

Antiretroviral therapy and the risk of sexual transmission of HIV: a systematic review and meta-analysis

M Davari,¹ HB Giwa ^{1,2} A Nabizade,¹ F Taheri³ and A Giwa²

¹Department of Pharmaco-Economics and Pharmaceutical Administration, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran, ²Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmaceutical Sciences, University of Ilorin, Ilorin, Nigeria and ³Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

Objectives

The aim of this study was to evaluate the effect of antiretroviral therapy (ART) with or without condom use on the risk of sexual transmission of HIV.

Methods

A search of the literature was conducted in the PubMed, Web of Science, Cochrane, SCOPUS and EMBASE databases for studies dating back to 2008. The results were summarized as relative risks and incidence rates with 95% confidence intervals (CIs). The effect sizes were pooled using random-effects models and heterogeneity was evaluated using the Cochrane Q test and I^2 .

Results

Of the 1424 studies retrieved in the initial search, 10 met the eligibility requirements. ART was associated with a 52% reduction in transmission risk compared to no ART, with a relative risk of 0.48 (95% CI 0.439–0.525) ($Q = 0.524$; $I^2 = 0.0\%$; overall effect $Z = 15.99$, $P < 0.0001$). ART *vs.* no ART caused a reduction in the risk from 5.6 person-years (95% CI 3.26–9.62 person-years) ($Q = 0.771$; $I^2 = 0.0\%$; overall effect $Z = 6.25$, $P < 0.0001$) in the untreated group to 0.85 person-years (95% CI 0.28–2.99 person-years) ($Q = 0.038$; $I^2 = 76.7\%$; overall effect $Z = 0.11$, $P = 0.772$) in the treated group, but not significantly so, which is equivalent to an 84% reduction in the risk of sexual transmission. In accordance with the Swiss National AIDS Commission declaration, ART with suppressed viral loads was associated with a minimal risk of transmission, with a median time at risk of 0.00 person-years (95% CI 0.00–0.00 person-years) ($Q = 1.00$; $I^2 = 0.0\%$; overall effect $Z = 6.80$, $P < 0.0001$).

Conclusions

ART and condom use were found to cause a significant reduction in the risk of sexual transmission of HIV in both homosexual and heterosexual populations, based on previous systematic reviews and meta-analyses.

Keywords: antiretroviral therapy, HIV, infection, infectivity, serodiscordant, transmission

Accepted 29 November 2019

Introduction

By the end of 2015, the World Health Organization estimated that there were 36.7 million people living with HIV/AIDS.

Antiretroviral therapy (ART) has been shown to cause a reduction in the vertical transmission of HIV and it is also used extensively for post-exposure and pre-exposure prophylaxis [1].

Historical events have shown that the effectiveness of ART in minimizing the sexual transmission of HIV has always been uncertain [2–4] and effectiveness in reducing sexual transmission can be determined by assessing the risk of horizontal HIV transmission between members of serodiscordant couples when the HIV-positive partner has full viral suppression with combination antiretroviral therapy (cART) [4].

Amid this uncertainty, the Swiss National AIDS Commission issued a statement in January 2008 specifying that “HIV infected individuals could be considered non-infectious if they met three conditions: adherence to cART under the care of an HIV physician, virologic

Correspondence: Halima Bukola Giwa, PhD Candidate, Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmaceutical Sciences, University of Ilorin, PMB1515 Ilorin, Nigeria. Tel: +989030749058; fax: 031221937; e-mail: hbfgiwa@yahoo.com

suppression below the level of detection for at least 6 months, and absence of concomitant sexually transmitted infections (STIs)" [4].

The Swiss statement was controversial because some studies were later carried out showing the presence of viral particles in the genital secretions of 5–48% of patients with undetectable plasma viraemia [5–7].

Since the Swiss statement, there has been an increase in the number of systematic reviews and meta-analyses performed that have addressed the risk of sexual transmission of HIV with ART [8].

In this study, a systematic review was performed of all systematic reviews and meta-analyses examining the effect of ART on the risk of sexual transmission of HIV that have been carried out from 2008 (when the Swiss statement was released) to date (encompassing all recent studies). A review of secondary data was performed, as such data can provide superior evidence as to the current risk of sexual transmission of HIV and would thus be of great value to policy makers in designing, implementing and improving HIV/AIDS prevention strategies.

