Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples (Review)

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[Intervention Review]

Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples

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ABSTRACT

Background

Antiretroviral drugs have been shown to reduce risk of mother-to-child transmission of human immunodeficiency virus (HIV) and are also widely used for post-exposure prophylaxis for parenteral and sexual exposures. Observational data, ecological studies and models suggest that sexual transmission may be lower in couples in which one partner is infected with HIV and the other is not and the infected partner is on antiretroviral therapy (ART).

Objectives

To determine if ART use in an HIV-infected member of an HIV-discordant couple is associated with lower risk of HIV transmission to the uninfected partner compared to untreated discordant couples.

Search strategy

We used standard Cochrane methods to search electronic databases and conference proceedings with relevant search terms without limits to language.

Selection criteria

Randomised controlled trials, cohort studies and case-control studies of HIV-discordant couples in which the HIV-infected member of the couple was being treated or not treated with ART

Data collection and analysis

Abstracts of all trials identified by electronic or bibliographic scanning were examined independently by two authors. We initially identified 1814 references and examined 23 in detail for study eligibility. Data were abstracted independently using a standardised abstraction form.

Main results

Seven observational studies and no randomised controlled trials were included in the review. These seven studies identified 436 episodes of HIV transmisison, 71 among treated couples and 365 among untreated couples. The summary rate ratio for all seven studies was 0.34 [95% CI 0.13, 0.92], with substantial heterogeneity (I^2=73%). After excluding two studies with inadequate person-time data, we found a summary rate ratio of 0.16 [95% CI 0.07, 0.35] with no noted heterogeneity (I^2=0%). We also performed subgroup analyses to see if the effect of ART on prevention of HIV differed by the index partner's CD4 cell count. Among couples in which the infected partner had >350 CD4 cells/μL, we estimated a rate ratio of 0.02 [95% CI 0.00, 2.87]. In this subgroup, there were 61 transmissions in untreated couples and none in treated couples.

Authors' conclusions

ART appears to be a potent intervention for prevention of HIV in discordant couples. However, the most important question from a clinical standpoint is whether being in a serodiscordant sexual relationship and having >350 CD4 cells/μL should be an indication for ART. In our analysis, there were broad confidence intervals in this subgroup, overlapping the null hypothesis of no effect. There is currently one large randomised controlled trial in the field, whose results are scheduled to be ready in 2015. Significant questions remain about durability of protection, when to start treating an infected partner (for instance, at diagnosis or at a specific CD4 level) and transmission of ART-resistant strains to partners.

PLAIN LANGUAGE SUMMARY

Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples

Antiretroviral drugs may prevent transmission of HIV from an infected sexual partner to an uninfected one by suppressing viral replication. We found seven observational studies that had examined this question. Overall we found that in couples in which the infected partner was being treated with antiretroviral drugs the uninfected partners had more than 5-times lower risk of being infected than in couples where the infected partner was not receiving treatment. Since WHO already recommends antiretroviral treatment for all persons with ≤350 CD4 cells/μL, we also examined studies that had looked at partners with CD4 counts higher than this level. We found that there was inconclusive evidence that in this group HIV was less likely to be transmitted. A large randomised trial is currently being conducted, and a more definitive answer should be available by 2015.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antiretroviral Therapy for HIV Prevention in Serodiscordant Couples (Part A)

Patient or population: patients with HIV Prevention in Serodiscordant Couples (Part A)
Settings: In Serodiscordant Couples
Intervention: Antiretroviral Therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antiretroviral Therapy				
HIV Incidence	**75 per 1000**[1,2]	**25 per 1000** (10 to 69)[1,2]	**Rate Ratio 0.34** (0.13 to 0.92)	6792 (7 studies)	⊕⊕⊕◯ **moderate**[3]	
HIV Incidence (Sensitivity)	**222 per 1000**[1,2]	**38 per 1000** (18 to 82)[1,2]	**Rate Ratio 0.17** (0.08 to 0.37)	2282 (5 studies)	⊕⊕⊕◯ **moderate**[4,5]	
HIV Incidence: CD4 Subgroups (<200 cells/μ)	**158 per 1000**[2,6]	**16 per 1000** (11 to 115)[2,6]	**RR 0.1** (0.07 to 0.73)	504 (4 studies)	⊕⊕◯◯ **low**[5,7,8]	
HIV Incidence: CD4 Subgroups (200-350 CD4 cells/μ)	**35 per 1000**[2,6]	**12 per 1000** (3 to 44)[2,6]	**RR 0.33** (0.09 to 1.27)	1686 (3 studies)	⊕◯◯◯ **very low**[3,8,9]	
HIV Incidence: CD4 Subgroups (350 or more CD4 cells/μ)	**19 per 1000**[2,6]	**0 per 1000** (0 to 55)[2,6]	**RR 0.02** (0 to 2.87)	3431 (2 studies)	⊕⊕◯◯ **low**[5,8,10]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Less than 5% of sample was imputed due to missing information in the denominator.
[2] Numerators and Denominators taken from text where possible. Numbers were not used to calculate the relative effect estimates.
[3] Rate Ratio <0.50
[4] Two studies were removed due to differences in intervention or incomplete data.
[5] RR <0.20
[6] Due to missing information in the denominator and/or numerator, some data were imputed from text.
[7] No person time available for 3 out of 4 studies.
[8] Few events and/or wide confidence interval.
[9] No person time available for 2 out of 3 studies.
[10] No person time available for 1 out of 2 studies.

BACKGROUND

Antiretroviral drugs have been shown to reduce risk of mother-to-child transmission of human immunodeficiency virus (HIV) (Volmink 2007, WHO 2010b), are widely used for post-exposure prophylaxis for parenteral and sexual exposures (Young 2007, Grant 2010), although these indications have not been examined in randomised controlled trials (Young 2007), and have recently been found to be efficacious for acquiring infection (pre-expsoure prophylaxis) (Grant 2010a). Increasing observational data suggest that sexual transmission may be lower in couples in which one partner is infected with HIV and the other is not and the infected partner is on antiretroviral therapy (ART) (Cohen 2007, Attia 2009, Venazza 2008, Cohen 2010, Cohen 2008), and models indicate widespread prevention benefit if large numbers of infected patients in a population are treated (Granich 2009). Ecological studies from Taiwan (Fang 2004), British Columbia (Gill 2010, Montaner 2010, Wood 2009) and San Francisco (Porco 2004, Das 2010) have found that transmission has decreased as the proportion of treated patients increases and community viral load decreases (Das 2010).

In a cohort analysis of couples followed in a trial of sexually transmitted disease control for prevention of HIV in the era before ART was widely available in rural Africa, risk of sexual transmission in discordant couples was lowest in couples in which the infected partner had an HIV serum viral load of <400 copies/mL (Quinn 2000). Similarly, data from trials and cohort studies of mother-to-child transmission of HIV have demonstrated that mothers with the lowest viral loads are the least likely to transmit (Jourdain 2007). While plasma (or serum in the case Quinn 2000), viral loads do not necessarily directly correlate with viral loads in semen or cervico-vaginal secretions and HIV can continue to be shed despite non-detectable plasma viral loads (Sheth 2009), the absence of detectable HIV RNA in plasma roughly corresponds to lower levels of HIV RNA in genital tract secretions (Vettore 2006, Lorella 2009). Moreover, a recently published simulation model aimed to estimate the risk of HIV transmission, in the context of condom use, from homosexual men treated with ART to their partners (Hallett 2011) and found that, even when never using condoms with long-term partners, the predicted risk of transmission to long-term partners was only 22%.

Taken together this body of literature suggests that treating an infected individual with ART may decrease the risk of sexual transmission to his or her uninfected partners. A large randomised controlled trial that can definitively answer this question is currently in the field, but results are not expected until 2015 (Cohen 2010). Specifically, this trial aims to estimate the impact of ART treatment in serodiscordant couples in which the index partner has more than 350 CD4 cells/μL. In this review we examine whether treating an HIV-infected partner with ART is associated with decreased risk of acquiring HIV in an uninfected member of a discordant couple.

Description of the condition

HIV infection is a chronic retroviral infection of humans that is almost universally fatal if left untreated. HIV can be transmitted sexually, parenterally or perinatally; globally sexual transmission accounted for about 70% of the 2.7 million new HIV infections in 2008 (UNAIDS 2009). Data from Africa suggest that more than half of new infections are occurring in stable monogamous couples who are serodiscordant for HIV infection, meaning that one member of the couple is infected and the other is not (Dunkle 2008, Mermin 2008).

Description of the intervention

Use of any antiretroviral drugs alone or in combination in HIV-infected members of discordant couples.

Inclusion criteria:

- Randomised controlled trial, cohort study or case-control study
- Compares HIV-discordant couples in which the HIV-infected member is treated or not treated
- Provides sufficient regimen-specific information about drugs to compare regimens and outcomes of interest

Exclusion criteria:

- Studies in which all HIV-infected members of discordant couples are either all treated or all not treated
- Letter, editorial, non-systematic review, case report, case series, cross-sectional study

How the intervention might work

By suppressing HIV replication systemically and decreasing HIV shedding in the genital tract.

Why it is important to do this review

If there is, indeed, prevention benefit from ART, in addition to its well-established therapeutic efficacy, the weight of evidence may shift to treating infected patients earlier in the course of their infection than is currently recommended (WHO 2010a).

OBJECTIVES

To assess if ART is associated with decreased risk of HIV transmission from an infected sexual partner to an uninfected sexual partner. Additionally, this review aims to assess specifically if ART in a patient with ≥350 CD4 cells/μL is also associated with a lowered risk of HIV transmission.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials, cohort studies and case-control studies that included data and analysis for the comparison of interest.

Types of participants

HIV-discordant couples that is, sexual partnerships in which one member is infected with HIV and the other uninfected. Both heterosexual and homosexual couples are eligible.

Types of interventions

Use of any antiretroviral drugs alone or in combination in HIV-infected members of discordant couples. Variations of interest included patients receiving HIV monotherapy, those receiving dual therapy and those receiving the current standard of three or more antiretroviral drugs (Jourdain 2007).

Types of outcome measures

Primary outcomes

- Incident HIV Infection

Secondary outcomes

- Acquisition of primary drug-resistant HIV. This is defined as an incident infection with an HIV strain resistant to one or more standard antiretroviral drugs.

Search methods for identification of studies

See search methods used in reviews by the Cochrane Collaborative Review Group on HIV Infection and AIDS.

Electronic searches

We formulated a comprehensive and exhaustive search strategy in an attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press and in progress). Full details of the Cochrane HIV/AIDS Review Group methods and the journals hand-searched are published in the section on Collaborative Review Groups in The Cochrane Library.

Journal and trials databases

We searched the following electronic databases, in the period from 01 January 1987 to 01 February 2011:

- PubMed
- EMBASE
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Web of Science
- LILACS

Along with MeSH terms and relevant keywords, we used the Cochrane Highly Sensitive Search Strategy for identifying reports of randomised controlled trials in MEDLINE (Higgins 2008), and the Cochrane HIV/AIDS Group's existing strategies for identifying references relevant to HIV/AIDS. The search strategy was iterative, in that references of included studies were searched for additional references. All languages were included. See Appendix 1 for example of our PubMed search strategy, which was modified as appropriate for use in the other databases.

