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Title: Heterosexual HIV-1 infectiousness and antiretroviral use: Systematic review of prospective studies of discordant couples

Running head: HIV-1 infectiousness according to antiretroviral use

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ABSTRACT

Background: Recent studies have estimated the reduction in HIV-1 infectiousness with antiretroviral therapy (ART), but high-quality studies such as randomized control trials, accompanied by rigorous adherence counselling, are likely to overestimate the effectiveness of treatment-as-prevention in real-life settings.

Methods: We attempted to summarize the effect of ART on HIV transmission by undertaking a systematic review and meta-analysis of HIV-1 infectiousness per heterosexual partnership (incidence rate and cumulative incidence over study follow-up) estimated from prospective studies of discordant couples. We used random-effects Poisson regression models to obtain summary estimates. When possible, the analyses were further stratified by direction of transmission (man-to-woman or woman-to-man) and economic setting (high- or low-income countries). Potential causes of heterogeneity of estimates were explored through subgroup analyses.

Results: Fifty publications were included. Nine allowed comparison between ART and non-ART users within studies (ART-stratified studies), where summary incidence rates were 3.6/100 person-years (95% confidence interval= 2.0-6.5) and 0.2/100 person-years (0.07-0.7) for non-ART- and ART-using couples, respectively ($p<0.001$), constituting a 91% (79%-96%) reduction in per-partner HIV-1 incidence rate with ART use. The 41 studies that did not stratify by ART use provided estimates with high levels of heterogeneity (I^2 statistic) and few reported levels of ART use, making interpretation difficult. Nevertheless, estimates tended to be lower with than without ART use. Infectiousness tended to be higher for low-income than high-income settings, but there was no clear pattern by direction of transmission (man-to-woman and woman-to-man).

Conclusions: ART substantially reduces HIV-1 infectiousness within discordant couples, based on observational studies, and could play a major part in HIV-1 prevention efforts. However the non-zero risk from partners receiving ART demonstrates that appropriate counselling and other risk reduction strategies for discordant couples are still required. Additional estimates of ART effectiveness by adherence level from real-life settings will be important, especially for persons starting treatment early without symptoms.

HIV-1 remains among the world's leading causes of mortality, with an estimated 2.7 million new infections in 2010.[1] Treatment-as-prevention has been proposed as a much-needed new tool to prevent HIV transmission.[2] Although the efficacy of ART for reducing the risk of HIV-1 transmission between stable partners has recently been estimated in the landmark HPTN 052 trial,[3] such results do not necessarily reflect what would happen in less controlled settings (with less intensive risk-reduction and adherence counselling, for example) or if ART was scaled up more widely as treatment-as-prevention. The objective of this study is to comprehensively review all prospective studies of discordant couples in order to summarize HIV-1 transmission estimates by level of ART use by the infected partner (index case). These include many early and observational studies that involve study populations more similar to real-life populations.

We examined studies that followed couples who were discordant by HIV-1 status, from the time of diagnosis of the index case. This design has some limitations, notably selection bias. Couples in stable partnerships may therefore be at lower risk of transmitting than those in the general population. Also, these studies are subject to left-censoring, or frailty-selection, whereby the most vulnerable couples of so-called "high and fast transmitters" rapidly become seroconcordant[4, 5] and therefore ineligible for recruitment. Combined, these factors may result in over-sampling of less infective index cases and less susceptible partners who remain uninfected longer, leading to underestimates of infectivity. Nonetheless, this study design is often judged preferable for estimation of per-partnership transmission because the enrollment of monogamous couples avoids having to account for partners with unknown serostatus. Also, the time of seroconversion of the susceptible partner can be determined more accurately than from cross-sectional studies. Studies with frequent follow-up can also provide more reliable information with less recall bias on frequency and type of contact.[6]

The aim of this study is to summarize HIV-1 infectiousness for discordant couples by level of ART use, through a systematic review and meta-analysis. Our first "within-study" analysis systematically reviews all prospective discordant-couple studies directly comparing couples where the index receives ART with those not receiving ART (ART-stratified studies). Our second, broader analysis includes all prospective heterosexual discordant-couple studies in order to provide a comprehensive summary of infectiousness estimates and to compare HIV-1 infectiousness estimates by level of ART use among each study sample. We also investigate the potential influence of direction of transmission (man-to-woman and woman-to-man) and setting (high- and low-income countries) on HIV-1 infectiousness and potential causes of heterogeneity across study estimates.

METHODS

Search strategy

The systematic review was undertaken according to the MOOSE checklist for review of observational studies.[7] Details of the search are published elsewhere,[6] with a subsequent update to 31 July 2011. Our search terms were intentionally broad to capture publications estimating HIV-1 infectiousness of all types and modes of transmission, for use in other HIV-1 infectiousness reviews.[6, 8-10] We searched bibliographies of relevant articles to find additional publications not identified by electronic search. The search was not limited to English language articles, and we translated papers from other languages where required. Additionally, we searched abstracts from the previous two years (2010, 2011) of International AIDS Society, Conference on Retroviruses and Opportunistic Infections and International Society of Sexually Transmitted Research on "discordant." Further search details are given in the eAppendix.

Selection criteria and data extraction

We extracted data on two outcome measures of sexual HIV-1 infectiousness, cumulative incidence of infection over study follow-up periods and incidence rate following exposure to an HIV-1-infected partner; we focus our analysis on incidence rate. We included all empirical prospective studies reporting either type of estimate, or studies from which such estimates could be derived. Infectiousness estimates for heterosexual sex (vaginal sex or vaginal and anal sex) are reported here; estimates for oral sex and for homosexual intercourse, with per-act transmission probabilities, are reported elsewhere.[6, 8, 10]

This analysis is reported in two parts. The first, "within-study" meta-analysis included ART-stratified studies. The second analysis included studies where infectiousness estimates were not stratified by the ART use of index cases (non-ART-stratified studies). We used these studies to compare estimates by level of ART use. Only the results from the control arms of RCTs of non-ART interventions were included (results from the intervention arm available on request). We excluded cross-sectional estimates, indirect estimates from transmission dynamics modelling studies, narrative or methodological reviews, abstracts pre-2000, and study estimates based on fewer than 10 subjects. Non-ART-stratified studies were categorized as no-ART-use if they: 1) reported <3% ART use by study participants; 2) did not report on ART use but follow-up was censored at 1996 or earlier[11] for high-income countries or 2005 or earlier[12] for low-income countries; or 3) if they did not state follow-up dates, and publication was before 1997 for high-income countries or before 2005 for low-income countries. All other estimates were classed as "any ART use". We allowed for up to 3% ART use as a maximum level of contamination within the no-ART-use group.

Where publications have been superseded by more recent information, the later source was included, unless an earlier source provided a larger sample size. Each relevant publication was examined by two reviewers (RFB and MCB or RGW) who compiled information on estimates

and on study and participant characteristics. Discrepancies were resolved by consensus. Where possible, couples reporting no sexual activity or 100% condom use were excluded. Nineteen authors were contacted to obtain additional information or to clarify potential overlap in study participants between publications; ten responded. A list of all included and excluded studies is available on request.