Objective of this study

The aim of this study was to evaluate the effect of ART with or without condom use on the risk of sexual transmission of HIV.

Research question

What is the effect of ART with or without condom use on the risk of sexual transmission of HIV?

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used to conduct this systematic review meta-analysis [9]. The protocol is registered with prospective register for systematic reviews registration number CRD42019136811.

Search strategy

Cochrane, Web of Science, EMBASE, SCOPUS and PubMed Central were searched for all relevant articles published from 2007 to 2019. The subject headings (MESH) and text words used to identify relevant articles are given in Appendix 1.

The following filters were used: English language, systematic reviews, meta-analysis and human species; conference papers were excluded.

Literature searches were downloaded into EndNote (version X8 for Windows; Thomson Reuters, Philadelphia, PA) to merge retrieved articles from different databases, to eliminate duplications and to facilitate the review process.

Eligibility criteria

Studies were eligible for inclusion if they fulfilled the following criteria: (1) the study design was a systematic review or meta-analysis; (2) the intervention was the use of ART with or without condom use, (3) the outcomes of interest were transmission of HIV events measured as the incidence rate (in person-years) or its equivalent, and (4) the population of interest was adults (aged > 18 years) who were members of heterosexual or homosexual serodiscordant couples.

Data extraction

All retrieved articles in the initial search were read independently by two reviewers (HB and AZ). First, the titles and abstracts were screened, then the full text was screened, and finally articles were retrieved. Any disagreements were discussed and resolved by consensus or by a third independent reviewer (MD) if necessary. The following data were retrieved from the full text of the selected articles: first author, year of publication, population, study period, data on the ART and non-ART arms, pooled incidence rate, pooled relative risk and A Measurement Tool to Assess Systematic Reviews (AMSTAR) score. These data were extracted and saved in tables depending on the category of the studies.

Quality assessment

The AMSTAR tool [10] was used for assessment of the quality of the included studies. This is a critical appraisal tool for systematic reviews that include randomized or nonrandomized studies of health care interventions, or both. It contains 16 main questions, and the total grade for each study was computed based on these unique questions. The scores were then computed based on a maximum of 10 points. The quality assessment was performed independently by two reviewers (HB and AZ), and discrepancies were resolved by a third party (MD).

Statistical analysis

Statistical analysis was performed using STATA software version 12 (STATA Corp., College Station, TX). The

pooled effect sizes had already been imputed into the tables and the next procedure involved pooling of the effect sizes (incidence rate and relative risk). The fixed-effects model was first used to assess heterogeneity. If significant heterogeneity was found, the random-effects model was then used. Heterogeneity was assessed using Cochrane χ^2 and I^2 . A subgroup analysis was then performed for the studies that investigated ART with viral load suppression as the intervention.

Results

Study selection

The initial search identified 1424 articles in the Cochrane, Web of Science, EMBASE, SCOPUS and PubMed Central databases, 22 of which were duplicates. Following the removal of duplicates, there was a total of 1402 articles, 1202 of which were removed following title and abstract screening, leaving a total of 200 studies. After full text

screening, 10 potentially eligible studies were retrieved (Fig. 1).

Characteristics of included studies

A summary of the included studies is given in Tables 1 and 2. The studies originated in the UK [1,11,12], the USA [13–17] Canada [8] and China [18]. All were published between 2007 and 2019. The study design was either a systematic review or meta-analysis, and the study population for all the studies consisted of heterosexual serodiscordant couples, except for one study [13] in which the study population was homosexual serodiscordant couples.

In the tables, the studies were classified into two distinct groups: unstratified and stratified studies (Tables 1 and 2, respectively).

