0.73 (.64–.83)	<.001	<0.001 (79)
Study type				
Cohort	18	0.78 (.63–.98)	.032	<0.001 (89)
Cross-sectional	38	0.71 (.60–.83)	<.001	<0.001 (64)
Sample size				
\leq 250 participants	18	0.84 (.63–1.13)	.25	0.01 (51)
>250 participants	38	0.71 (.61–.82)	<.001	<0.001 (83)
Study location				
High-income country	38	0.85 (.73–.99)	.036	<0.001 (66)
United States	23	0.81 (.65–1.00)	.057	<0.001 (71)
Other than United States	15	0.91 (.73–1.13)	.39	0.002 (58)
Low- or middle-income country	18	0.57 (.46–.72)	<.001	<0.001 (87)
Study quality				
Higher-quality score	32	0.68 (.58–.79)	<.001	<0.001 (77)
Higher-quality cohort	9	0.71 (.54–.93)	.013	<0.001 (84)
Higher-quality cross-sectional	23	0.66 (.54–.81)	<.001	<0.001 (72)
Lower-quality score ^a	24	0.84 (.66–1.09)	.20	<0.001 (82)
Outcome assessment ^b				
Any unprotected intercourse	47	0.73 (.63–.84)	<.001	<0.001 (82)
Any UAI	6	0.75 (.56–1.01)	.055	0.32 (16)
Receptive UAI	2	0.42 (.07–2.48)	.34	0.12 (59)
Insertive UAI	3	0.84 (.54–1.31)	.44	0.27 (23)
Sex ^c				
Male	15	0.79 (.57–1.09)	.15	<0.001 (77)
Female	15	0.78 (.59–1.02)	.070	<0.001 (83)
Sexual behavior ^c				
MSM	11	1.02 (.73–1.42)	.91	<0.001 (68)
Heterosexual	3	0.50 (.36–.71)	<.001	0.86 (0)
Sexual partners ^c				
Regular partner only	8	0.69 (.44–1.07)	.098	<0.001 (77)
Casual partners only	7	1.02 (.73–1.43)	.90	0.12 (41)
HIV RNA load ^c				
Detectable	2	1.14 (.29–4.40)	.86	<0.001 (88)
Undetectable	3	1.67 (.69–4.05)	.26	0.034 (70)
HIV status of sexual partners ^c				
HIV-positive	2	0.78 (.54–1.13)	.19	0.16 (0)
HIV-negative/unknown	11	0.64 (.46–.88)	.006	<0.001 (71)
HIV acquisition route ^c				
Injecting drug use	3	0.54 (.31–.94)	.03	0.17 (43)
Sexual transmission	2	1.15 (.28–4.77)	.85	<0.001 (94)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; MSM, men who have sex with men; UAI, unprotected anal intercourse.

^a Includes 2 unpublished studies that could not be fully assessed for quality.

^b The total number of studies in this subgroup comparisons is greater than the total ($n = 56$) because some studies reported multiple comparisons by different sexual practice.

^c The total number of studies in these subgroup comparisons is less than the total ($n = 56$) because data were not available for every comparison in each study.

42% lower odds of STI diagnosis among patients on ART (Figure 3). High statistical heterogeneity ($\chi^2 P < .001$; $I^2 = 92\%$) was chiefly due to 1 outlier [90] that assessed STI diagnosis in a

predominantly female cohort with low ART uptake (17%). This study found an increased odds of STI diagnosis with ART use (OR, 3.66 [95% CI, 2.57–5.22]) [90]. Without this