Using a variety of relevant terms, we also searched the clinical trials registry at the US National Institutes of Health's ClinicalTrials.gov (www.clinicaltrials.gov). One ongoing study was identified that potentially met our inclusion criteria. This study was ultimately not included in the review.

Limits. The searches were performed without limits to language or setting and limited to human studies published from 1987 (start of the antiretroviral era) to the present.

Searching other resources

Conference abstract databases

We searched the Aegis archive of HIV/AIDS conference abstracts (www.aegis.org), which includes the following conferences:

- British HIV/AIDS Association, 2001-2008
- Conference on Retroviruses and Opportunistic Infections (CROI), 1994-2008
- European AIDS Society Conference, 2001 and 2003
- International AIDS Society, Conference on HIV Pathogenesis, Treatment and Prevention (IAS), 2001-2005
- International AIDS Society, International AIDS Conference (IAC), 1985-2004
- US National HIV Prevention Conference, 1999, 2003, and 2005

We also searched the CROI and International AIDS Society web sites for abstracts presented at conferences subsequent to those listed above (CROI, 2009-2010; IAC, 2006-2010; IAS, 2007-2009).

Using different combinations of relevant search terms, such as -antiretroviral, -couples, -discordant, -partners, -sero-discordant, -serodiscordant, -viral load, and other terms in combination, 188 conference abstracts were initially identified. 172 irrelevant abstracts were excluded in the first screening. None were ultimately included in the review. One was included as an ongoing study.

Researchers and relevant organizations. We contacted individual researchers working in the field, such as the AIDS Clinical Trials Group, and policymakers based in inter-governmental organizations including the Joint United Nations Programme on HIV/AIDS (UNAIDS) and WHO to identify studies either completed or ongoing.

Reference lists. We checked the reference lists of all studies identified by the above methods and examined the bibliographies of any systematic reviews, meta-analyses, or current guidelines we identified during the search process.

Data collection and analysis

The methodology for data collection and analysis was based on the guidance of Cochrane Handbook of Systematic Reviews of Interventions (Higgins 2008). Abstracts of all trials identified by electronic or bibliographic scanning were examined by two authors (AA and GWR) working independently. Where necessary, the full text was obtained to determine the eligibility of studies for inclusion.

Selection of studies

After removing duplicate references, a Cochrane research specialist made the first broad cut of these results, excluding those that were clearly irrelevant (e.g. animal studies, editorials, pediatric studies, studies without HIV endpoints).

Two authors (AA and GWR) then independently selected potentially relevant studies by scanning the titles, abstracts, and descriptor terms of the remaining references and applied the inclusion criteria. Irrelevant reports were discarded, and the full article or abstract was obtained for all potentially relevant or uncertain reports. The two authors independently applied the inclusion criteria. Studies were reviewed for relevance, based on study design, types of participants, exposures and outcomes measures. A neutral third party was available to adjudicate any disagreements that could not have been resolved by discussion.

Data extraction and management

After initial search and article screening, two reviewers independently double-coded and entered information from each selected study onto standardised data extraction forms. Extracted information included:

- **Study details***:* citation, start and end dates, location, study design and details.

- **Participant details***:* study population eligibility (inclusion and exclusion) criteria, ages, population size, attrition rate, details of HIV diagnosis and disease and any clinical, immunologic or virologic staging or laboratory information on the infected partner.

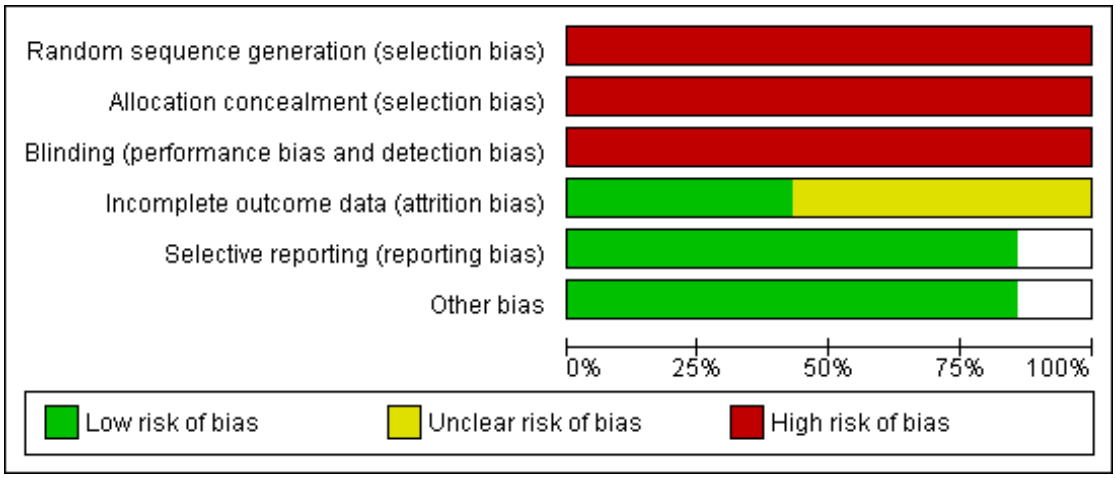
- **Interventions details:** Drug names, doses, duration and any other information on adherence or resistance.

- **Outcome details:** Incident HIV infection in the uninfected partner, acquisition of a drug-resistant strain of HIV

Assessment of risk of bias in included studies

We used the Cochrane Collaboration tool for assessing the risk of bias for each individual study and present results in a summary table (Figure 1). For trials, the Cochrane tool assesses risk of bias in individual studies across six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential biases.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Sequence generation

- Adequate: investigators described a random component in the sequence generation process, such as the use of random number table, coin tossing, card or envelope shuffling, etc.
- Inadequate: investigators described a non-random component in the sequence generation process, such as the use of odd or even date of birth, algorithm based on the day or date of birth, hospital, or clinic record number.
- Unclear: insufficient information to permit judgement of the sequence generation process.

Allocation concealment

- Adequate: participants and the investigators enrolling participants cannot foresee assignment (e.g., central allocation; or sequentially numbered, opaque, sealed envelopes).
- Inadequate: participants and investigators enrolling participants can foresee upcoming assignment (e.g., an open random allocation schedule, a list of random numbers); or envelopes were unsealed or non-opaque or not sequentially numbered.
- Unclear: insufficient information to permit judgement of the allocation concealment or the method not described.

Blinding

- Adequate: blinding of the participants, key study personnel, and outcome assessor, and unlikely that the blinding could have been broken. No blinding in the situation where non-blinding is not likely to introduce bias.
- Inadequate: no blinding or incomplete blinding when the outcome is likely to be influenced by lack of blinding.
- Unclear: insufficient information to permit judgement of adequacy or otherwise of the blinding.

Incomplete outcome data

- Adequate: no missing outcome data, reasons for missing outcome data unlikely to be related to true outcome, or missing outcome data balanced in number across groups.
- Inadequate: reason for missing outcome data likely to be related to true outcome, with either imbalance in number across groups or reasons for missing data.
- Unclear: insufficient reporting of attrition or exclusions.

Selective reporting

- Adequate: a protocol is available which clearly states the primary outcome as the same as in the final trial report.
- Inadequate: the primary outcome differs between the protocol and final trial report.
- Unclear: no trial protocol is available or there is insufficient reporting to determine if selective reporting is present.

Other forms of bias

- Adequate: there is no evidence of bias from other sources.
- Inadequate: there is potential bias present from other sources (e.g., early stopping of trial, fraudulent activity, extreme baseline imbalance, or bias related to specific study design).
- Unclear: insufficient information to permit judgement of adequacy or otherwise of other forms of bias.

The Newcastle-Ottawa Scale (Newcastle-Ottawa) was used to assess the quality and risk of bias in non-randomised studies. Specifically, the scale uses a star system to judge three general areas: selection of study groups, comparability of groups, and ascertainment of outcomes (in the case of cohort studies). As a result, this instrument can assess the quality of non-randomised studies so that they can be used in a meta-analysis or systematic review. Please see Figure 2 and Appendix 2 for details.

Figure 2. Newcastle-Ottawa Scale for Bias Assessment

Summary of critical appraisal of included studies using the Newcastle-Ottawa Quality Assessment Scale for cohort studies

Study ID	Selection (max 4 stars)	Comparability (max 2 stars)	Outcome (max 3 stars)
Del Romero et al (2010)	****	--	***
Donnell et al (2010)	****	*	***
Wang et al (2010)	****	--	**
Reynolds et al (2011)	****	*	**
Sullivan et al (2009)	****	*	**
Melo et al (2008)	****	--	***
Musicco et al (1994)	****	*	***

Selection
1) Representativeness of intervention cohort—a] Truly representative of average, treated serodiscordant couple*; b] somewhat representative of average, treated, serodiscordant couple*; c] only selected group of patients; no description of derivation of cohort
2) Selection of non intervention cohort—a] drawn from same community as intervention cohort*; b] drawn from different source; c] no description of the derivation of the non intervention cohort
3) Ascertainment of intervention—a] health record*; b] structured interview*; c] written self-report; d] no description
4) Demonstration that outcome was not present at start of study—a] yes*; b] no
Comparability
1) Comparability of cohorts on basis of design or analysis—a] study controls for age, sex, or frequency of sex*; b] study controls for any additional factors*
Outcome
1) Assessment of outcome—a] independent blind assessment*; b] record linkage*; c] self report; d] no description
2) Was follow up long enough for outcomes to occur—a] yes (median duration of follow up >6 months)*; b] no
3) Adequacy of follow up of cohort—a] complete follow up*; b] minimal loss to follow up (<=20%); c] follow up rate < 80% and no description of losses to follow up; d] no statement

Assessment of Quality of Evidence Across Studies

We assessed the quality of evidence across a body of evidence (i.e., multiple studies with similar interventions and outcomes) with the GRADE approach (Guyatt 2008), defining the quality of evidence for each outcome as "the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest" (Higgins 2008). The quality rating across studies has four levels: high, moderate, low or very low. Randomised controlled trials are categorised as high quality but can be downgraded; similarly, other types of controlled trials and observational studies are categorised as low quality but can be upgraded. Factors that decrease the quality of evidence include limitations in design, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results or high probability of publication bias. Factors that can increase the quality level of a body of evidence include a large magnitude of effect, if all plausible confounding would lead to an underestimation of effect and if there is a dose-response gradient.

See Summary of findings for the main comparison and Summary of findings 2. GRADE evidence profiles for these comparisons are also available and can be found on the following Cochrane HIV/AIDS Group web site: www.igh.org/Cochrane/GRADE/ART-serodiscordant

Measures of treatment effect

We used Review Manager 5 provided by the Cochrane Collaboration for statistical analysis and GRADEpro software (GRADEpro 2008) to produce GRADE Summary of Findings tables and GRADE evidence profiles.

We summarised dichotomous outcomes for effect in terms of risk ratio (RR), rate ratio and number needed to treat (NNT) with their 95% confidence intervals. Tests for interaction (i.e. Ratio of Risk Ratios, RRR) were performed to compare estimates within subgroups using methods described in Altman et al (Altman 2003).

We summarised rate data in terms of rate ratios with their 95% confidence intervals. Standard errors for each estimate were estimated using methods described in Rothman et al (Rothman 1998).