This imputation into tables was carried out in an attempt to separate studies that had clinical heterogeneity and to unite studies with clinical homogeneity. It was

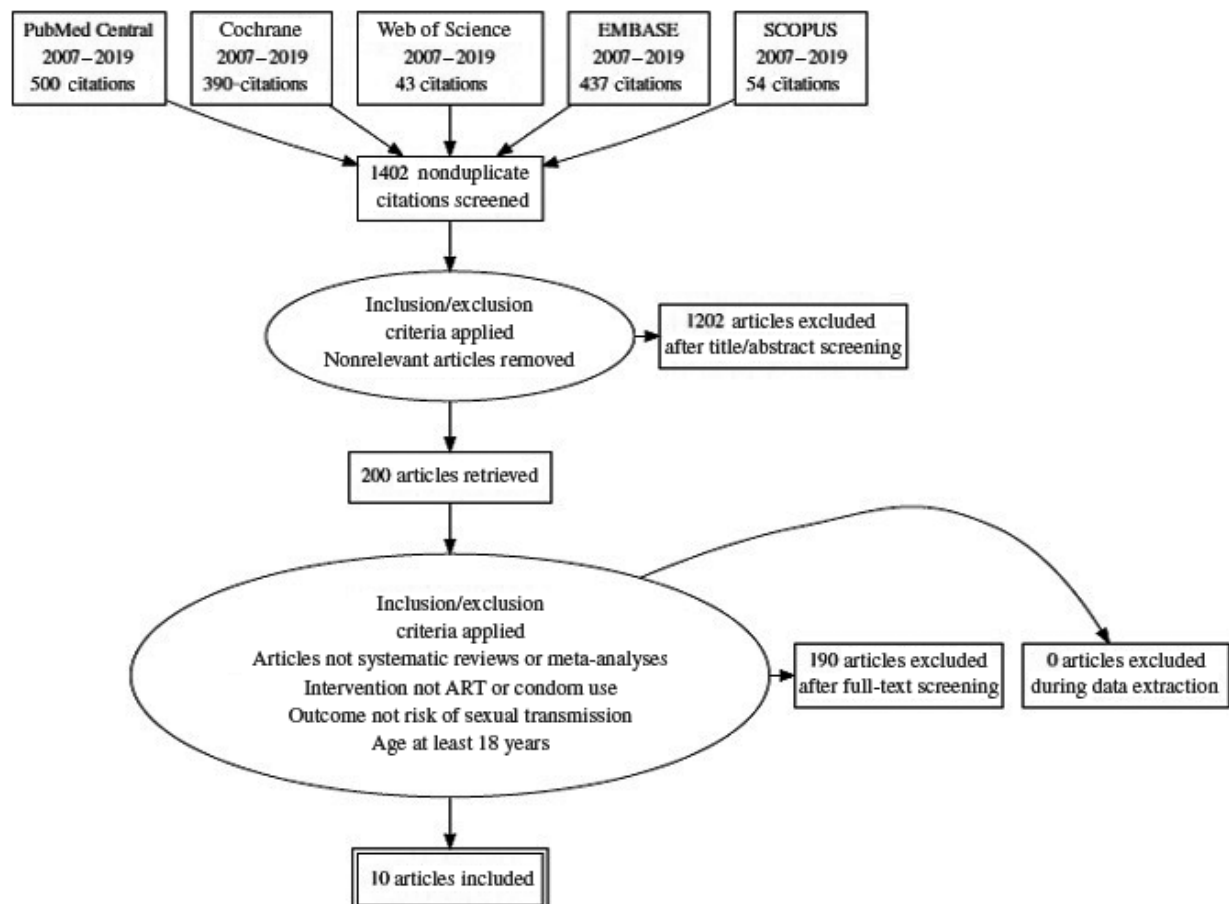


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. ART, antiretroviral therapy.

Table 1 Characteristics of included studies with unstratified outcomes

Study number	Authors, year of publication	Population, study period	Antiretroviral therapy				AMSTAR score
			Untreated		Treated		
			Pooled incidence rate (95% CI)	Pooled relative risk (95% CI)	Pooled incidence rate (95% CI)	Pooled relative risk (9% CI)	
1	Attia <i>et al.</i> , 2009[11]	HSSD, 1996–2009	5.64 (3.28–9.70)		0.46 (0.19–1.09)		5
2	Anglemyer <i>et al.</i> , 2013[1]	HSSD, 1994–2012				0.58 (0.35–0.96)	8
3	Baggaley <i>et al.</i> , 2013[14]	HSSD, 1996–2009				0.58 (0.41–0.80)	6
4*	Patel <i>et al.</i> , 2014[12]	HSSD, 2008–2012				0.08 (0.00–0.57)	6
5*	Liu <i>et al.</i> , 2014[15]	HSSD, 2014				0.47 (0.43–0.52)	7
6	Zang <i>et al.</i> , 2011[18]	HSSD, 1994–2012	2.13 (0.00–4.63)		1.44 (0.62–2.26)		4