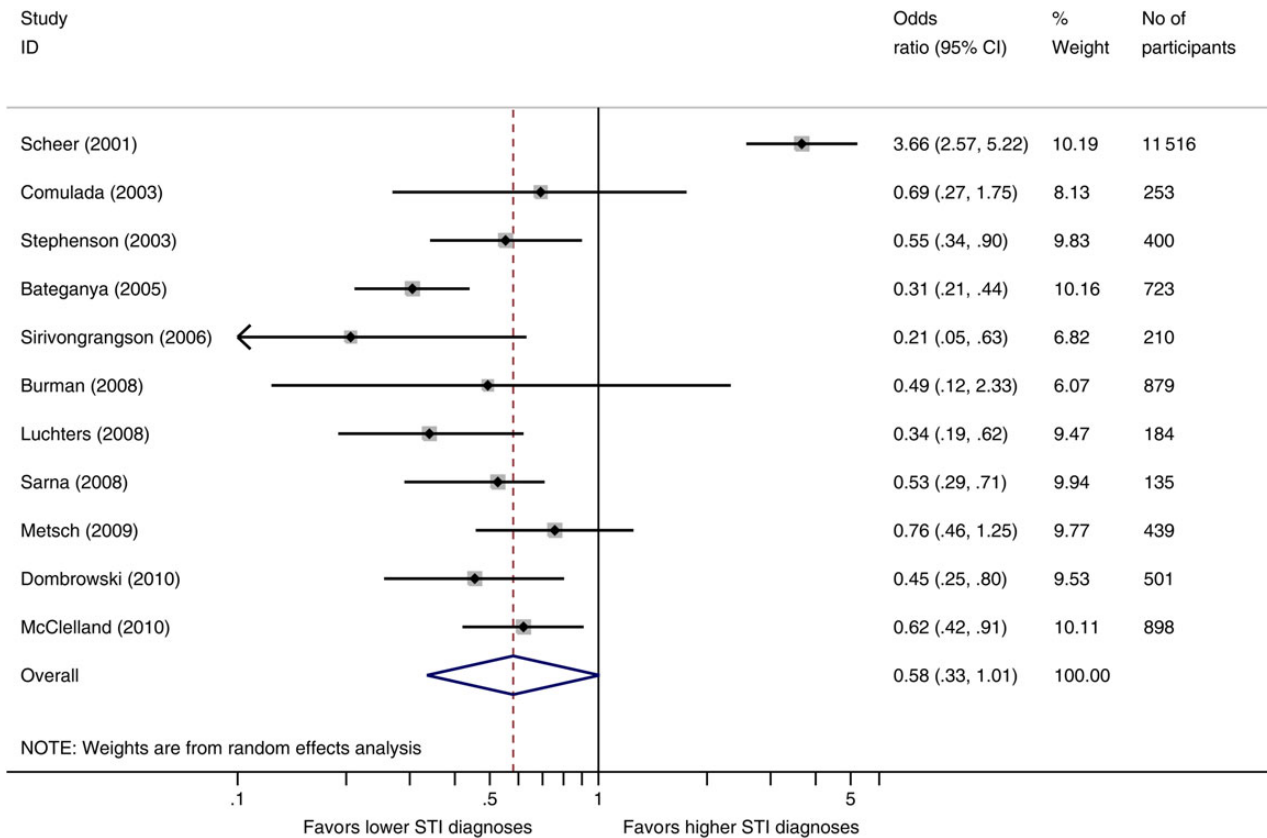


Figure 3. Random-effects meta-analysis of effects of antiretroviral therapy on sexually transmitted infection diagnosis. Abbreviations: CI, confidence interval; STI, sexually transmitted infection.

outlying study, a clear association existed between lowered STI diagnosis and ART with low heterogeneity (OR, 0.48 [95% CI, .38–.61]; $P < .001$; heterogeneity $\chi^2 P = .10$; $I^2 = 39\%$).

Among the 3 cohort studies [75, 79, 90] STI incidence did not differ (OR, 0.93 [95% CI, .22–3.89]; $P = .92$), but heterogeneity was significant ($\chi^2 P < .001$; $I^2 = 97\%$). Among cross-sectional studies [47, 53, 57, 64, 81, 88, 91, 93], ART use and reduced STI prevalence were associated (OR, 0.48 [95% CI, .36–.63]; $P < .001$), with low heterogeneity ($\chi^2 P = .1$; $I^2 = 41\%$). Other study characteristics used in the sensitivity analysis produced no substantial change in overall effect or heterogeneity (Table 3).

Injecting Risk-Taking Behavior

Four studies containing 1600 participants (median = 284) reported unsafe injecting behavior with a pooled OR of 0.90 (95% CI, .60–1.35; $P = .6$), suggesting no difference in risk with ART use (Supplementary Figure 3). These studies had similar effect estimates with very low heterogeneity ($\chi^2 P = .7$; $I^2 = 0\%$). Although definitions of unsafe injecting differed, risk-taking did not, with 1 study [53] having very few high-risk-behavior events and considerable uncertainty in the estimate.