We calculated summary statistics using meta-analytic methods and present findings in GRADE Summary of Findings tables and GRADE Evidence Profiles for all outcomes of interest.

Unit of analysis issues

The unit of analysis was the individual partner in the discordant couple who was uninfected at baseline in each study.

Dealing with missing data

Study authors were contacted when missing data were an issue.

Assessment of heterogeneity

We examined heterogeneity among all studies using the χ^2 statistic with a significance level of 0.10, and the I^2 statistic. We interpreted an I^2 estimate greater than 50% as indicating moderate or high levels of heterogeneity and investigated its causes by sensitivity analysis. If heterogeneity persisted, we presented results separately and reported reasons for the observed heterogeneity.

Assessment of reporting biases

We assessed the potential for publication bias using funnel plots. We attempted to minimise the potential for publication bias by our comprehensive search strategy that included evaluating published and unpublished literature.

Data synthesis

When interventions and study populations were sufficiently similar across different studies, we pooled the data across studies and estimated summary effect sizes using both fixed- and random-effects models. Specifically, we estimated the log(rate ratio) for each included study and used the inverse variance method to calculate study weights. The inverse variance method assumes that the variance for each study is inversely proportional to its importance, therefore more weight is given to studies with less variance than studies with greater variance.

We summarised the quality of evidence for each outcome for which data are available in GRADE Summary of Findings tables and GRADE evidence profiles (Guyatt 2008).

Subgroup analysis and investigation of heterogeneity

We performed sub-group analysis by baseline CD4 counts in index partners and by gender of index partners. Heterogeneity was explored using further sub-group analyses by setting (middle- or low- versus high-income country). A test for interaction was performed for each subgroup comparison.

Sensitivity analysis

If pooled results were heterogeneous, we conducted sensitivity analyses to identify studies with outlying results for further examination.

RESULTS

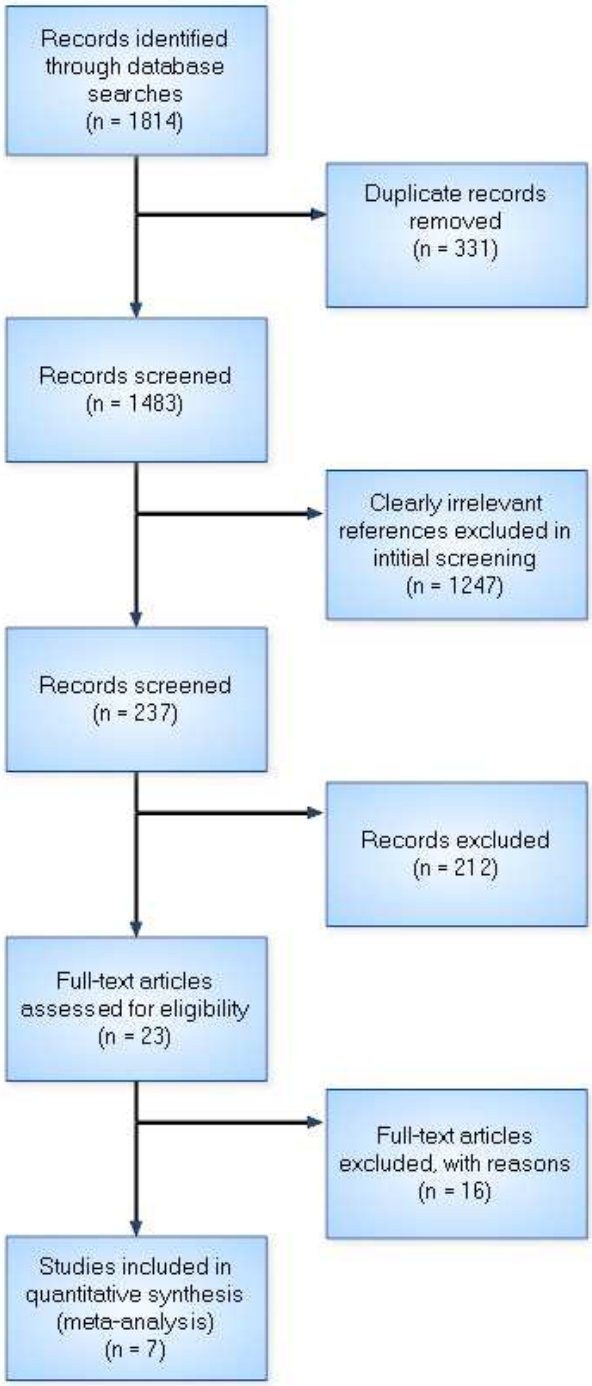
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

Searches were conducted on February 1, 2011, and produced 1483 titles after 331 duplicates were removed (Figure 3). After initial screening of titles by a Cochrane research specialist, 237 titles and abstracts were selected for further review by two authors (AA and GWR). AA and GWR independently conducted the selection of potentially relevant studies by scanning the titles, abstracts, and descriptor terms of all downloaded material from the electronic searches. Irrelevant reports were discarded, and the full article was obtained for all potentially relevant or uncertain reports. AA and GWR independently applied the inclusion criteria. NS acted as arbiter where there was disagreement. Studies were reviewed for relevance, based on study design, types of participants, exposures and outcomes measures. Finally, where resolution was not possible because further information was required, the study was allocated to the list of those awaiting assessment. Attempts to contact authors to provide further clarification of data are ongoing.

Figure 3. Flow-chart of screening process



Twenty-three full-text articles were closely examined by two authors (AA and GWR). Seven cohort studies were identified as meeting inclusion criteria for data extraction, coding, and potential meta-analysis. No randomised trials were identified.

Included studies

The seven included cohort studies were conducted in Italy (Musicco 1994), Brazil (Melo 2008), Zambia and Rwanda (Sullivan 2009), Uganda (Reynolds 2011), Spain (Del Romero 2010), China (Wang 2010), and the following African countries: Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia (Donnell 2010). Two studies appeared both in abstract and print form (Donnell 2010, Del Romero 2010). Five of the seven studies were of partners of persons infected heterosexually (Musicco 1994, Sullivan 2009, Reynolds 2011, Donnell 2010, Wang 2010), and two were predominantly of heterosexual partners of injection drug users (Del Romero 2010, Melo 2008). In 6 studies (Melo 2008, Sullivan 2009, Reynolds 2011, Del Romero 2010, Wang 2010, Donnell 2010) infected partners received three or more antiretroviral drugs, and in one early study they received zidovudine (AZT) monotherapy only (Musicco 1994).

Musicco 1994: Musicco and colleagues conducted a cohort study in Italy, which was published in 1994 in the era before the advent of combination ART. They followed a cohort of 436 monogamous HIV-uninfected female sexual partners of HIV-infected men recruited from 16 centres in Italy. Seventy-nine percent of the male index patients had histories of injection drug use, 25% had symptoms of AIDS, and 48% had fewer than 400 CD4 cells/µL. There were 27 seroconversions observed, 21 in partners of men who were not receiving AZT monotherapy and 6 in partners of men who were. Incidence in the untreated group was 4.4 per 100 person years (95% confidence interval [CI] 2.6-5.7) and 3.8 (95% CI 1.4-8.3) in the treated group (unadjusted rate ratio 0.88, 95% CI 0.36-2.16). However, when adjusted for consistent condom use, presence of p24 antigen in infected male partners, infected male partners' CD4 counts and symptoms of AIDS in infected male partners, the relative risk of female partners of men treated with AZT acquiring HIV was 50% lower (RR 0.5, 95% CI 0.1-0.9) when compared to female partners of men not treated with AZT.

Del Romero 2010: Del Romero and colleagues analysed data from 648 heterosexual couples attending a clinic in Madrid, Spain, from 1989 to 2008, where uninfected partners were examined for prevalent HIV infection. Five hundred thirty-five (83%) of the index cases were male and 113 (17%) female. Of the 648 index cases, 494 (76%) had histories of injection drug use. Median CD4 count was 500 cells/µL. Clinical AIDS had been diagnosed at baseline in 107 (17%) of index cases. Forty-six partners were found to have prevalent HIV infection when examined prior to follow-up. Forty-four of these occurred in partners of index cases who had received no ART, and 2 were in partners of index cases who had received either monotherapy or dual therapy. Four hundred twenty-four serodiscordant couples had follow-up information collected over 1355 couple years. Five transmission events occurred in untreated couples over 863 couple years, and no transmissions occurred among treated couples over 492 couple years (rate ratio= 0.21; 95% CI 0.01, 3.75). Earlier studies also analysed this cohort (Castilla 2005).

Melo 2008: Melo and colleagues followed a cohort of 93 discordant couples in Porto Alegre, Brazil, in which the female member of the couple was infected in 67 (72%) and the male in 26 (28%). Fifteen (58%) of the 26 male and 6 (9%) of the female index cases had histories of injection drug use. Of the 26 male index cases, 5 (19%) had CD4 counts <350 cells/µL; of the 67 female index cases, 3 (5%) had <350 CD4 cells/µL, and 33 (49%) were pregnant at baseline. Comparing treated to untreated serodiscordant couples, their results suggest a protective effect of ART (rate ratio= 0.10; 95% CI 0.01-1.67).

Reynolds 2011: Reynolds and colleagues reported data from a cohort of 250 HIV-discordant couples from Rakai, Uganda. They observed 42 seroconversions over 459 person-years of exposure to index patients not on ART (incidence 9.2 per 100 person-years, 95% CI 6.6-12.4) and none over 53.6 person-years on ART (rate ratio=0.10; 95% CI 0.01-1.64).

Sullivan 2009: Sullivan and colleagues presented data from two cohorts of 2,993 HIV-discordant couples in Rwanda and Zambia followed from 2002 to 2008. No additional background data on cohort members were available from the conference abstract. They observed 175 new infections of which 4 were from partners of index cases on ART. Incidence density was 3.4% per 100 person-years for those whose partners were not taking ART and 0.7% for those whose partners were taking ART (rate ratio = 0.21, 95% CI 0.08-0.59). An earlier abstract also reported on this cohort (Kayitenkore 2006).

Donnell 2010: Donnell and colleagues reported data in an abstract from a prospective cohort analysis of a randomised controlled trial of heterosexual African adults who were seropositive for both HIV and herpes simplex virus type 2 (HSV-2) and their HIV-uninfected sexual partners. Three thousand four hundred eight couples were enrolled from seven countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda and Zambia). Of the 3,381 infected index cases, 2,284 (68%) were female and 1,097 (32%) were male. The median CD4 count of index patients was 462 cells/µL, the median plasma viral load was 4.1 $\log_{10}$ copies/mL, and 34% of infected male partners and 55% of uninfected male partners were circumcised. One hundred three genetically linked new infections were identified in partners; one was in the partner of a treated index case. The incidence in partners of untreated index cases was 2.24 (1.84-2.72) per 100 person-years as compared

to 0.37 (95% CI 0.09-2.04) per 100 person-years in partners of treated index cases (adjusted incidence rate ratio 0.08, 95% CI 0.00-0.57). This population was previously analysed in another abstract (Donnell 2009).