AMSTAR, A Measurement Tool to Assess Systematic Reviews; CI, confidence interval; HSSD, heterosexual serodiscordant couples. *These studies appear in both the stratified and unstratified groups.

observed generally that groups that were administered the intervention (ART/condom use) had point estimates < 1, showing the beneficial effects of these interventions, while groups with no intervention had point estimates > 1. Heterogeneity was high for these studies as a result of differences in the study populations (homosexual or heterosexual individuals included), the types of sexual activity in which subjects engaged, whether the two interventions were administered in isolation or combined, and so on. This led to slightly different point estimates in the stratifications. The quality scores were found to range from 4 to 8 points out of 10.

Meta-analysis

The first meta-analysis included a cohort of four studies that reported the risk of transmission associated with ART versus no ART. The point estimate for these four studies was relative risk. The summary risk for ART compared with no ART was 0.48 with a 95% CI of 0.439–0.525, as illustrated in Figure 2. The results were significant, with very low heterogeneity using both fixed- and random-effects models ($Q = 0.524$; $I^2 = 0.0\%$; overall effect $Z = 15.99$, $P < 0.0001$).

The second meta-analysis, which included two cohorts, also estimated the risk of transmission associated with ART versus no ART, with the point estimate being the incidence rate. The summary risk for the ART untreated group was 5.6 person-years, 95% CI of 3.26–9.62 ($Q = 0.771$; $I^2 = 0.0\%$; overall effect $Z = 6.25$, $P < 0.0001$) (Fig. 3).

The ART-treated groups showed summary risks of 0.85 person-years with a 95% CI of 0.28–2.99. This group

showed a high level of heterogeneity and a nonsignificant P -value ($Q = 0.038$; $I^2 = 76.7\%$; overall effect $Z = 0.11$, $P < 0.0001$) (Fig. 3).

The third meta-analysis involved a cohort in which patients on ART had suppressed viral loads and was a subgroup analysis of two studies [8,16]. The summary time at risk was also found to be 0.00 person-years (95% CI 0.00–0.00 person-years; $Q = 1.00$; $I^2 = 0.0\%$; overall effect $Z = 6.80$, $P < 0.0001$) (Fig. 4).

Further meta-analysis could not be carried out because of the heterogeneity of the studies in terms of the study population or the stratified outcome.

Discussion

We carried out a systematic review and meta-analysis of all systematic reviews and meta-analyses that have been conducted from the time of the controversial Swiss statement (2008) to date addressing the effect of ART and condom use on the risk of sexual transmission of HIV. Our review encompassed all 10 studies that had the two interventions.

All the included studies found that there was a reduction in the risk of sexual transmission of HIV with the use of ART in both heterosexual serodiscordant couples and homosexual [men who have sex with men (MSM)] serodiscordant couples (Tables 1 and 2). Condom use also led to a reduction in the risk of sexual transmission in both a study that examined condom use in isolation [8] and a study that examined condom use combined with ART [15]. Consistent condom use was found to lead to a further reduction in the risk of transmission [15] (Table 2). The risk of sexual transmission of the disease was also