Data analysis and statistical methods

Forest plots were used to explore graphically the heterogeneity among study estimates.[13] Heterogeneity was also explored using Cochran's Q-statistic[14] and I^2 statistic.[15] If there was significant heterogeneity (using $p<0.05$ as a guideline but taking into account sample size and without a strict cut-off), no overall pooled estimate was provided on forest plots. We explored potential causes of heterogeneity through subgroup analyses based on condom use, presence of STIs, HIV-1 infection stage of index [based on clinical stage or CD4 count data – see eAppendix for classification methods], prevalence of male circumcision, study design (RCT/observational), and population characteristics (region, i.e., Americas and Europe/Africa/Asia), and country-level prevalence of male circumcision). There were insufficient data to investigate other risk factors such as HIV-1 viral load. We used forest plots to explore graphically the heterogeneity among random-effects summary estimates calculated for subgroups.[13]

Regarding condom use, STIs and infection stage, we created aggregate study-level variables due to incomplete and non-comparable reporting of these risk factors among studies (see eAppendix and figure legends for details). An ecologic analysis pairing estimates with country-level male circumcision prevalence data[16] was used, due to the lack of information on male circumcision in most studies.

Where relevant, we used random-effects Poisson-regression models to obtain summary estimates for HIV-1 incidence and cumulative incidence, with 95% confidence intervals (95% CIs). For each study or stratum, the total number of events was considered to be Poisson distributed for a given sum of person-years. Poisson regression models were fitted with a logarithmic link function. Total exposure time (incidence rate) or initial number of couples at risk (cumulative incidence) per study were used as an offset variable, with γ-distributed random effects at the study level. Further details of the methods are provided in the eAppendix.

RESULTS

Summary of search

Fifty prospective studies of discordant couples were included (eFigure 1). Nine studies fit the inclusion criteria for the first analysis, with HIV-1 transmission stratified by ART use of the index case[3, 17-25] (one study was reported in two abstracts[20, 21]). Forty-one non-ART-stratified studies provided estimates for the second analysis, reporting either no (n=29[26-54]) or any (n=12[55-66]) ART use. Eighteen studies were excluded based on eligibility criteria (study details available on request). Several publications were excluded because they were superseded by more recent articles. Although Musicco et al[17] and Saracco et al[59] are from the same study, both were included (Musicco for the first analysis, Saracco for the second) because the former reports estimates stratified by ART status while the latter does not; the same was true for Donnell et al[24] and Celum et al.[28] Most studies reported estimates of both HIV-1 incidence rate and cumulative incidence.

Among all publications included in these analyses, more were from low-income (n=34) than high-income (n=17) countries. (Cohen et al[3] provide results from nine countries, only one of which is high-income, and so the study is classified here as low-income). Seven publications reported results from RCTs, one study testing ART use of the index (early versus delayed

ART),[3] one testing pre-exposure prophylaxis,[67] one testing Herpes Simplex Virus (HSV) suppressive therapy (Celum non-ART-stratified,[28] Donnell ART-stratified[24]), one testing male circumcision for prevention of man-to-woman HIV-1 transmission[53] and two cluster randomized controlled trials (RCTs) of a behavioral intervention[55] and a STI treatment intervention.[43] The remainder were observational studies.

ART-stratified studies (within-study comparisons)

One of the nine studies reporting HIV-1 transmission stratified by ART use (Figure 1[3, 17-25]) was excluded because the therapy was zidovudine monotherapy.[17] An additional conference abstract reported stratification of ART use in the form of pre-exposure prophylaxis[67]; this study was included in the forest plot but not the pooled ART effect estimate. The included studies reported combined man-to-woman and woman-to-man transmission and were from low-income settings, except for one from Spain (22) and the one combining results from nine study countries (of which one was high-income).[3] All studies provided incidence-rate estimates (or data from which such estimates could be derived) except Wang et al.[23] Cohen et al[3] was included, although it should be noted that a small number of same-sex couples were included in the analysis (2% men who have sex with men, <0.1% women who have sex with women). Four studies did not state cumulative incidence.[19-21, 25, 67] Summary incidence rate was 0.2/100 person-years (95% CI= 0.07-0.7) among ART-receiving couples and 3.6/100 person-years (2.0-6.5) among non-ART-receiving couples (studies from all settings, n=7[3, 18-22, 24, 25] incidence rate ratio (IRR)=0.09 (0.04-0.21), p<0.001, Table), constituting a 91% (79%-96%) reduction in per-partner HIV-1 incidence rate with ART use. As only two included studies reported results stratified by direction of transmission (20, 21, 68), we did not perform stratified meta-analyses. Further details of studies are shown in eTable 2.

Non-ART-stratified studies (between study comparisons)

Infectiousness by ART use

HIV-1 incidence rate estimates ranged from 0.0 to 17.4/100 person-years for high-income settings (Figure 2) and from 0.0 to 33.7/100 person-years for low-income settings (Figure 3). Forest plots highlight the considerable heterogeneity among study estimates for low-income settings (Figure 3, $p<0.001$ test for heterogeneity for all no-ART-use estimates and combined man-to-woman woman-to-man any ART use; insufficient data for any-ART use by direction of transmission). High-income settings were more homogeneous, probably due to the small numbers of estimates per strata (Figure 2; for combined transmission: no ART use, $I^2=33\%$, $p=0.110$, n=6; any ART use, $I^2=0\%$, $p=0.764$, n=2; for man-to-woman transmission: no ART use $I^2=0\%$, $p=0.388$, n=4; any ART use $I^2=60\%$, $p=0.032$, n=2; female-to-male transmission: insufficient estimates). This heterogeneity and lack of sufficient estimates for some strata prevent straightforward interpretation of summary estimates. We therefore omitted these from the forest plots but have provided them in eTable 3. However, while absolute values of summary transmission rate estimates by level of ART use may not be reliable, the IRR of 0.31 (95% CI= 0.14-0.69, p=0.001) for difference in infectiousness, any versus no ART use (combined male-to-female female-to-male, all settings) is compelling.

Study estimates in Figures 2 and 3 are presented in order of increasing ART coverage, but few non-ART-stratified studies reported the precise level of ART use among study participants (n=12), and thus no strong dose-response relationship is observed (see eFigure 3 for additional plots). However, for the stratum with the most estimates (combined man-to-woman and woman-to-man transmission for low-income countries, Figure 3A) there were sufficient data to analyze the IRR by ART level (Figure 4). Changing the comparison from no versus any ART use to none/any versus 100% use decreased the IRR to 0.04 (95% CI= 0.005-0.36,p=0.004).

Infectiousness by setting

Incidence rates tended to be smaller in high-income countries (Figure 2) than in low-income countries (Figure 3). There were many estimates of zero transmission rates from high-income countries, even among the no-ART-use studies.[37, 40, 42, 50, 52] Of the 15 high-income estimates, only three[35, 41, 57] were ≥5.0/100 person-years. Robertson and colleagues[57] reported on any ART use (prevalence of ART use not stated), but study subjects came from a population where index cases were current or former intravenous drug users, and so there may be risk from needle contamination. There is no obvious explanation for the high estimate from Laurian et al[35] (9.7/100 person-years for partners of hemophiliacs) but the sample size was small (n=17). Thirty-three percent of couples followed by Operskalski et al[41] reported anal intercourse.