Wang 2010: Wang and colleagues analysed data from a prospective cohort study that enrolled 1927 heterosexual couples between January 2006 and December 2008 for testing and treatment at county hospitals in China. Serodiscordant couples were identified through an HIV database and enrolled at local hospitals and health centres. The couples received HIV testing every 6 months and in the event of transmission to an uninfected partner, a recent history of sexual behaviours was taken from the participants. Of the 1927 couples, there were 1092 (57%) HIV-infected male partners and 835 (43%) HIV-infected female partners. The last recorded CD4 count was <200 cells/μL for 422 index spouses (23%), and ≥350 cells/μ for 675 (35%) index partners. Approximately 80% of the studied couples were treated with antiretroviral therapy. Eighty-four (4%) partners seroconverted by the end of follow up, yielding an overall rate of 1.71 per 100 person-years. There was no relationship between the rate of seroconversion and last CD4 count in the index spouse. There was also no effect of ART on preventing HIV transmission in this study as 4.8% of treated couples and 3.2% of untreated couples seroconverted (yielding a non-significant rate ratio=1.44; 95% CI 0.85-2.44).

Excluded studies

We excluded data from 13 couples transmission studies in which ART was not given (Brill 2003, Baeten 2010, Fideli 2001, Peters 2008, Peterson 2007, Wawer 2005, Quinn 2000, Mehendale 2004, Operskalski 1997, Ragni 1998, Tovanabutra 2002, Gray 2001, Kayitenkore 2006) and 3 couples transmission studies in which all index cases received ART (Barreiro 2006, Bunnell 2006, Bunnell 2008). See Excluded studies for details.

Risk of bias in included studies

The Newcastle-Ottawa Scale for bias assessment within observational studies was applied to all included studies (Newcastle-Ottawa). The risk of bias for the included studies was assessed on the data and outcomes published within the manuscripts. Please see Figure 2 and Figure 1 for assessment results from the Newcastle-Ottawa Scale and Cochrane risk of bias assessments. All studies had cohorts that were representative of average, treated and untreated, serodiscordant couples. Only three out of the seven included studies that estimated the effect of ART after adjusting for either age, sex, or frequency of sex among serodiscordant couples. Four out of seven studies explicitly described complete follow up of the study participants and/or described the characteristics of the participants lost to follow up.

Allocation

Only non-randomised studies were found to be eligible for this review.

Blinding

Only non-randomised studies were found to be eligible for this review.

Incomplete outcome data

Three of seven included studies discussed either complete follow up of subjects or characteristics of those lost to follow up.

Selective reporting

We assessed publication bias with funnel plots. When considering all studies, publication bias seems to be possible (Figure 4), though upon removing one study (Wang 2010) with insufficient person time data, we found that the suspected publication bias seen in the funnel plot was likely a result of methodological heterogeneity between studies (Figure 5).

Figure 4. Funnel plot of comparison: 1 Treated with ART vs Not Treated with ART (IR), outcome: 1.1 Incident HIV Infection.

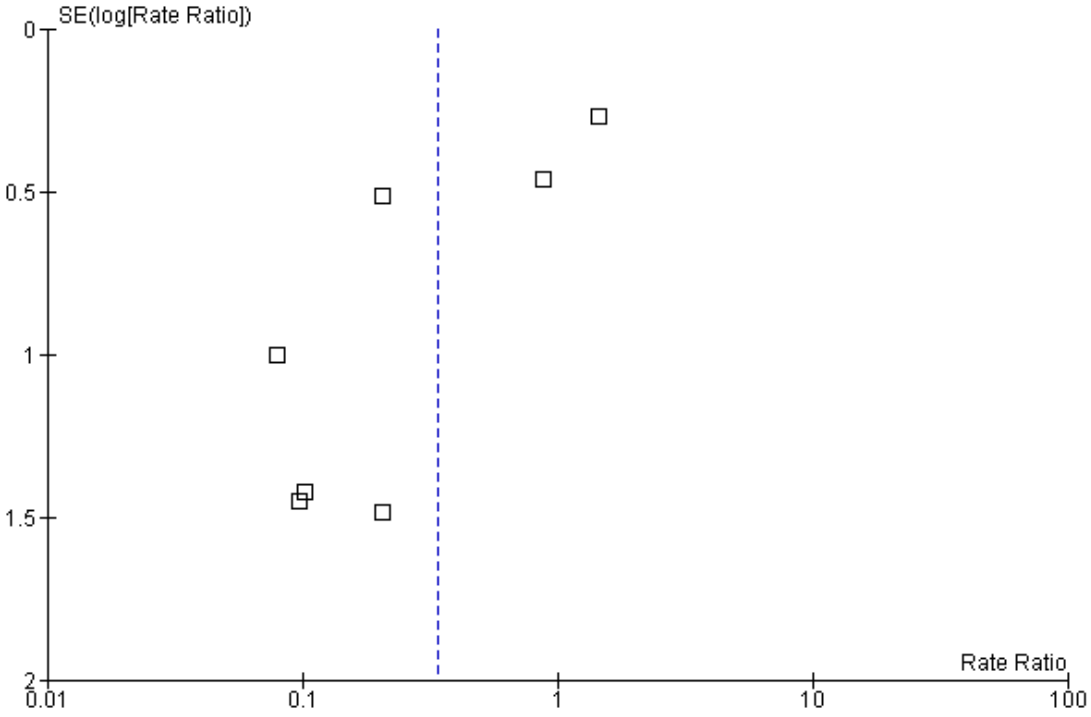
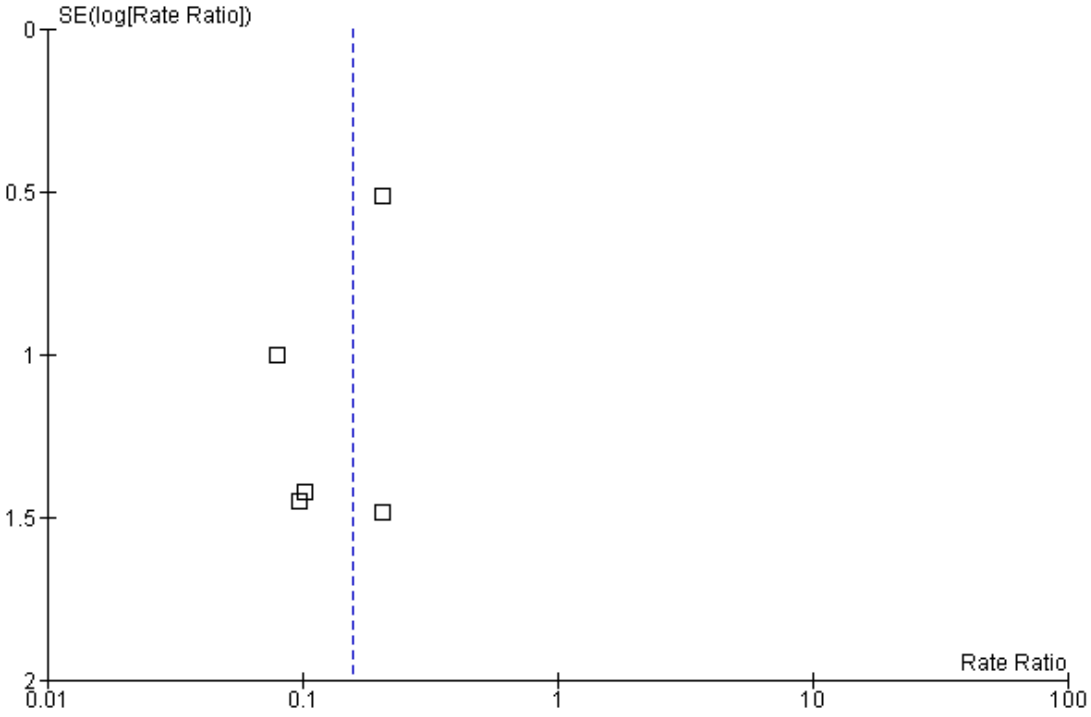


Figure 5. Funnel plot of comparison: 2 Treated with ART vs Not Treated with ART (IR, sensitivity), outcome: 2.1 Incident HIV Infection.



Other potential sources of bias

None detected.

Effects of interventions

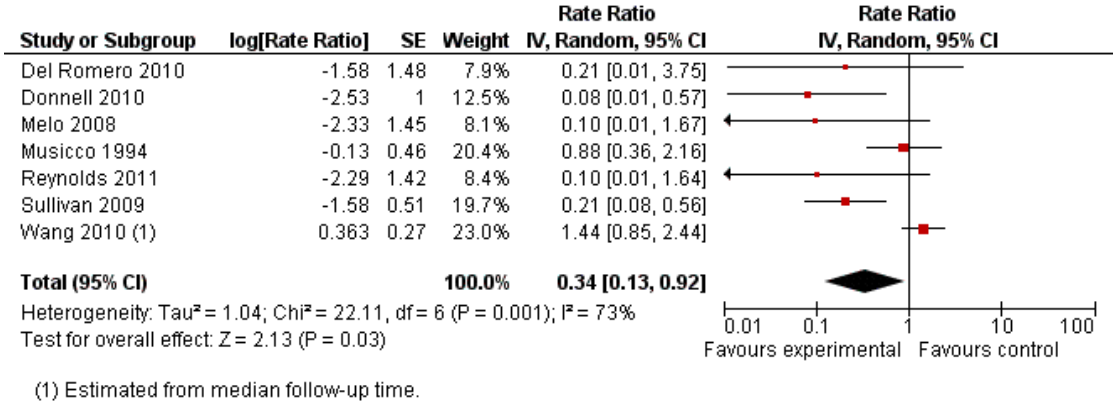
See: **Summary of findings for the main comparison** Antiretroviral Therapy for HIV Prevention in Serodiscordant Couples (Part A); **Summary of findings 2** Antiretroviral Therapy for HIV Prevention in Serodiscordant Couples (Part B)

In six of seven of the cohort studies we analysed, ART was associated with a decreased risk of transmission from infected index cases to uninfected partners, ranging from rate ratios of 0.08 to 0.88. The only cohort study that we identified that did not find this decreased, unadjusted risk was Wang 2010, which did not provide person time data needed to calculate a rate ratio. Using the median person time for both treated and untreated groups in Wang 2010, the rate ratio comparing treated couples with untreated couples was RR=1.44 [0.85, 2.44].