Table 2 Studies with stratified outcomes

Antiretroviral therapy									
Study number	First author, year of publication	Population, study period	Stratification of study	RR of stratification (95% CI)	Untreated				AMSTAR score
					Pooled incidence rate (95% CI)	Pooled relative risk (95% CI)	Pooled incidence rate	Pooled relative risk (95% CI)	
7	Baggaley <i>et al.</i> , 2018 [13]	MSM, February 2018	URAI, $P = 0.955$ UIAI, $P = 0.955$	1.25 (0.55–2.23) 0.17 (0.09–0.26)		1.67 (0.443.67) 0.14 (0.04–0.29)		0.14 (0.04–0.29) 0.18 (0.09–0.31)	5
Antiretroviral therapy									
Study number	First author, year of publication	Population, study period	Stratification of studies	RR of stratification	Untreated			Treated	
					Pooled incidence rate	Pooled relative risk	Pooled incidence rate (95% CI)	Pooled relative risk	AMSTAR score
8	Le Messurier <i>et al.</i> , 2018 [8]	HSSD, 2007–2017	ART + suppressed VL ART + condom use ART + suppressed VL + condom use				0.00 (0.00–0.28) Not given Not given		8
9	Liu <i>et al.</i> , 2014 [15]	HSSD, up to 2014 Consistent condom use only ART + consistent condom use ART minus consistent condom use	Condom use ART				1.14 (0.56–2.04) 0.47 (0.43–0.52)		7
10	Loutfy <i>et al.</i> , 2013 [16]	ART + VL suppression	3 studies: confirmed VL suppression 3 studies: unconfirmed VL suppression 6 studies: combined URAI				0.02 (0.01–0.04) 0.01 (0.00–0.13) 0.33 (0.17–0.64) 0.00 (0.00–0.03)		8
11	Patel <i>et al.</i> , 2014 [12] ART	HSSD, 2008–2012	UIAI		6.0 (1.0–29)		0.14 (0.04–0.31) 0.00 (0.00–0.01) 138 (102–186)		8
12	Suprevine <i>et al.</i> , 2014 [17]	HSSD, six months	ART vs. no ART		0.4 (0.1–3.0) 0.32 (0.06–1.7) 0.16 (0.02–1.3) 0.04 (0.01–0.27) 0.08 (0.00–0.57)		11 (4–28) 8 (6–8) 4 (1–19)		7

AMSTAR, A Measurement Tool to Assess Systematic Reviews; ART, antiretroviral therapy; CI, confidence interval; HSSD, heterosexual serodiscordant couples; MSM, men who have sex with men; RR, relative risk; UIAI, insertive anal intercourse; URAI, receptive anal intercourse; VL, viral load; PY, person-years.

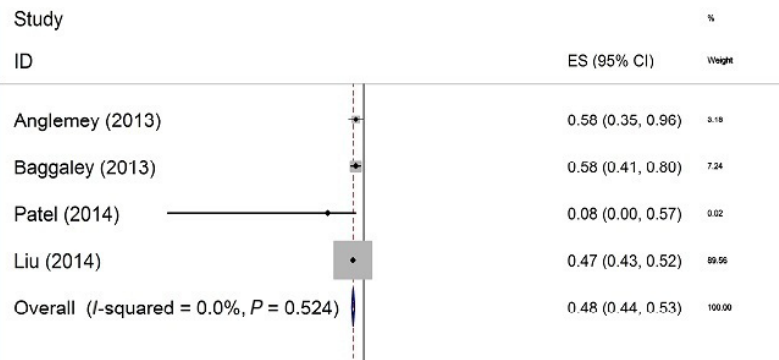


Fig. 2 Forest plot of antiretroviral therapy treated groups for studies reporting relative risks. CI, confidence interval; ID, identification.

found to be lower for vaginal intercourse when compared to anal intercourse [12]. In a study by Baggaley *et al.*, in MSM, receptive anal intercourse was found to have a higher risk of transmission than insertive anal

intercourse, but an increased risk of transmission was observed in women who participated in any form of anal intercourse (heterosexual anal intercourse) [13]. This study in MSM is important because it focused on anal