Methodological Quality

We critically appraised studies using the Newcastle-Ottawa Scale except for 2 studies of unpublished data (Supplementary Table 3). Selection biases were common, with participants and nonparticipants differing substantially, low participation rates, and systematic differences between people receiving and not receiving ART. Performance biases were uncommon and cross-over impossible in most studies. All studies had detection biases; few studies mentioned blinding the researchers to antiretroviral status when measuring sexual behavior.

DISCUSSION

This review found that unprotected sex is rarer among HIV-positive people taking ART than among those who are not. This effect was consistent across studies, with no differences evident in the effect according to gender, sexual practices, or geographic location. Importantly, in studies that clearly documented episodes of HIV transmission risk (ie, unprotected sex with HIV-negative partners or partners with unknown HIV status), ART use was associated with less unprotected sex. ART may also be associated with fewer STI diagnoses.

Table 3. Effect of Antiretroviral Therapy (ART) Versus no ART on Sexually Transmitted Infection Diagnosis

Variable	No. of Studies	Odds Ratio (95% CI)	P Value	Heterogeneity χ^2 Test ($I^2\%$)
Overall	11	0.58 (.33–1.01)	.053	<0.001 (92)
Study type				
Cohort	3	0.93 (.22–3.89)	.92	<0.001 (97)
Cross-sectional	8	0.48 (.36–.63)	<.001	0.11 (41)
Sample size				
≤ 250 participants	2	0.31 (.18–.53)	<.001	<0.001 (93)
>250 participants	9	0.67 (.37–1.24)	.20	0.48 (0)
Study location				
High-income country	6	0.82 (.35–1.93)	.65	<0.001 (92)
United States	4	0.99 (.33–2.99)	.98	<0.001 (94)
Other than United States	2	0.55 (.35–.87)	.010	0.88 (0)
Low- or middle-income country	5	0.41 (.30–.59)	<.001	0.05 (58)
Study quality				
Higher-quality score	8	0.64 (.30–1.34)	.24	<0.001 (94)
Higher-quality cohort	2	1.13 (.11–11.6)	.92	<0.001 (98)
Higher-quality cross-sectional	6	0.49 (.35–.68)	<.001	0.08 (48)
Lower-quality score	3	0.51 (.10–1.55)	.45	<0.001 (98)
Outcome assessment				
Any STI	10	0.59 (.33–1.08)	.089	<0.001 (93)
Gonorrhoea diagnosis	1	0.45 (.26–.81)	.007	...
Chlamydia diagnosis	1	0.69 (.37–1.28)	.24	...
Early syphilis diagnosis	1	1.10 (.61–2.01)	.75	...

Abbreviations: CI, confidence interval; STI, sexually transmitted infection.

Both measures refute the hypotheses that ART is associated with increased risk-taking behavior. However, too few studies exist for meaningful comment on the effect of ART on injecting behavior ($n = 4$). We cannot comment on ART used prophylactically given the differences between ART and pre-/postexposure prophylaxis interventions. The few studies of HIV postexposure prophylaxis reporting behavior outcomes have demonstrated no increase in sexual risk-taking [78, 89, 107]. However, with emerging experimental data examining the effectiveness of HIV preexposure prophylaxis, exploration of behavioral effects of antiretroviral prophylaxis will soon be possible [11–13, 108].

HIV-infected individuals commencing ART may reduce their risk-taking behavior partly due to awareness of their HIV status, and the commencement of treatment is usually negotiated between individuals and their physician. Individuals choosing ART may be more amenable to reducing risk-taking behavior [109]. In addition, individuals on ART who receive regular monitoring and ongoing medical care, including ongoing counseling, have more opportunities for reinforcement of preventive health messages, and this could fortify decisions to reduce risk. Using this rationale, ART might be just one of several health interventions delivered to HIV-infected individuals that, combined with other supports or prevention messages, reduce risk-taking behavior. Nevertheless, it is important to note that

in this synthesis, a lack of individual data on both time on ART and CD4 lymphocyte count at ART commencement precluded examination of the effect of these variables on the relationship between ART use and reduced risk-taking. These factors may be important and warrant further investigation.