Meta-analysis

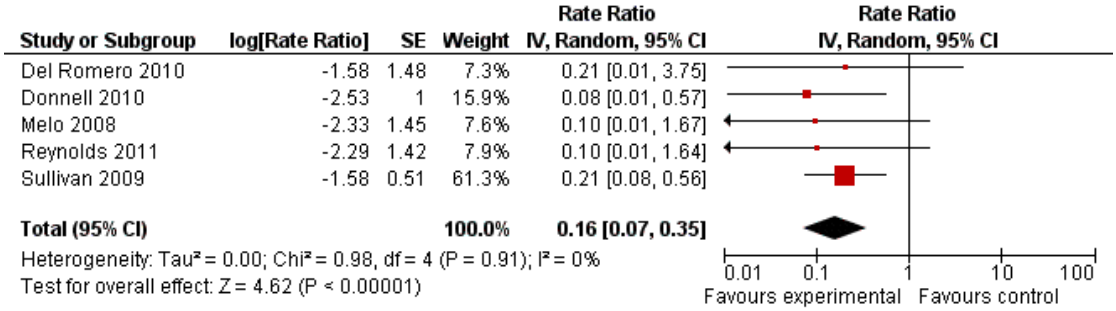
We performed a meta-analysis of the seven identified studies to estimate the effect of ART on HIV incidence reduction for partners of infected spouses. The summary rate ratio for all seven studies was 0.34 [95% CI 0.13, 0.92], with substantial heterogeneity (I^2= 73%) (see Figure 6). The total number of HIV transmissions from all seven studies was N=436, with 71 among treated couples and 365 among untreated couples. To explore the potential influence of the study without adequate person time data (Wang 2010) or monotherapy (Musicco 1994), we performed a sensitivity analysis removing the results of these studies. The meta-analysis of the remaining five studies yielded a rate ratio of 0.16 [95% CI 0.07, 0.35] with no noted heterogeneity (I^2=0%) (see Figure 7). Furthermore, we analysed the remaining five studies with a fixed-effects model to see if there was any consistency between the two approaches. The fixed-effects model yielded a similar rate ratio and confidence interval.

Figure 6. Forest plot of comparison: 1 Treated with ART vs Not Treated with ART (IR), outcome: 1.1 Incident HIV Infection.



(1) Estimated from median follow-up time.

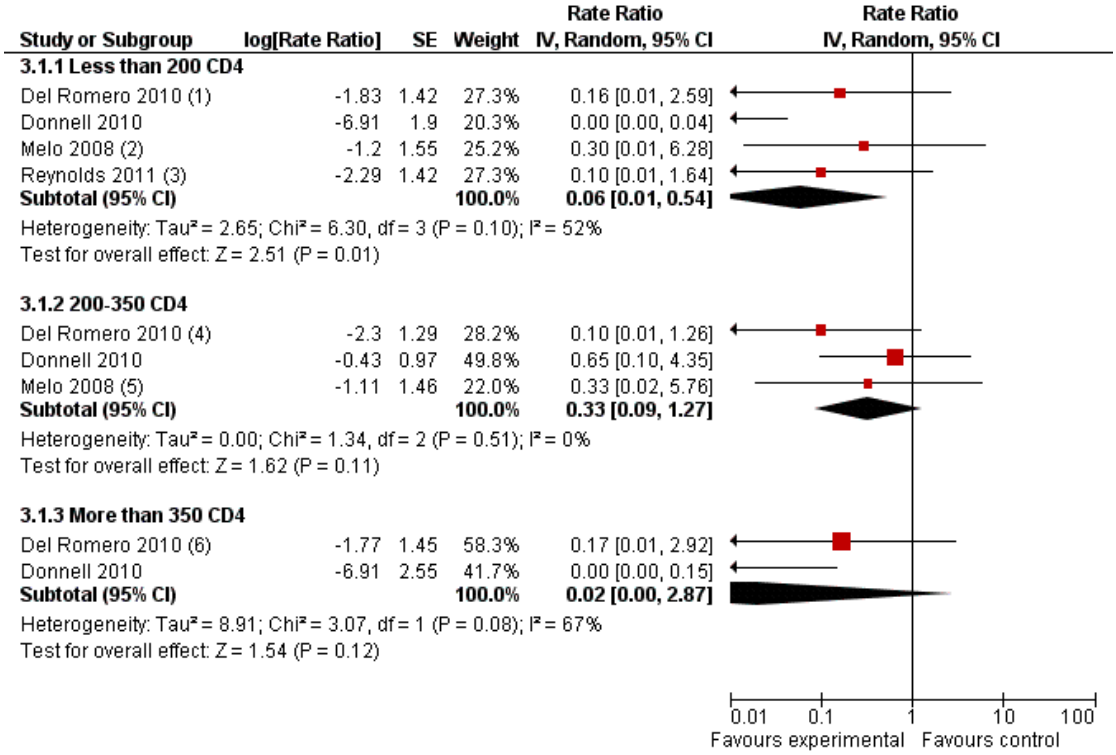
Figure 7. Forest plot of comparison: 2 Treated with ART vs Not Treated with ART (IR, sensitivity), outcome: 2.1 Incident HIV Infection.



We also performed subgroup analyses to see if the effect of ART on prevention of HIV differed by the level of CD4 in the index partner(see Figure 8). Specifically, we categorised CD4 into three groups-- <200 cells/μ, 200-349 cells/μL, and ≥350 cells/μL. Four studies had data available for subjects whose CD4 was less than 200 cells/μL (Donnell 2010, Del Romero 2010, Melo 2008, Reynolds 2011), three studies had data for subjects whose CD4 was 200-349 cells/μL (Donnell 2010, Del Romero 2010, and Melo 2008), and only two studies had data for subjects whose CD4 was ≥350 cells/μ (Donnell 2010 and Del Romero 2010). The subgroup analysis of studies with patients with <200 cells/μL yielded a rate ratio of 0.06 [95% CI 0.01, 0.54] with substantial heterogeneity (I^2= 52%). The total number of HIV transmissions in this subgroup was 62; all were among untreated couples. The subgroup analysis of studies with patients with 200-349 cells/μL yielded a rate ratio of 0.33 [95% CI 0.09, 1.27] with no heterogeneity (I^2=0%). The total number of HIV transmissions in this subgroup was 55, with all but one case among untreated couples. Finally, a rate ratio of 0.02 [95% CI 0.00, 2.87] was estimated from the subgroup analysis of studies with patients with ≥350 cells/μL. Among this subgroup, the total number of HIV transmissions was 61, with all cases among untreated couples. Tests for interaction between the CD4 subgroups were performed and yielded no statistically significant difference between groups. Specifically, the test for interaction between the <200 cells/μL group and the group with 200-349 cells/μL was RRR=0.18 (95% CI 0.02-1.35). Further, when comparing the <200 cells/μL group with the ≥350 cells/μ group, the test for interaction was RRR=3.00 (95% CI 0.06-142.59). Finally, a test for interaction between the group with 200-349 cells/

µL and the ≥350 cells/µ group yielded a RRR=0.06 (95% CI 0.00-1.63).

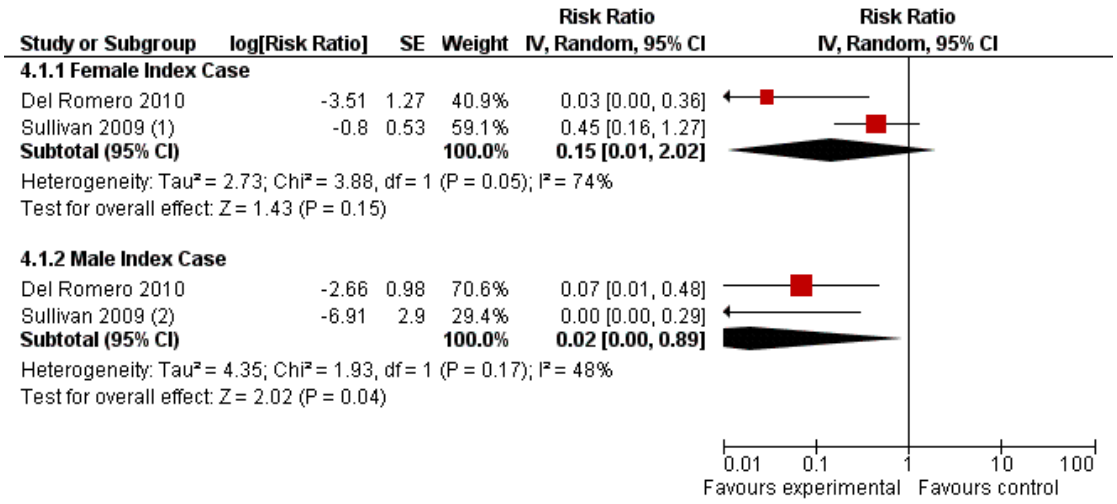
Figure 8. Forest plot of comparison: 3 Treated with ART vs Not Treated with ART (< 200, 200-350, and > 350 CD4 Subgroup Analysis), outcome: 3.1 Incident HIV Infection.



(1) Risk ratio.
(2) 0/8 treated subjects whose CD4 < 350. Risk Ratio.
(3) All subjects < 250 CD4.
(4) Risk ratio.
(5) 0/8 treated subjects whose CD4 < 350. Risk Ratio.
(6) Risk ratio.

Additionally, we performed a subgroup analysis of the effect of ART on HIV prevention by the gender of the index case (see Figure 9). Only two studies provided enough data to analyse this subgroup (Del Romero 2010 and Sullivan 2009). A summary estimate of the effect of ART on incident HIV among female index cases showed a non-significant trend toward a reduction of risk when compared to untreated female index cases (relative risk=0.15; 95% 0.01-2.12). Similarly, if a treated man was the index case, the risk of transmission was significantly lower when compared to untreated index male cases (relative risk=0.02; 95% CI 0.00-0.89). Tests for interaction showed no statistically significant difference between index case subgroups (RRR=7.46, 95% CI 0.17-327.01).

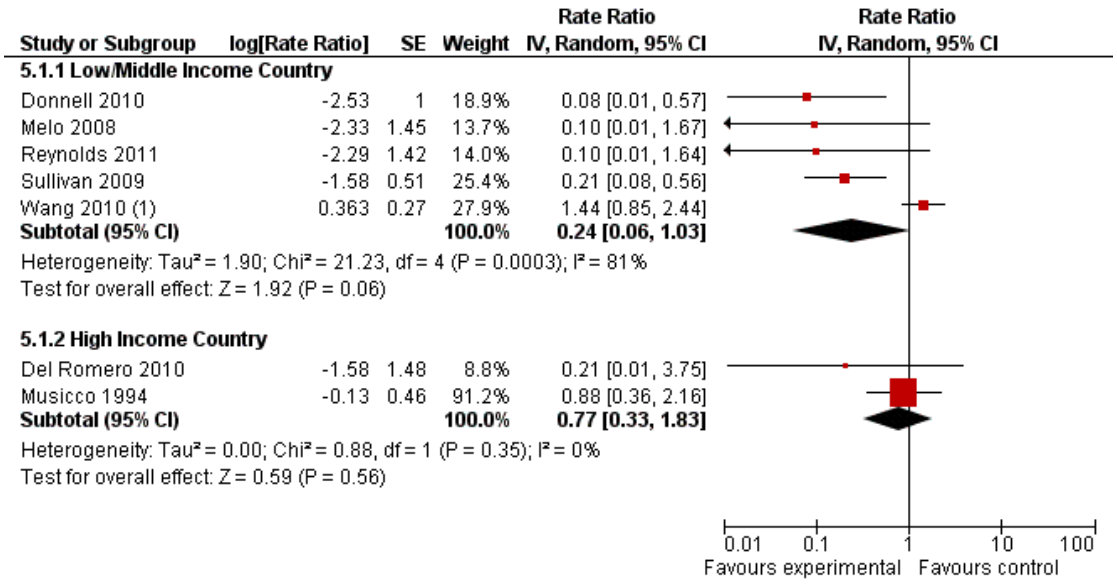
Figure 9. Forest plot of comparison: 4 Treated with ART vs Not Treated with ART (Female/Male Subgroup Analysis), outcome: 4.1 Incident HIV Infection.