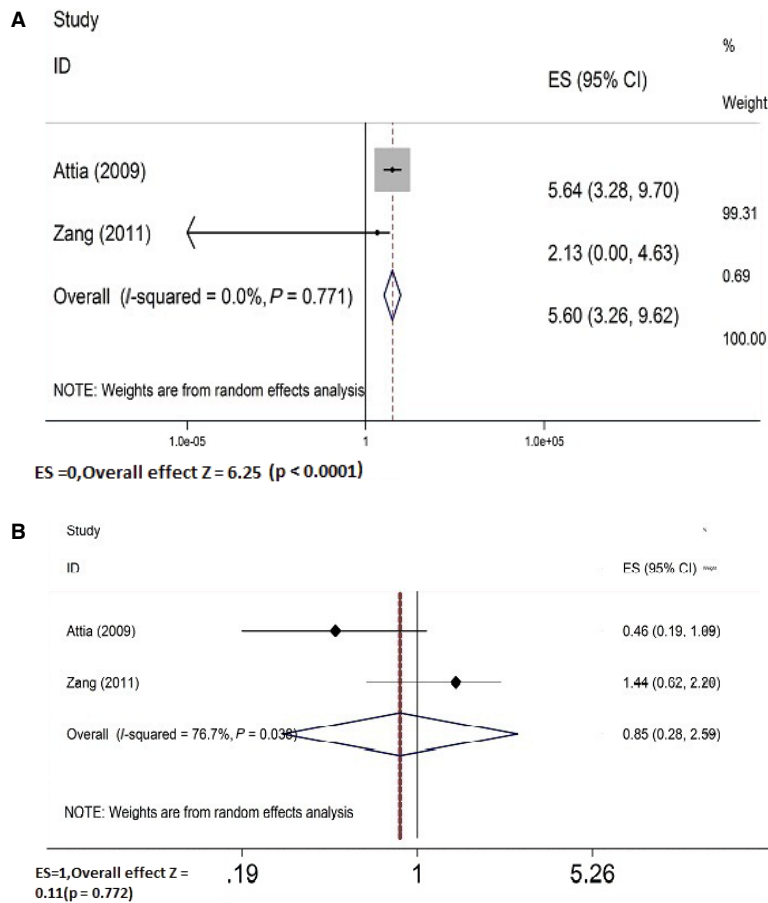


Fig. 3 Forest plot for antiretroviral therapy for studies reporting incidence rates (a, forest plot for ART Untreated patients; b, forest plot for ART Treated patients). CI, confidence interval; ID, identification.

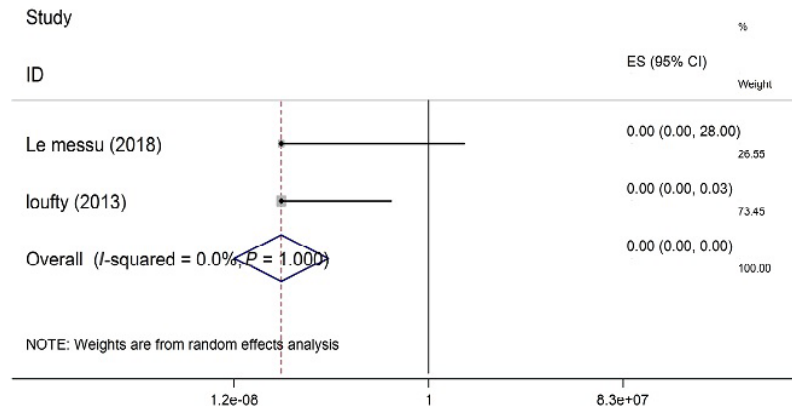


Fig. 4 Forest plot for studies including patients receiving antiretroviral therapy with suppressed viral load (data are reported as incidence rates). CI, confidence interval; ID, identification

Table 3 Overall summary of results

Intervention	Pooled relative risk (95% CI)	Pooled incidence rate (95% CI) (PY)	Incidence of disease in negative partners
ART vs. no ART	0.48 (0.439–0.525) ($Q = 0.524$; $I^2 = 0.0\%$; $P < 0.0001$)		52% reduction*
ART, treated groups		0.85 (0.28–2.99) ($Q = 0.038$; $I^2 = 76.7\%$; $P = 0.772$)	
ART, untreated groups		5.6 (3.26–9.62) ($Q = 0.771$; $I^2 = 0.0\%$; $P < 0.0001$)	84% reduction*
ART + suppressed viral loads		0.00 (0.00–0.00) ($Q = 1.00$; $I^2 = 0.0\%$; $P < 0.0001$)	Minimal incidence of the disease in negative partners

ART, antiretroviral therapy; CI, confidence interval; PY, person-years.