In contrast to the low estimates from high-income settings, there were many high incidence rate estimates from low-income settings (Figure 3). For combined man-to-woman and woman-to-man transmission, only 11 of 24 (46%) estimates were <5.0/100 people-years,[28, 39, 46, 54, 58, 60-65] four of which were from no-ART studies.[28, 39, 46, 54] Two large studies of no ART use reported particularly low infectiousness estimates[28, 39] and three small studies produced particularly high estimates (33, 34, 38). The high estimate from Hugonnet et al[34] was from partners of people who seroconverted during follow-up and therefore included the period of high infectiousness associated with acute infection. The index cases in the study by Hira et al[33] were mostly symptomatic (14% AIDS, 82% AIDS-related complex) and therefore also likely to be more infectious. The paucity of information reported by Mao et al[38] regarding risk factors makes interpretation of their high estimate difficult. Low-income studies were also more recent and tended to be far larger than those from high-income settings, particularly the RCTs. There were eight any-ART-use studies,[56, 58, 60-65] which tended to be more recent (published 2006-2011) than the no-ART studies (1990-2010).

Infectiousness by direction of transmission

There was no clear pattern regarding HIV-1 infectiousness by direction of transmission, woman-to-man compared with man-to-woman. Of the publications providing man-to-woman and woman-to-man infectiousness estimates from the same study, seven[26,29-31,33,34,41] reported no significant difference between them, with the eighth[27] being significant before adjustment but non-significant after adjusting for age.

Subgroup analyses

We undertook subgroup analyses to identify sources for the heterogeneity of infectiousness estimates. However, there was a lack of comparable information on HIV-1 risk factors. For example, of the 22 studies reporting no ART use for combined man-to-woman woman-to-man transmission, only five provided data on the prevalence of male circumcision. Very few differences in summary estimates by subgroup reached statistical significance, and those that did may be due to chance. Nevertheless, the data available do allow trends to be identified. Subgroup summary estimates are plotted for no-ART-use studies from high- and low-income settings for combined transmission, and for low-income settings for man-to-woman and woman-to-man transmission (eFigure 2A-D respectively). There were insufficient data to provide meaningful plots for any-ART-use estimates and woman-to-man and man-to-woman no-ART-use estimates from high-income countries.

Summary incidence rate estimates were lowest for studies from Europe and the Americas (combined transmission, no ART use 3.6/100 person-years, [95% CI= 0.4-32.6]), then Africa (7.7/100 person-years [5.5-10.7]) and highest for Asia (10.9/100person-years [1.7-69.5]) (eFigures 2A and 2B). There were no substantial differences in summary estimates by level of

condom use and STIs. HIV-1 infection stage classified studies as having index cases who were more (high proportion of late stage or acute stage HIV-1) or less infectious. For the majority of strata, the "more-infectious" subgroup had the higher summary incidence rates, although this was not the case for combined transmission high-income estimates (but only three studies reported relevant data[40, 41, 52]) and for woman-to-man low-income estimates (five studies[28, 30, 39, 43, 69]). In the first case, Operskalski et al[41] was an outlier with very high infectiousness, as discussed above. In the second case, the only two studies in the "more infectious" subgroup had very small sample sizes.[39, 69]

Although male circumcision status was not well reported, we found that studies with higher prevalence levels had lower summary incidence rate. The ecologic analysis using country-level circumcision prevalence data found no difference in summary estimates for woman-to-man transmission from low-income settings (5.8/100 person-years [95% CI= 3.5-9.5]) for high prevalence settings; 5.8/100 person-years [3.7-9.1] for low prevalence settings, eFigure 2D). Pooled estimates by study type were higher for trials than for observational studies for combined and man-to-woman transmission, and roughly equal for woman-to-man transmission, but interpretation is limited because of the small number of trials included.

The inconsistent reporting of risk factors for HIV-1 transmission across studies means that only univariate analysis was possible for the subgroup analysis. The trends identified by each HIV-1 risk factor are generally as expected and therefore explain some of the heterogeneity in study estimates within each stratum. For most subgroup pooled estimates, substantial heterogeneity remained (for example, combined transmission no-ART-use all settings: 13 of 15 pooled estimates had $I^2 \geq 50\%$, data not shown).

DISCUSSION

HIV-1 infectiousness with ART

Our systematic review and meta-analysis of per-partner HIV-1 infectiousness includes all published prospective studies of discordant couples, and suggests a 91% reduction (95% CI= 79%-96%) in infectiousness with ART use by the index case from ART-stratified observational studies. Our results from non-ART-stratified studies support this observation for populations that more closely resemble real-world settings. The IRR of 0.04 for 100% versus <100% ART use among index cases does not mean a 96% reduction in infectiousness. We are not comparing consistent use with zero use, we cannot directly compare populations from different studies conducted in different settings at different time points, and we are relying on two small studies representing 100% ART use (60, 63). However the estimate does demonstrate a striking reduction in transmission within discordant couples with ART use for observational studies. Together with the stratified study analysis, there is compelling evidence for a reduction in HIV-1 infectiousness with ART use.

The HPTN 052 RCT provides gold-standard evidence of the efficacy of ART for reducing the risk of HIV-1 transmission, finding a 96% reduction in linked HIV-1 transmission events within heterosexual stable couples.[3] Our analysis summarizing findings from all ART-stratified studies found a 91% reduction. The other ART-stratified studies included in our review are observational and tended to involve ART-receiving index cases with more advanced HIV-1 disease than untreated index cases, probably with less intensive risk reduction and adherence counselling; thus, a slightly lower effect of ART is unsurprising. This proof of concept that ART does indeed reduce sexual transmission of HIV-1 is not enough to predict the population-level impact of ART interventions on HIV-1 spread. Such predictions would require more data on the effectiveness of infectiousness reduction with ART when adherence-promotion counseling is set at the more modest intensity characteristic of existing ART programmes, and would need to look back at the incidence rates from the non-ART-stratified discordant couple studies reviewed here to estimate transmission rates within stable partnerships in real-world

settings – again, without risk-reduction counseling being as intensive as now justifiably required for prospective HIV-1 studies.

Incidence rate estimates from no-ART-use studies appear to have reduced over time (e.g. Figure 3A, combined man-to-woman and woman-to-man transmission, low-income settings). It is difficult to estimate a "typical" transmission risk to use for HIV-1 projections because 1) it is difficult to define a "typical" discordant couple, 2) levels of counselling differ between studies, and 3) awareness among the general population of HIV/AIDS and risks for transmission varies by time and location. However, the 5-10/100 person-years incidence rates reported between 1992 and 2001 by the majority of low-ART, low-income studies is a reasonable starting point from which to base predictions of the impact of ART, or, indeed, pre-exposure prophylaxis or other HIV-1 interventions, within discordant couples from low-income settings.