(1) Estimate is a rate ratio.
(2) Estimate is a rate ratio.

We also performed a subgroup analysis of the effect of ART on HIV prevention by income level of the country (see Figure 10). Specifically, the effect of ART on HIV prevention in low- and middle-income countries was estimated at RR=0.24 [95% CI 0.06, 1.03], with significant heterogeneity (I^2=81%). The effect of ART on HIV prevention in high-income countries was estimated at RR=0.77 [95% CI 0.33, 1.83], with low heterogeneity (I^2=0%). Again, tests for interaction yielded no statistically significant difference between subgroups of income level (RRR=0.31, 95% CI 0.06-1.62).

Figure 10. Forest plot of comparison: 5 Treated with ART vs Not Treated with ART (Subgroup Analysis: LMIC), outcome: 5.1 Incident HIV Infection.



(1) Estimated from median follow-up time.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Antiretroviral Therapy for HIV Prevention in Serodiscordant Couples (Part B)

Patient or population: patients with HIV Prevention in Serodiscordant Couples (Part B)
Settings: In Serodiscordant Couples
Intervention: Antiretroviral Therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antiretroviral Therapy				
HIV Incidence: Gender Subgroup (Female Cases)	**275 per 1000**[1,2]	**41 per 1000** (3 to 555)[2]	**RR 0.15** (0.01 to 2.02)	704 (2 studies)	⊕⊕◯◯ **low**[3,4]	
HIV Incidence: Gender Subgroup (Male Cases)	**159 per 1000**[1,2]	**3 per 1000** (0 to 142)[1,2]	**RR 0.02** (0 to 0.89)	1115 (2 studies)	⊕⊕◯◯ **low**[3,4]	
HIV Incidence: Low-/Middle-Income Countries	**83 per 1000**[1,2]	**22 per 1000** (6 to 94)[1,2]	**RR 0.27** (0.07 to 1.13)	5617 (5 studies)	⊕⊕◯◯ **low**[3,5]	
HIV Incidence: High Income Countries	**31 per 1000**[1,2]	**24 per 1000** (10 to 57)[1,2]	**RR 0.77** (0.33 to 1.83)	1061 (2 studies)	⊕◯◯◯ **very low**[3]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Numerators and denominators taken from text where possible. Numbers were not used to calculate the relative effect estimates.
[2] Due to missing information in the denominator and/or numerator, some data were imputed from text.
[3] Few events and/or wide confidence interval.
[4] RR <0.20
[5] Rate Ratio <0.50

DISCUSSION

Summary of main results

We found that ART was associated with decreased risk of transmission of HIV in discordant couples. This intervention effect appeared in several studies that had adjusted for a variety of cofactors for transmission. Interestingly, the largely historical analyses of Musicco 1994 and Del Romero 2010 of patients on monotherapy and dual therapy even found pronounced independent effects for ART. More recent studies, such as Donnell 2010, Sullivan 2009 and Reynolds 2011, have found even larger effects, suggesting that more potent ART regimens are associated with even greater reductions in transmission. Only one study found an increased risk, albeit statistically non-significant, of HIV transmission among ART treated couples compared to untreated couples (Wang 2010). The authors' study objective was not to examine the effect of ART in serodiscordant couples but rather to estimate HIV incidence and clinical progression, quality of life and behavioural risk factors. Unpublished data suggest that the treated couples were followed for nearly three times longer than untreated couples (3532 years and 1385 years, respectively), thus, possibly allowing for more opportunity for infection among the treated couples. Nevertheless, it should be noted that the authors found no difference in rates of HIV transmission between ART-treated couples (4.8%) and untreated couples (3.2%).

The effect of ART on transmission risk of HIV in discordant couples was explored in CD4 subgroup analyses to see if the effect changed by CD4 subgroup. Unfortunately, most studies did not report risk of HIV transmission stratified by the index case's baseline CD4. However, there is an ongoing trial, HPTN 052, which aims to estimate the effect of ART on serodiscordant couples in which the index case's CD4 is >350 cells/μ at enrolment (see Characteristics of ongoing studies). Due to the lack of data on the effect of ART in CD4 subgroups, specifically among couples with ≥350 CD4 cells/μ, more research is needed in order to help guide providers and construct clinical guidelines regarding ART provision for HIV-discordant couples.

Overall completeness and applicability of evidence

These data are all from observational cohort studies and unmeasured confounding remains a significant issue. Given that we did not conduct an individual patient database meta-analysis, we were unable to control for a variety of cofactors, such as number of exposures, circumcision, HIV viral load, sexually transmitted infections, condom use or potency of ART. Nonetheless, the strength and consistency of the evidence argue in favour of a potent biological effect of ART on reducing risk of HIV transmission in discordant couples.

Quality of the evidence

GRADE

In the GRADE system, observational studies without any special strengths (and without additional limitations) provide low-quality evidence. The quality of evidence provided by a body of literature comprised exclusively of such studies, as is the case in this review, would thus be graded as "low." Given the biological plausibility of the relationship, however, between partners' exposure to ART and subsequent seroconversion, as well as the strength, temporality and the consistency of this relationship, as observed in several studies in several different countries, we found that the quality of evidence for this intervention could be upgraded to moderate. Please see Summary of Findings tables for details.

Potential biases in the review process

Biases in the review process were minimised by not limiting the search by language, by performing a comprehensive search of databases and conference proceedings and by contacting experts in the field for unpublished and ongoing studies. Publication bias was explored by using funnel plots (see Figure 4 and Figure 5). Based on only 7 studies, it is difficult to adequately assess publication bias. However, Figure 4 does suggest perhaps a publication bias, but the assymetry in the plot could also be an artefact of the true effect size differences between high precision studies and the low precision studies. Furthermore, rate ratio data were not available for all studies, which in turn could have influenced these estimated effect sizes.

Agreements and disagreements with other studies or reviews

Our findings are consistent with other recent reviews, including Attia 2009 and Cohen 2010.

AUTHORS' CONCLUSIONS

Implications for practice

From the evidence provided by these observational studies, ART appears to be a potent intervention for prevention of HIV in discordant couples. However, the most important question from a clinical standpoint is whether being in a serodiscordant relationship and having ≥350 CD4 cells/μL should be an additional indication for ART under WHO guidelines (WHO, 2010a). European and U.S. guidelines already allow for starting at up to 500 CD4 cells/μL routinely and even higher for certain subgroups and based on clinician judgment (European AIDS Clinical Society 2009; Panel on Antiretroviral Guidelines 2011). In our analysis, there were broad confidence intervals in this subgroup, overlapping the null hypothesis of no effect; this may well be the result

of Type II error because of the relatively low number of events. A related policy question is how much effort should be focused on treating individuals with ≥350 CD4 cells/μL when access to ART for persons with <350 CD4 cells/μL is far from universal. There is one large randomised controlled trial in the field currently, whose results are scheduled to be ready in 2015. Significant questions remain about durability of protection, cumulative antiretroviral toxicity, when to start treating an infected partner (for instance, at diagnosis or at a specific CD4 or plasma viral load level) and transmission of ART-resistant strains to partners.

Implications for research

Additional data are needed on durability of protection for uninfected partners as well as the potential for risk compensation. Given the growing use of ART worldwide, there are multiple opportunities to examine these issues in existing cohorts.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Del Romero 2010

Methods	Observational Cohort
Participants	648 heterosexual couples attending a clinic in Madrid, Spain, from 1989 to 2008
Interventions	ART
Outcomes	Incident HIV Infection
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised study
Allocation concealment (selection bias)	High risk	Non-randomised study
Blinding (performance bias and detection bias) All outcomes	High risk	Non-randomised study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up. All subjects accounted for.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Donnell 2010

Methods	Observational Cohort
Participants	Heterosexual African adults who were seropositive for both HIV and herpes simplex virus type II (HSV-2) and their HIV-uninfected sexual partners. Three thousand four hundred eight couples were enrolled from seven countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia).
Interventions	ART
Outcomes	Incident HIV Infection
Notes	

Donnell 2010 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised study
Allocation concealment (selection bias)	High risk	Non-randomised study
Blinding (performance bias and detection bias) All outcomes	High risk	Non-randomised study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Subjects lost to follow up discussed.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Melo 2008

Methods	Observational Cohort
Participants	93 discordant couples, in which the female member of the couple was infected in 67 (72%) and the male in 26 (28%).
Interventions	ART
Outcomes	Incident HIV Infection
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised study
Allocation concealment (selection bias)	High risk	Non-randomised study
Blinding (performance bias and detection bias) All outcomes	High risk	Non-randomised study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Subjects lost to follow up discussed.

Melo 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Musicco 1994

Methods	Observational Cohort	
Participants	A cohort of 436 monogamous HIV-uninfected female sexual partners of HIV-infected men recruited from 16 centres in Italy	
Interventions	Zidovudine	
Outcomes	Incident HIV Infection	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised study
Allocation concealment (selection bias)	High risk	Non-randomised study
Blinding (performance bias and detection bias) All outcomes	High risk	Non-randomised study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Reynolds 2011

Methods	Observational Cohort
Participants	250 HIV-discordant couples from Rakai, Uganda.
Interventions	ART
Outcomes	Incident HIV Infection
Notes	

Reynolds 2011 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised study
Allocation concealment (selection bias)	High risk	Non-randomised study
Blinding (performance bias and detection bias) All outcomes	High risk	Non-randomised study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Sullivan 2009

Methods	Observational Cohort
Participants	2,993 HIV-discordant couples in Rwanda and Zambia followed from 2002 to 2008
Interventions	ART
Outcomes	Incident HIV Infection
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised study
Allocation concealment (selection bias)	High risk	Non-randomised study
Blinding (performance bias and detection bias) All outcomes	High risk	Non-randomised study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement

Sullivan 2009 (*Continued*)

Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Wang 2010

Methods	Observational Cohort
Participants	1927 heterosexual couples between January 2006 and December 2008 for testing and treatment at county hospitals in China
Interventions	ART
Outcomes	Incident HIV Infection
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised study
Allocation concealment (selection bias)	High risk	Non-randomised study
Blinding (performance bias and detection bias) All outcomes	High risk	Non-randomised study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Baeten 2010	ART was not given
Barreiro 2006	all index cases received ART
Brill 2003	ART was not given
Bunnell 2006	all index cases received ART

(*Continued*)

Bunnell 2008	all index cases received ART
Fideli 2001	ART was not given
Gray 2001	ART was not given
Kayitenkore 2006	ART was not given
Mehendale 2004	ART was not given
Operskalski 1997	ART was not given
Peters 2008	ART was not given
Peterson 2007	ART was not given
Quinn 2000	ART was not given
Ragni 1998	ART was not given
Tovanabutra 2002	ART was not given
Wawer 2005	ART was not given

Characteristics of ongoing studies *[ordered by study ID]*

Kumarasamy 2010

Trial name or title	HPTN 052
Methods	Phase III, two-arm, multi-site, randomised trial
Participants	Serodiscordant couples in which index case's CD4 is greater than 350 cells
Interventions	HAART
Outcomes	HIV Incidence
Starting date	Registered - 4/1/2005 Open to Accrual - 11/7/2005 Enrolling - 11/10/2005 Enrollment Closed - 12/16/2009
Contact information	Nagalingeshwaran Kumarasamy
Notes	