*Indicates percentage reduction in incidence of the disease in negative partners, when the positive partners are treated with ART.

intercourse, which is practised mainly by MSM and which has been found to act as a driving force of infection in HIV epidemics. Regarding early treatment *vs.* delayed treatment, the risk was found to be lower for early treatment than for late treatment and also for ART compared to no ART [12] (Table 2).

Our meta-analysis showed that ART, compared to no ART, was associated with a lower risk of transmission, with a significantly lower relative risk of 0.48 (95% CI 0.439–0.525) ($Q = 0.524$; $I^2 = 0.0\%$; overall effect $Z = 15.99$, $P < 0.0001$) for the cohorts that had effect sizes as relative risks. This shows that there was a 52% reduction in the risk of transmission in groups on ART compared to those not on ART. ART *vs.* no ART was associated with a reduction in the time at risk from 5.6 person-years (95% CI 3.26–9.62 person-years) ($Q = 0.771$; $I^2 = 0.0\%$; overall effect $Z = 6.25$, $P < 0.0001$) in the untreated groups to 0.85 person-years (95% CI 0.28–2.99 person-years) ($Q = 0.038$; $I^2 = 76.7\%$; overall effect $Z = 0.11$, $P = 0.772$) in the treated groups (for the cohorts that had effect sizes as incidence rates). This implies an 84% reduction in the risk of transmission in the treated group, as a result a reduction in the incidence of the disease in negative partners

(Table 3). The treatment group had an overall effect size 0.772 which is not a significant result.

Regarding the effect of the risk of bias on the meta analysis, the only study with a high risk of bias that was included in the meta analysis was the study by Zang *et al.* [18] when it was omitted, in a sensitivity analysis, the effect sizes changed to incidence rates of 0.46 person-years (95% CI 0.19–1.09 person-years) for the treated group and 5.64 person-years (95% CI 3.28–9.70 person-years) for the untreated group. Thus, the reduction in transmission risk for the treated group was even lower in the sensitivity analysis (incidence rate 0.46 person-years in the treated group) than in the original analysis (0.85 person-years).

In accordance with the Swiss National AIDS Commission statement, patients taking ART with suppressed viral loads had a very low risk of transmission [incidence rate 0.00 person-years (95% CI 0.00–0.00); $Q = 1.00$; $I^2 = 0.0\%$; overall effect $Z = 6.8$, $P < 0.0001$].

The strength of this study is that we conducted a systematic review and stratified the results in various ways; for example, by type of sexual intercourse, direction of intercourse, ART plus condom use compared to no ART

or condom use, ART plus consistent condom use compared to inconsistent condom use, early treatment versus delayed treatment, and ART versus no ART. Also, results were obtained in both homosexual and heterosexual populations. The findings, including those of the meta-analysis, will be of value to policy makers in designing, implementing and improving HIV/AIDS prevention strategies and also inform mathematical models [13].

Conclusions

ART and condom use were associated with a significant reduction in the risk of sexual transmission of HIV in both homosexual and heterosexual populations, based on previous systematic reviews. Increased risk reductions could be accomplished by combining ART and effective use of condoms. A lower risk of transmission was associated with vaginal sex compared to anal sex, early ART compared to late ART, and ART compared to no ART.

The information obtained in this study will be of use to policy makers for the development, implementation and improvement of HIV/AIDS prevention strategies.

Limitations

A limitation of this study is that it did not include factors such as the effect of sexually transmitted infections and circumcision.

Acknowledgements

Conflicts of interest: The authors have no conflicts of interest to declare.

Financial disclosure: This study was funded by Tehran University of Medical Sciences.

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Appendix 1

Search strategy

("HIV"[All Fields] OR "human immunodeficiency virus"[All Fields] OR "AIDS"[All Fields] OR "acquired immunodeficiency syndrome"[All Fields]) AND (Couples[title/

abstract] OR (sex*[title/abstract] AND partner*[title/abstract]) OR spouse*[title/abstract] OR dyad*[title/abstract] OR married[title/abstract] OR marital[title/abstract] OR "Marriage"[MeSH] OR "spouses" [MeSH] OR serodiscord*[title/abstract] OR sero-discord* [title/abstract] OR discord*[title/abstract]) AND (transmission[title/abstract] OR infection [title/abstract] OR infectivity[title/abstract] OR infectiousness.