In 2009, Attia et al[70] reviewed five cohorts reporting HIV-1 transmission rates among heterosexual discordant couples with ART-treated index cases, finding that no transmission events occurred in patients who were treated with ART and who had viral loads <400 copies/ml. While our findings are not able to stratify risk by viral load of the index, maintaining a lower or undetectable viral load on ART probably reduces transmission risk even further.[70] Since the report by Attia and colleagues, a re-analysis of the Partners in Prevention data (represented in our analysis by Celum et al[28] and Donnell et al[24]) has supported Attia's findings, with higher viral load increasing risk of HIV-1 transmission.[71] No transmission events were observed from index cases with undetectable viral load in their blood, but there were a small number from people with undetectable viral load in genital fluids.[72] In addition to the ART-stratified trials, we looked at all prospective discordant-couple studies and provided estimates of per-partner incidence rate from older studies, many of which did not involve such

intensive risk-reduction counseling. These older studies may provide more real-world incidence rates, more accurately reflecting conditions for discordant couples in the general population.

Infectiousness by setting

Rates of HIV-1 transmission to partners were generally higher in low-income than high-income countries. There may be several explanations, including differences in methodology, rates of monogamy, rates of circumcision, differences in the stage of the HIV-1 epidemic or the proportion of symptomatic cases, patterns of sexual behavior, prevalence of other STIs, and variations in viral strains. More recent studies have used more sophisticated phylogenetic analyses to exclude transmissions that originated outside the partnership (e.g. [28, 31]).

Infectiousness by direction of transmission

There was no clear difference in HIV-1 infectiousness by direction of transmission. For high-income settings this may be due to the lack of studies (only one incidence rate for woman-to-man transmission was identified). In low-income countries, a higher prevalence of HIV-1 cofactors such as STIs may mask a true biologic difference in HIV-1 infectiousness. These findings are consistent with results from a previous meta-analysis of per-sexual-act HIV-1 infectiousness.[6]

Study limitations

Transmission probabilities are affected by a combination of risk factors for the person transmitting the virus (infectiousness) and the partner acquiring it (susceptibility). Factors known to affect HIV-1 infectiousness include stage of infection,[73] viral subtype,[74] STIs,[75] type of sexual act[76] and male circumcision.[77] Therefore, average transmission probabilities will depend on the distribution of these measured and unmeasured risk factors, and it may not be

appropriate to generalize across populations. Discordant-couple studies usually recruit monogamous couples, who may have lower prevalence and incidence of various risk factors than the general population (e.g. lower incidence of STIs). Furthermore, self-reported data on sexual behavior are often inaccurate due to recall and social-desirability bias,[78] leading to imprecise estimates of frequency of sexual contacts, condom use and reports of monogamy. There is more potential for bias in our non-ART-stratified study comparison than our ART-stratified comparison because we are comparing different studies, where distributions of these risk factors will differ between populations by place and time.

Our HIV-1 cumulative incidence and incidence rates show considerable heterogeneity, likely due to different distributions in HIV-1 risk factors across study populations. While a meta-analysis is presented, care must be taken with the interpretation of summary estimates from such heterogeneous data and from studies with such different patterns of risk factors. This meta-analysis is informative at a qualitative level, identifying trends in estimates between risk groups. However with incomplete or non-comparable reporting of HIV-1 risk factors and cofactors, we cannot adequately control for differences among studies. For non-ART-stratified studies, our distinction of no and any ART usage is based on inferences from the study dates. There was incomplete reporting on dates, as well as on many other HIV-1 risk factors and cofactors, which we therefore could not adequately control for in our analysis. Our analysis by ART use is also limited by the ecologic nature of our measure: for studies with ART use between 0% and 100%, we do not know which of the transmitting and non-transmitting couples included index cases who received ART.

The quality and emphasis placed on risk-reduction counseling of participating discordant couples is likely to have varied substantially among studies and over time. For example, couples identified as discordant only retrospectively by Quinn et al[43] may have different risk behavior patterns from those who were aware of their serostatus. Such study designs are

unlikely to be replicated. In contrast, the RCTs had intensive levels of risk-reduction counseling.

It has been stated that, "longitudinal studies of discordant couples are the preferred epidemiologic design for the investigation of heterosexual HIV transmission."[34] However, this design misses primary infection and involves left-censoring selection bias, selecting for couples with biologic or behavioral characteristics that impart a lower risk of HIV-1 transmission. Therefore the rates derived are likely to underestimate the true average HIV-1 transmission risk. To avoid this bias would require prospective recruitment of concordant HIV-1 negative couples to measure transmission rates from the time of HIV-1 acquisition of the index case. Such a large trial would be so costly as to be infeasible. The exceptions are the Rakai Project Study,[43] which retrospectively identified those persons who were in stable partnerships, and as a result has been able to provide HIV-1 transmission risk for the acute stage of infection[73] – although it seems unlikely that such a study design will be replicated.[79] By overcoming left censoring, Quinn et al[43] did indeed estimate a higher infectiousness than other studies: the third highest transmission rate of 16 male-to-female low ART resource-poor setting estimates (Figure 3B) and the highest of 13 for female-to-male estimates (Figure 3C). The second exception is Operskalski et al.[41] The extremely high incidence rate (17.4/100 person-years) would be even higher if we took into account the two couples who were concordant positive at recruitment, and for whom time since sexual contact began was known, following a blood transfusion of the index (incidence rate 22.0/100 person-years).

Prospective discordant-couple studies are also limited either by the small number of participants or the small number of seroconversions resulting from dissolution of couples, intensive condom promotion, short follow-up periods, or falling rates of transmission over time because of behavioral change or exhaustion of susceptible persons. They cannot allow for partnerships that have broken up (which often happens after an HIV-1 diagnosis). Nonetheless,

monogamous HIV-1-discordant couples provide the best means of estimating HIV-1 infectiousness for sexual transmission because they (in principle) eliminate contamination from outside sources. For the purposes of comparison (such as by ART use, setting, direction of transmission), these limitations in study design are less important because they are applicable to virtually all studies. However, in the absence of better data, these transmission rates are also used to inform trials and modelling studies. Therefore it is important to appreciate the biases, especially the likely underestimation in risk due to left censoring.

Conclusion

ART reduces viral loads, and thus has been thought to reduce infectiousness. In the last five years, studies have demonstrated that this reduction in infectiousness can be dramatic.[3, 80] Therefore widespread access to ART has the potential to have an impact on HIV-1 transmission, both at the individual level (reducing transmission risk and thus allowing a safer route to conception for many couples) and, potentially, at the population level, as an HIV-1 prevention tool.[2, 81-83] The use of ART has been broadened from a therapeutic role to prevention, not just by reducing infectiousness as shown here, but also by its use as pre-exposure prophylaxis for reduction of susceptibility.[84] Our study reinforces the results of previous studies and meta-analyses[70, 85] that have shown how ART can reduce a person's infectiousness through sexual transmission in trial or intervention scenarios. The conditions under which this potential has been demonstrated do not seamlessly translate to a prediction of ART's effects in real-life situations, while our meta-analysis, with its inevitable limitations, illustrates that real-world studies of such interventions can provide useful estimates of their likely public health benefit.

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Figure legends

Figure 1 Forest plot summary of HIV-1 incidence rate estimates per heterosexual partnership for ART-stratified studies, with 95% confidence intervals. The first row for each study denotes couples where the index was receiving ART (forest plot boxes in blue); the second row denotes couples with no ART received (forest plot boxes in red). Size of boxes is proportional to number of couples, except for Watera et al 2009 (19) and Sullivan et al 2009 (20, 21) which do not provide these data. Baeten* et al (67) refers to ART for the initially uninfected partner rather than the index (pre-exposure prophylaxis) and is shown in the figure but has not been included in the summary estimates. Inc indicates per partnership HIV-1 incidence rate per 100 person-years; n, number of HIV-1 discordant couples; NR, not recorded in publication; x, number of HIV-1 transmitting couples.