The meta-regression findings that an undetectable HIV RNA load is associated with slightly higher sexual risk-taking might reflect awareness among participants that HIV transmission risk is reduced with virological suppression. This is a potentially important observation that might underestimate unprotected sex as emerging evidence of “treatment as prevention” benefits become well known [110]. However, this is a weak finding, as meta-regression infers study-level characteristics to individual participants, and we could only draw on data from 19 of the 56 included studies. In addition, viral load was reported to be an independent predictor in only 3 articles [62, 65, 70], and there was no variation in sexual behavior with ART except among an MSM subgroup in 1 study [70]. This relationship warrants further investigation, particularly as fully suppressed HIV virus is becoming the norm.

Strengths of our review included breadth of database searches, assessment of publication bias, use of 2 independent reviewers, and thorough sensitivity analyses. Several limitations exist. Any meta-analytical synthesis can magnify the limitations of

included studies, and some authors assert that these techniques should be reserved only for randomized trials [111–113]. We took several steps to ensure validity in our qualitative and quantitative syntheses. First, unlike previous reviews, we specifically assessed study quality in the final analysis. We retained cross-sectional studies along with the 18 cohort studies in the main analysis to allow for comparison with previous reviews and to document the expansion in literature over time [29]. Importantly, the sensitivity analysis demonstrates that study type or quality does not affect conclusions about unprotected sex (Table 2). Second, sources of heterogeneity were searched for thoroughly in the sensitivity analysis, with all clinically and methodologically important differences proposed a priori. Third, given the qualitative differences in the included studies, pooling of results was performed cautiously using a random-effects model. Finally, in addition to quantitative aggregation, we compared the included studies qualitatively; both methods suggested that antiretroviral use was associated with less, not more, unprotected sex.

We note several weaknesses in our evidence that may affect the generalizability of review findings. The first limitation is that the risk-taking behavior data in all cases was reliant on self-report, which might be prone to differential underreporting in individuals receiving ART. Although underreporting of unprotected sex and injecting risk-taking behavior is widely described [114, 115], it is not universal [116]. Differential reporting could plausibly affect these results in either direction: Individuals on ART may be less likely to report unprotected sex with their treating doctor, a form of social desirability bias [115], whereas those not taking ART may underreport risk-taking because they perceive themselves as more infectious. Exploring laboratory-confirmed new STI diagnoses counters this limitation in part. Second, most studies measured sexual behavior or STI diagnosis within 1 year of starting ART, and few studies followed patients longitudinally to assess persistence of ART effects. Longer follow-up would enable exploration of whether HIV virological suppression truly has an impact on risk-taking behavior, as suggested in the regression analysis. Third, this study could not evaluate risk-taking behavior among HIV-uninfected individuals, or whether HIV “treatment optimism” modifies behavior among high-risk populations. Finally, unprotected sex and unsafe injecting behaviors cannot be equated directly to HIV transmission risk, particularly given the absence of information on sexual or injecting partners’ HIV serostatus.

CONCLUSIONS

ART use does not appear to increase unprotected sex, STI diagnosis, or unsafe injecting behavior among those on treatment. Although it is plausible that HIV treatment and prevention messages could mutually reinforce risk reduction among HIV-positive individuals selected for ART, the observation

that reductions in unprotected sex are associated with ART use must be interpreted cautiously, as limited data are available to accurately assess a causal relationship. The current practice of providing ART with counseling, education, and ongoing clinical care probably offers an optimal strategy of ensuring that individuals on ART minimize risks associated with unsafe sex. These findings suggest that campaigns or treatment strategies that scale up use of treatment are unlikely to adversely increase compensatory risk-taking behavior; however future research needs to continue to measure risk behaviors after long-term ART to ensure that this effect is sustained and to measure changes induced by treatment-as-prevention messages. Furthermore, these findings should allay concerns that expanding antiretroviral provision to affected populations will undermine HIV prevention efforts.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Disclaimer. Y.-R. L. is a staff member of the World Health Organization (WHO). The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of the WHO. None of the funding sources had any involvement in the conduct, analysis, or reporting of the study.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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