DATA AND ANALYSES

Comparison 1. Treated with ART vs Not Treated with ART (IR)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incident HIV Infection	7		Rate Ratio (Random, 95% CI)	0.34 [0.13, 0.92]

Comparison 2. Treated with ART vs Not Treated with ART (IR, sensitivity)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incident HIV Infection	5		Rate Ratio (Random, 95% CI)	0.16 [0.07, 0.35]

Comparison 3. Treated with ART vs Not Treated with ART (< 200, 200-349, and ≥350 CD4 Cells/µL Subgroup Analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incident HIV Infection	4		Rate Ratio (Random, 95% CI)	Subtotals only
1.1 Less than 200 CD4	4		Rate Ratio (Random, 95% CI)	0.06 [0.01, 0.54]
1.2 200-350 CD4	3		Rate Ratio (Random, 95% CI)	0.33 [0.09, 1.27]
1.3 More than 350 CD4	2		Rate Ratio (Random, 95% CI)	0.02 [1.39, 2.87]

Comparison 4. Treated with ART vs Not Treated with ART (Female/Male Subgroup Analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incident HIV Infection	2		Risk Ratio (Random, 95% CI)	Subtotals only
1.1 Female Index Case	2		Risk Ratio (Random, 95% CI)	0.15 [0.01, 2.02]
1.2 Male Index Case	2		Risk Ratio (Random, 95% CI)	0.02 [4.52, 0.89]

Comparison 5. Treated with ART vs Not Treated with ART (Subgroup Analysis: Low-/Middle-Income vs High-income))

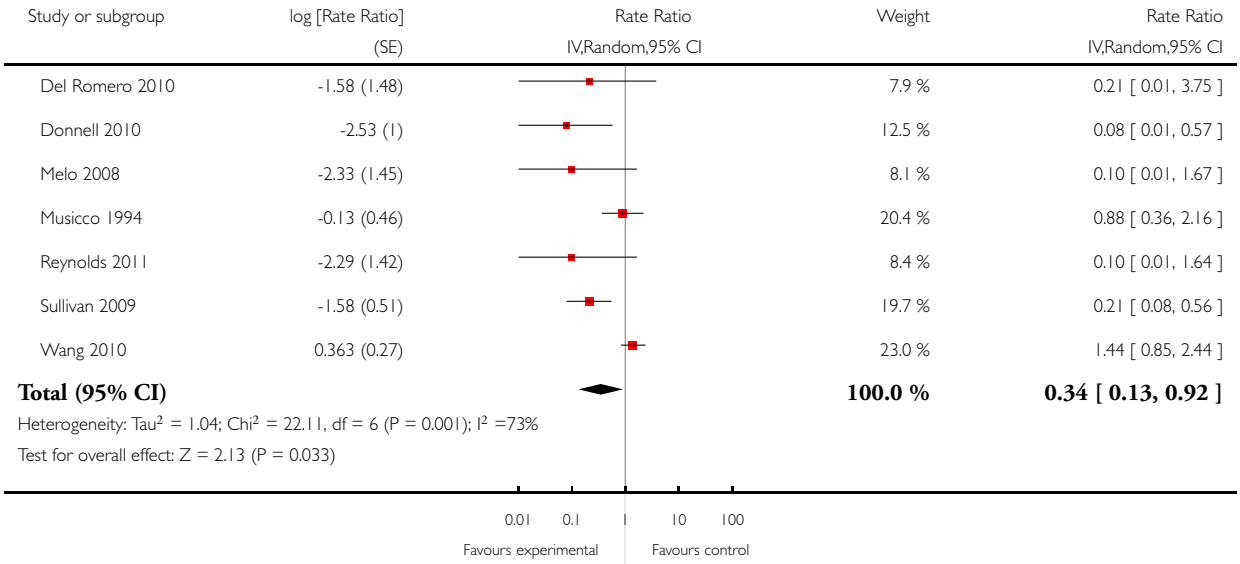
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incident HIV Infection	7		Rate Ratio (Random, 95% CI)	Subtotals only
1.1 Low/Middle Income Country	5		Rate Ratio (Random, 95% CI)	0.24 [0.06, 1.03]
1.2 High Income Country	2		Rate Ratio (Random, 95% CI)	0.77 [0.33, 1.83]

Analysis 1.1. Comparison 1 Treated with ART vs Not Treated with ART (IR), Outcome 1 Incident HIV Infection.

Review: Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples

Comparison: 1 Treated with ART vs Not Treated with ART (IR)

Outcome: 1 Incident HIV Infection

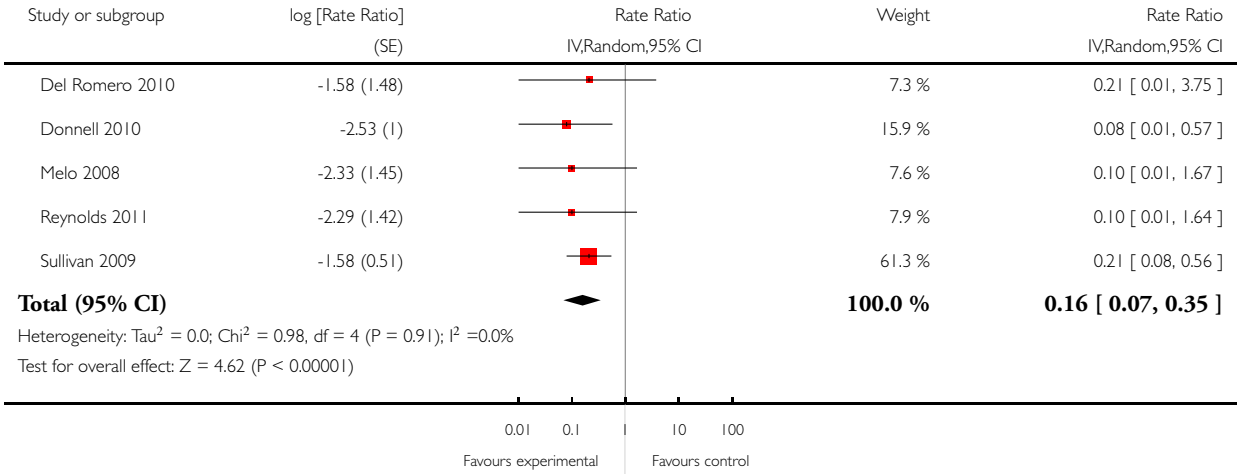


Analysis 2.1. Comparison 2 Treated with ART vs Not Treated with ART (IR, sensitivity), Outcome 1 Incident HIV Infection.

Review: Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples

Comparison: 2 Treated with ART vs Not Treated with ART (IR, sensitivity)

Outcome: 1 Incident HIV Infection

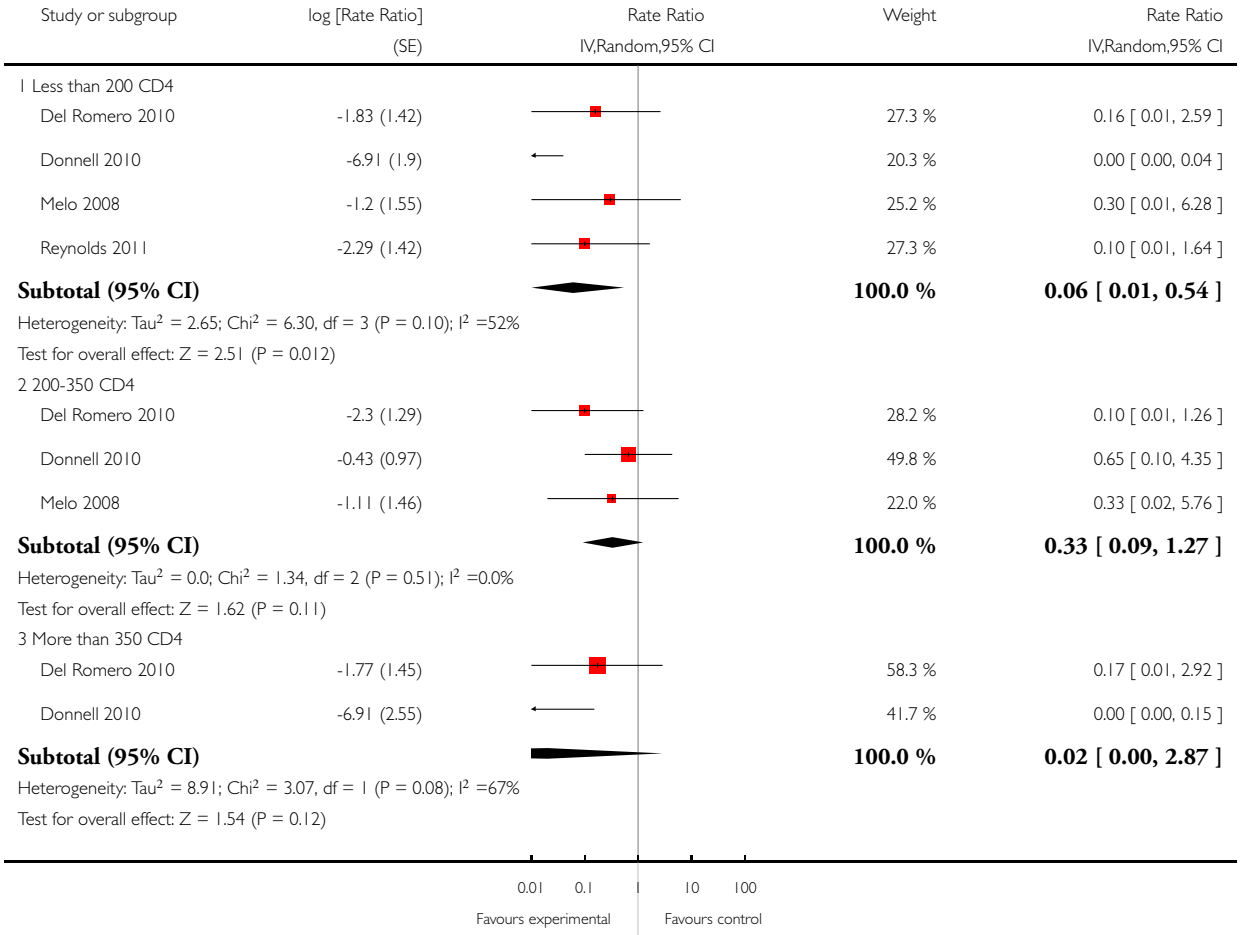


Analysis 3.1. Comparison 3 Treated with ART vs Not Treated with ART (< 200, 200-349, and ≥350 CD4 Cells/µL Subgroup Analysis), Outcome 1 Incident HIV Infection.