Figure 2 Forest plot summary of HIV-1 incidence rate estimates per heterosexual partnership, with 95% confidence intervals, for non-ART-stratified studies from high-income settings, by direction of transmission: A. combined male-to-female and female-to-male transmission; B. male-to-female transmission; and C. female-to-male transmission. Estimates are classified as no ART use (up to 3% antiretroviral use by study participants – see Methods for classification criteria) and any ART use. Within these two groups, study estimates are plotted in order of increasing ART use and then chronologically. Size of boxes is proportional to number of couples. ART indicates reported percentage ART usage among index cases; Inc, per partnership HIV-1 incidence rate per 100 person-years; NR, not recorded in publication.

Figure 3 Forest plot summary of HIV-1 incidence rate estimates per heterosexual partnership, with 95% confidence intervals, for non-ART-stratified studies from low-income settings, by direction of transmission: A. combined male-to-female and female-to-male transmission; B.

male-to-female transmission; and C. female-to-male transmission. Estimates are classified as no ART use (up to 3% antiretroviral use by study participants – see Methods for classification criteria) and any ART use. Within these two groups, study estimates are plotted in order of increasing ART use and then chronologically. Size of boxes is proportional to number of couples. Hugonnet et al 2002 (34) provides two per partnership estimates: one risk for partners of infected individuals at baseline and one risk for partners of individuals who seroconverted during follow-up. ART indicates reported percentage ART usage among index cases; Inc, per partnership HIV-1 incidence rate per 100 person-years; NR, not recorded in publication.

Figure 4 Incidence rate ratios for HIV incidence rate estimates from low-income countries for combined male-to-female female-to-male transmission, by ART coverage of index cases within each study. Estimates included in the analysis are shown in Figure 3A. Li et al (64) and Guthrie et al (62) are included in the no-versus-any-ART use scenario but excluded from the other IRR calculations because their level of ART coverage was not reported. Error bars represent 95% confidence intervals.

Table

Table Meta-analysis of incidence rate ratios for ART-stratified study estimates, comparing ART use among index cases to no ART use.

	ART			
	No	Yes		
Setting	**Incidence[a] (95%CI)**	**Incidence[a] (95%CI)**	**Incidence rate ratio (95%CI)**	**Reference numbers of Studies**
All settings	3.6 (2.0-6.5)	0.2 (0.07-0.7)	0.09 (0.04-0.21)	(3, 18-22, 24, 25)
High-income[b]	0.6 (0.2-1.3)	0.0 (0.0-0.9)[c]	-	(22)
Low-income[b]	4.7 (2.9-7.8)	0.5 (0.2-1.2)	0.14 (0.06-0.34)	(18-21, 24, 25)

[a] Incidence rate/100 person-years. Analysis excludes data from Musicco et al[17] because ART use refers to zidovudine monotherapy only; Wang et al[23] and Melo et al[18] because no incidence estimates were provided; and Baeten et al[67] because ART use was among initially HIV-1 negative partners rather than index cases (i.e. PrEP). Sullivan et al data came from two conference abstracts.[20, 21]

[b] Cohen et al[3] excluded from analysis stratified by setting because results are from high- (US) and low- (Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand) income settings.

[c] Combination ART only; mono and dual therapy excluded.

n indicates number of study estimates; "-", insufficient observations.

Figure 1
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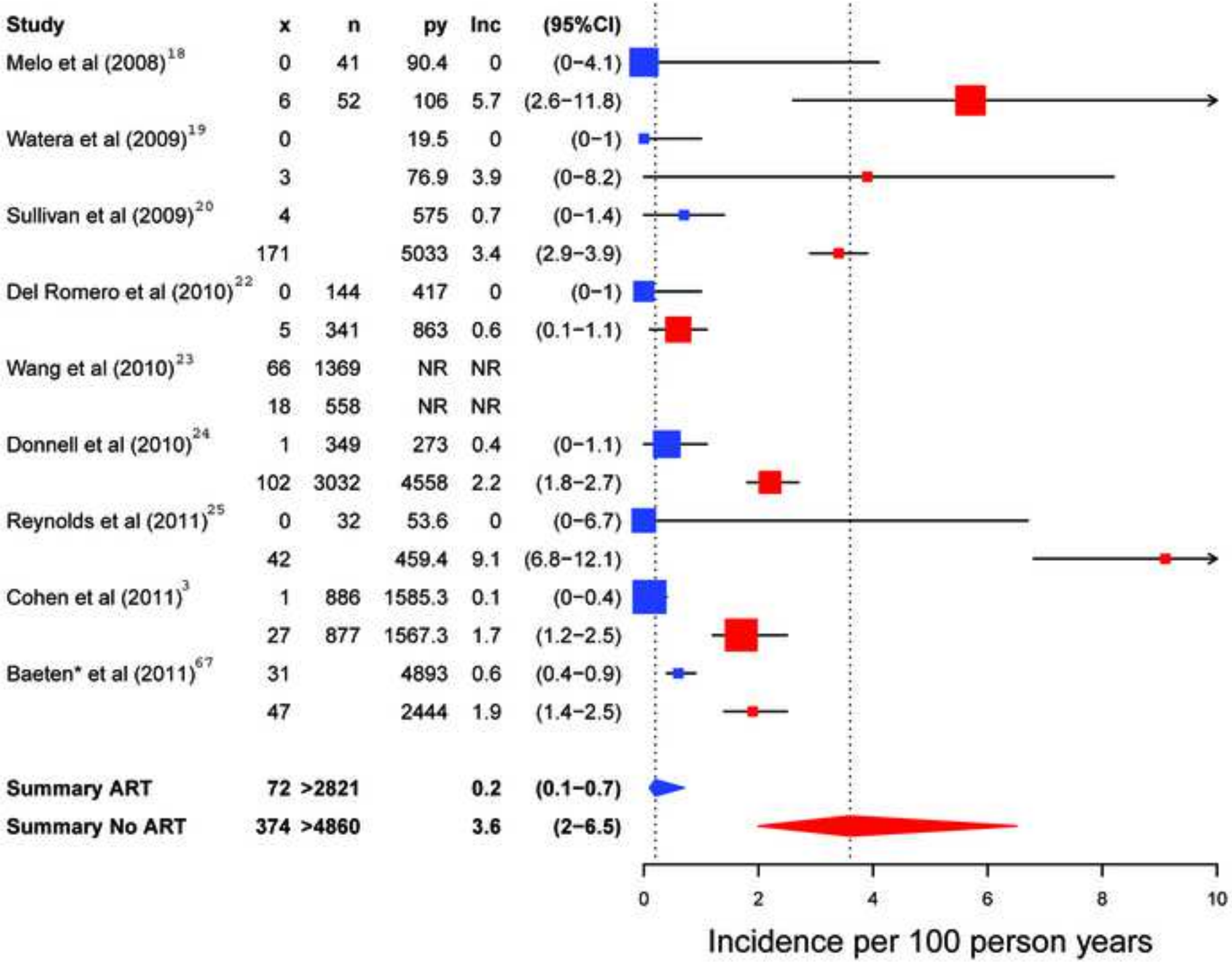

Figure 2a
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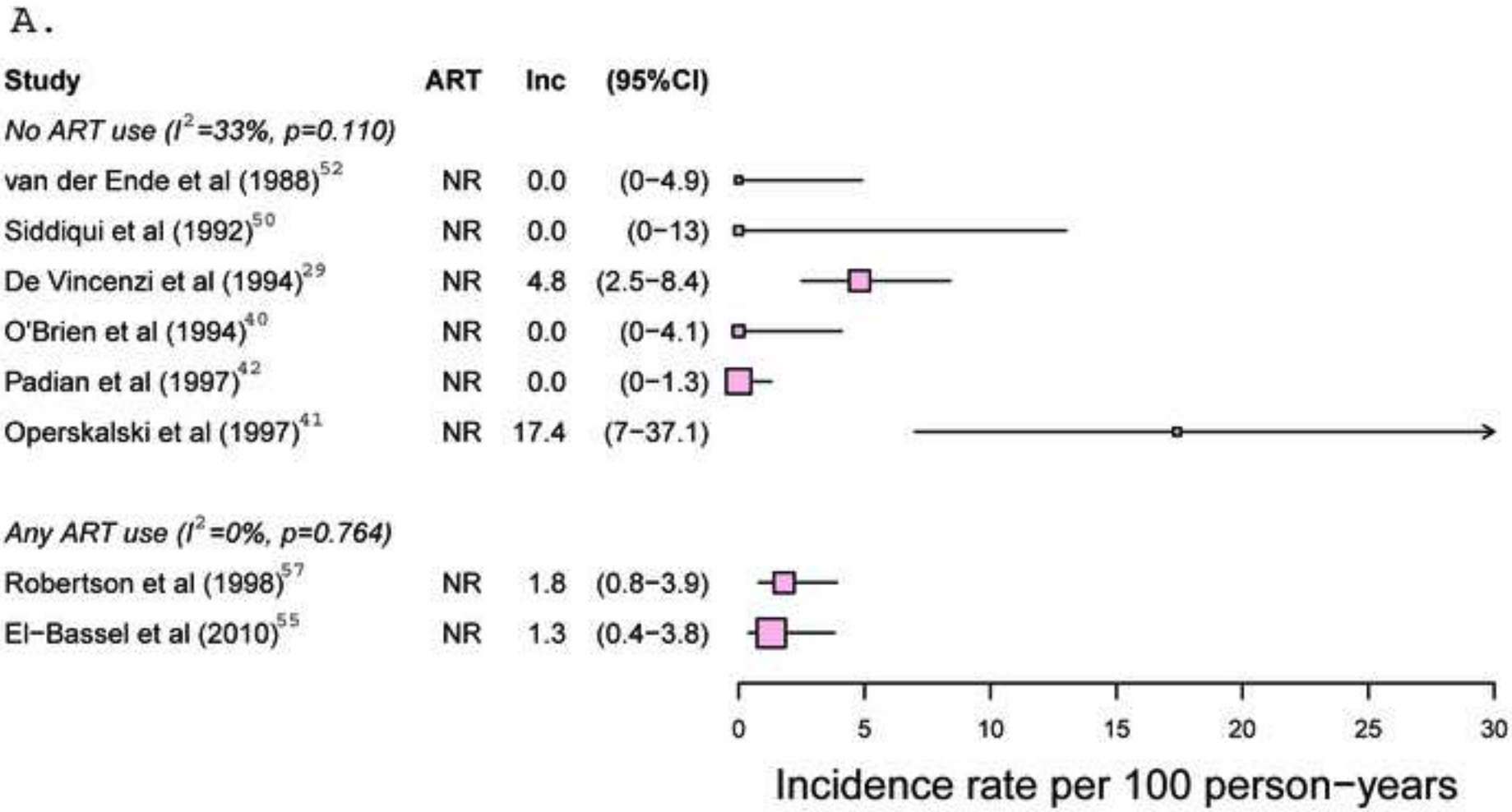

Figure 2b
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B.