Review: Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples

Comparison: 3 Treated with ART vs Not Treated with ART (< 200, 200-349, and ≥350 CD4 Cells/L Subgroup Analysis)

Outcome: 1 Incident HIV Infection

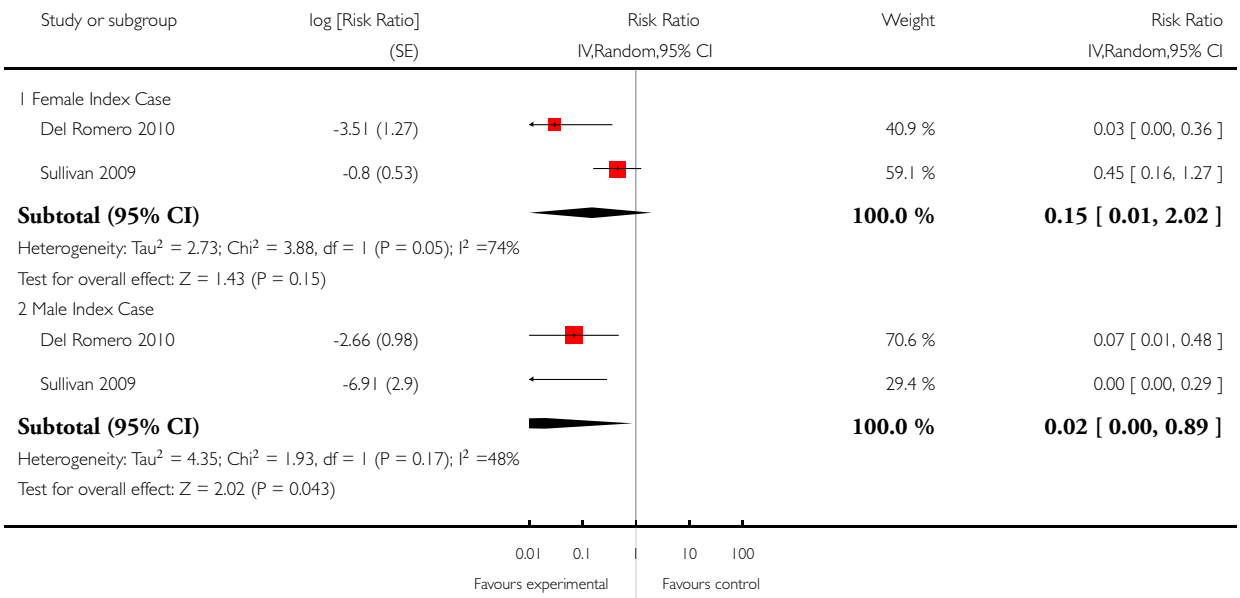


Analysis 4.1. Comparison 4 Treated with ART vs Not Treated with ART (Female/Male Subgroup Analysis), Outcome 1 Incident HIV Infection.

Review: Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples

Comparison: 4 Treated with ART vs Not Treated with ART (Female/Male Subgroup Analysis)

Outcome: 1 Incident HIV Infection

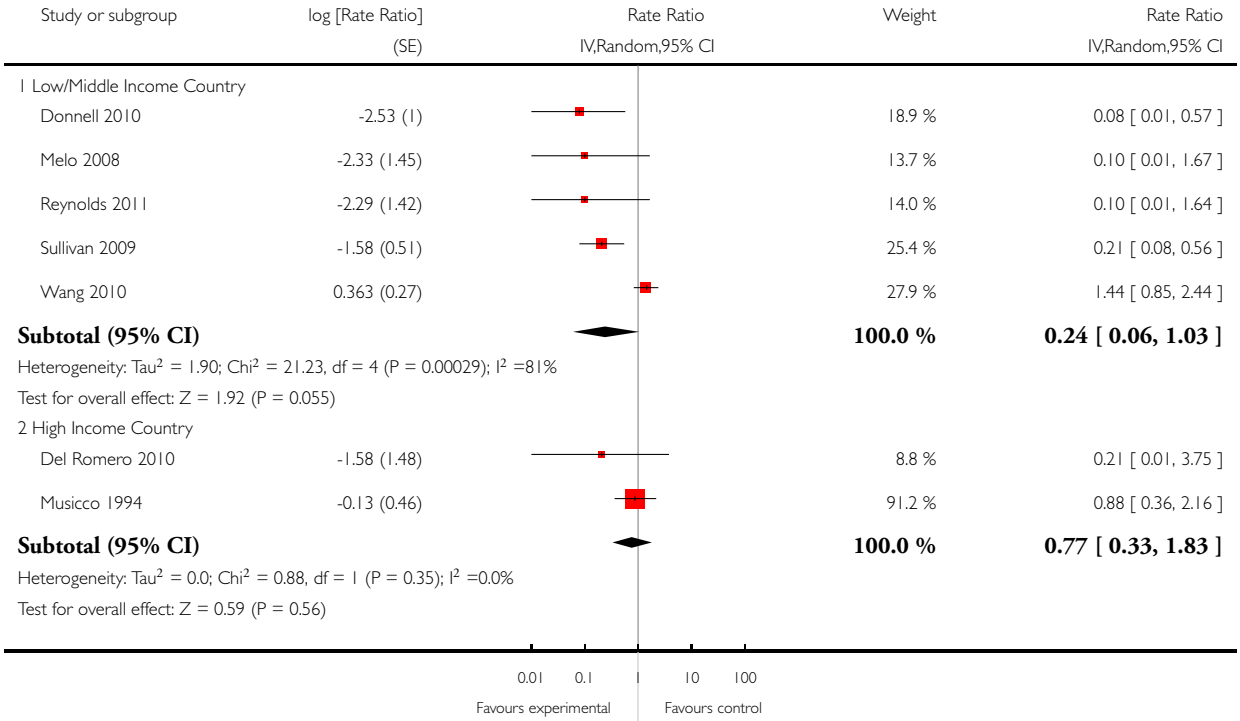


Analysis 5.1. Comparison 5 Treated with ART vs Not Treated with ART (Subgroup Analysis: Low-/Middle-Income vs High-income)), Outcome 1 Incident HIV Infection.

Review: Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples

Comparison: 5 Treated with ART vs Not Treated with ART (Subgroup Analysis: Low-/Middle-Income vs High-income))

Outcome: 1 Incident HIV Infection



APPENDICES

Appendix 1. Example of search strategy used in PubMed (modified as needed for use in the other databases)

Search	PubMed search strategy, 1 February 2011	Result
#5	Search (((#16) AND #17) AND #18) AND #19 Limits: Publication Date from 1987/01/01 to 2011/02/01	1218

(*Continued*)

#4	Search (randomised controlled trial[pt] OR controlled clinical trial[pt] OR randomised controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR non-randomi*[tw] OR before after study[tw] OR time series[tw] OR "case control"[tw] OR prospective*[tw] OR retrospective*[tw] OR cohort[tw] OR cross-section*[tw] OR prospective[tw] OR retrospective[tw] OR research design [mh:noexp] OR comparative study[mh] OR evaluation studies[mh] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw] OR longitud*[tw] OR descripti*[title/abstract] OR study[title/abstract] OR evaluat*[title/abstract] OR "odds ratio"[tw] OR "hazard ratio"[tw] OR "relative risk"[tw] OR "risk ratio"[tw] OR AOR[tw] OR RRR[tw] OR NNT[tw]) Limits: Publication Date from 1987/01/01 to 2011/02/01	5826158
#3	Search (Couples[title/abstract] OR (sex*[title/abstract] AND partner*[title/abstract]) OR husband[title/abstract] OR wife[title/abstract] OR boyfriend*[title/abstract] OR girlfriend*[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]) Limits: Publication Date from 1987/01/01 to 2011/02/01	99727
#2	Search (HAART[title/abstract] OR ART[title/abstract] OR ARV[title/abstract] OR ARVs[title/abstract] OR antiretroviral[title/abstract] OR anti-retroviral[title/abstract] OR antiviral[title/abstract] OR antiviral[title/abstract] OR "Antiretroviral Therapy, Highly Active"[Mesh] OR "Anti-Retroviral Agents"[Mesh]) Limits: Publication Date from 1987/01/01 to 2011/02/01	112655
#1	Search (HIV Infections[MeSH] OR HIV[MeSH] OR hiv[title/abstract] OR hiv-1[title/abstract] OR hiv-2*[title/abstract] OR hiv1[title/abstract] OR hiv2[title/abstract] OR hiv infect*[title/abstract] OR human immunodeficiency virus[title/abstract] OR human immune deficiency virus[title/abstract] OR human immuno-deficiency virus[title/abstract] OR human immune-deficiency virus[title/abstract] OR ((human immun*) AND (deficiency virus[title/abstract])) OR acquired immunodeficiency syn-	256073

(*Continued*)

	dromes[title/abstract] OR acquired immune deficiency syndrome[title/abstract] OR acquired immuno-deficiency syndrome[title/abstract] OR acquired immune-deficiency syndrome[title/abstract] OR ((acquired immun*) AND (deficiency syndrome[title/abstract])) or "sexually transmitted diseases, viral"[mh]) OR HIV[title/abstract] OR HIV/AIDS[title/abstract] OR HIV-infected[title/abstract] OR HIV[title] OR HIV/AIDS[title] OR HIV-infected[title]) Limits: Publication Date from 1987/01/01 to 2011/02/01	

Appendix 2. Newcastle Ottawa Quality Assessment Scale

COHORT STUDIES (Newcastle-Ottawa)

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average treated serodiscordant couple in the community

b) somewhat representative of the average treated serodiscordant couple in the community

c) selected group of users eg nurses, volunteers, HIV clinic patients

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record (eg surgical records)

b) structured interview

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for or matches on disease status when comparing treated and untreated couples

b) study controls for any additional factor **?** (e.g. age or sex)

Outcome

1) Assessment of outcome

a) independent blind assessment

b) record linkage

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest)

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for

b) subjects lost to follow up unlikely to introduce bias - small number lost - > 79% (select an adequate %) follow up, or description provided of those lost)

c) follow up rate < 20% (select an adequate %) and no description of those lost

d) no statement

NOS - CODING MANUAL FOR COHORT STUDIES

SELECTION

1) Representativeness of the Exposed Cohort (NB exposure = intervention)

Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the study sample from some general population. For example, subjects derived from groups likely to contain exposed people are likely to be representative of exposed individuals, while they are not representative of all people the community.

Allocation of stars as per rating sheet

2) Selection of the Non-Exposed Cohort

Allocation of stars as per rating sheet

3) Ascertainment of Exposure

Allocation of stars as per rating sheet

4) Demonstration That Outcome of Interest Was Not Present at Start of Study

In the case of mortality studies, outcome of interest is still the presence of a disease/ incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

A maximum of 4 stars can be allotted in Selection.

COMPARABILITY

1) Comparability of Cohorts on the Basis of the Design or Analysis

Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

A maximum of 2 stars can be allotted in this category.

OUTCOME

2) Assessment of Outcome

For some outcomes, reference to the medical record is sufficient to satisfy the requirement for confirmation. This may not be adequate for other outcomes where reference to specific tests or measures would be required.

a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (health records, etc.)

b) Record linkage (e.g. identified through ICD codes on database records)

c) Self-report (i.e. no reference to original health records or documented source to confirm the outcome)

d) No description.

3) Was Follow-Up Long Enough for Outcomes to Occur

An acceptable length of time should be decided before quality assessment begins.

4) Adequacy of Follow Up of Cohorts

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.

A maximum of 3 stars can be allotted in this category.

HISTORY

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CONTRIBUTIONS OF AUTHORS

All authors contributed to the design and conduct of this review, as well as with manuscript drafting and submission.

DECLARATIONS OF INTEREST

None known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

NOTES

None.