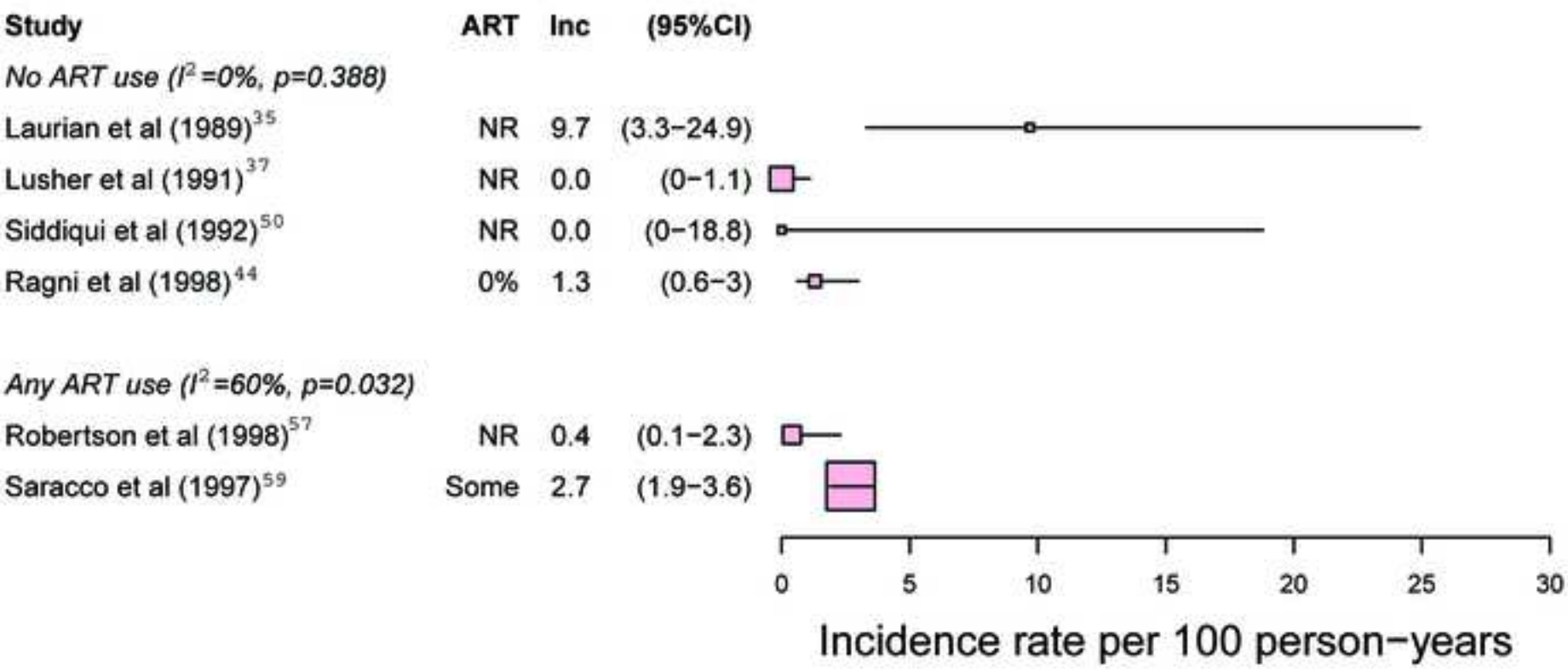

Figure 2c
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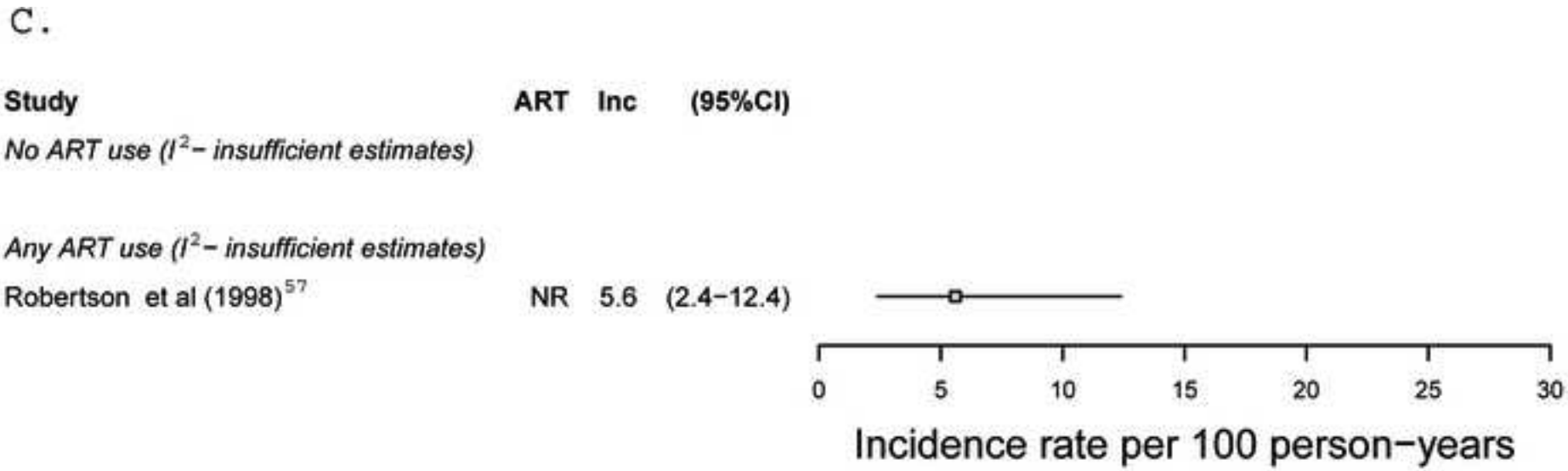

Figure 3a
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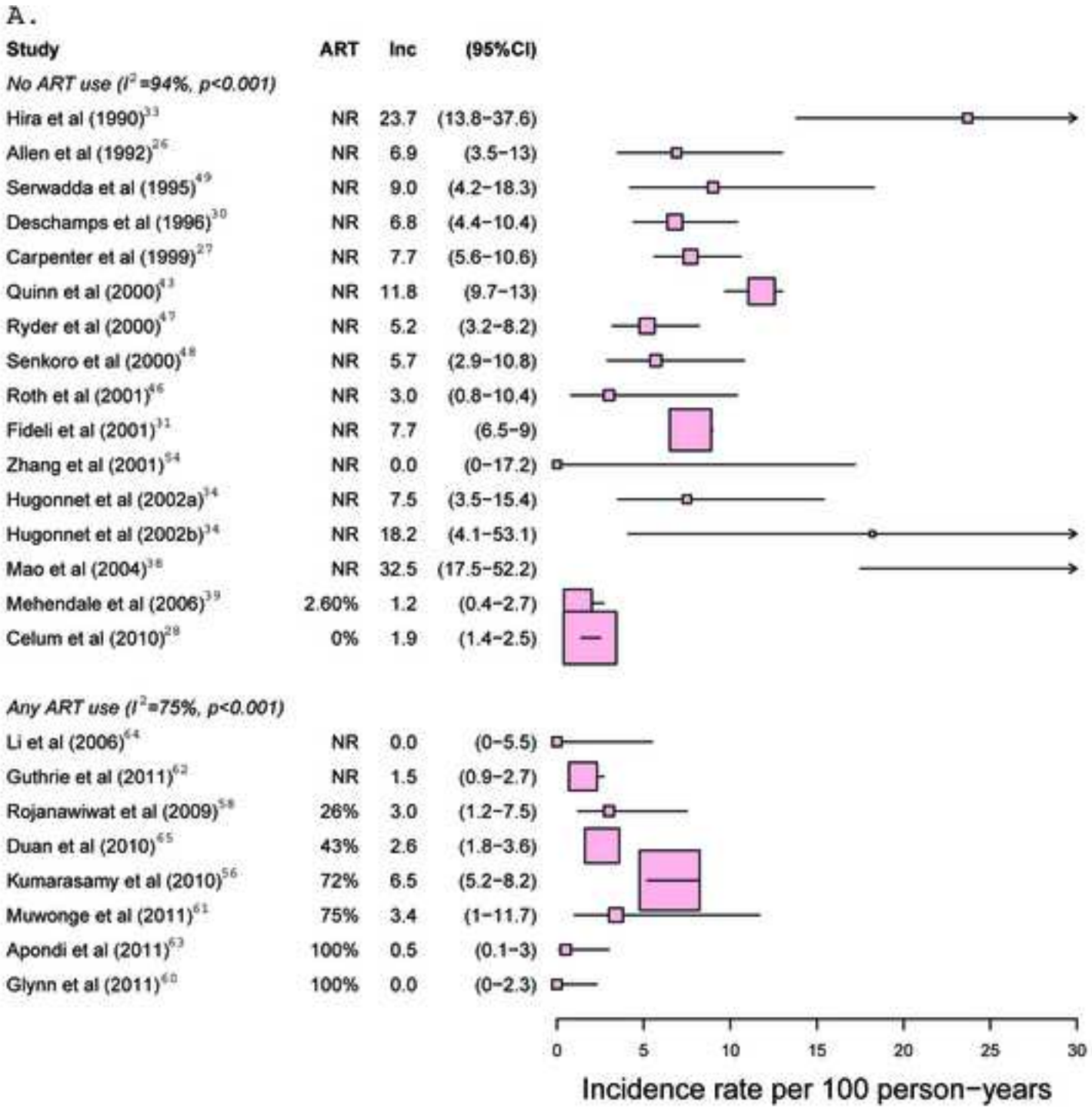

Figure 3b
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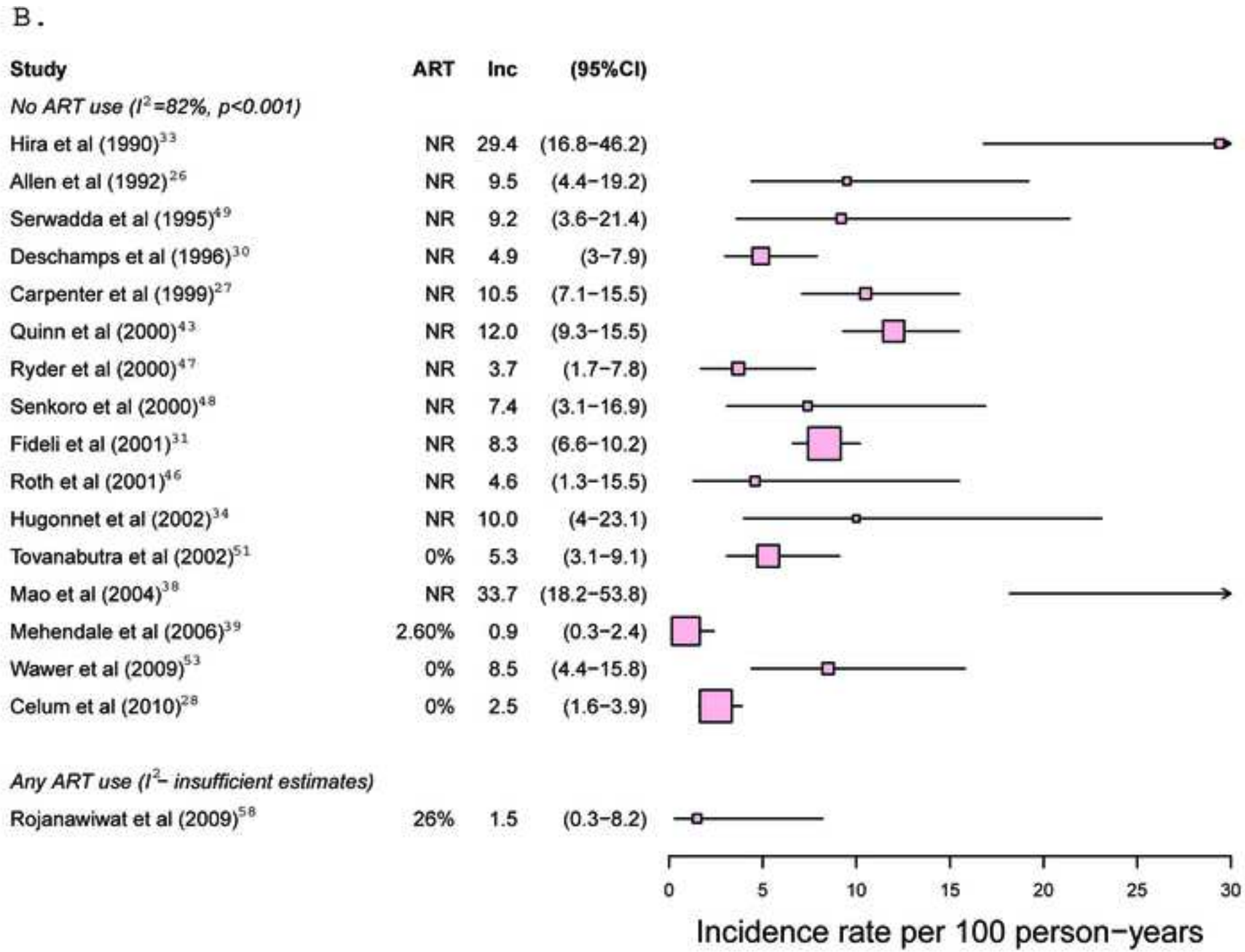

Figure 3c
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C.

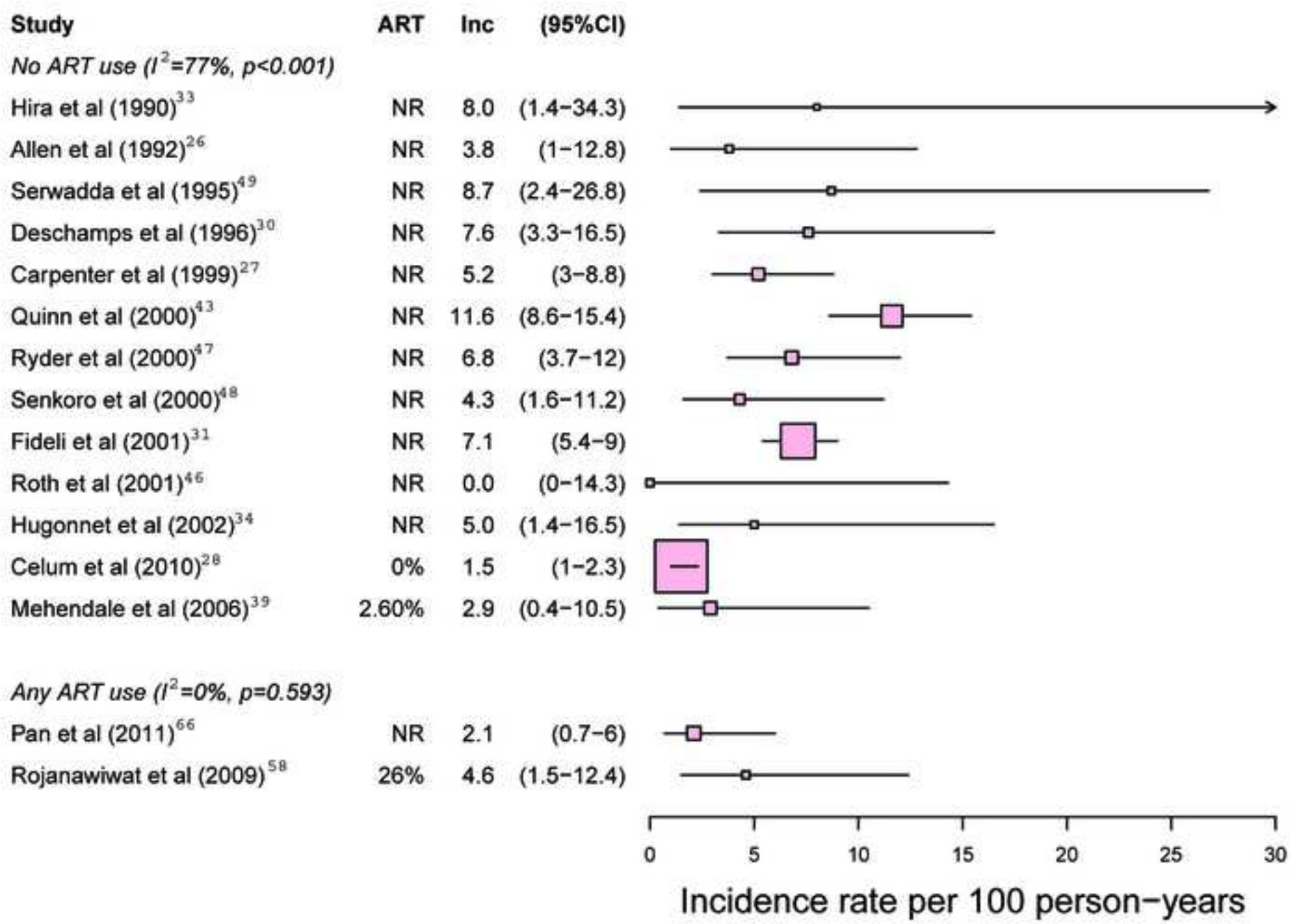
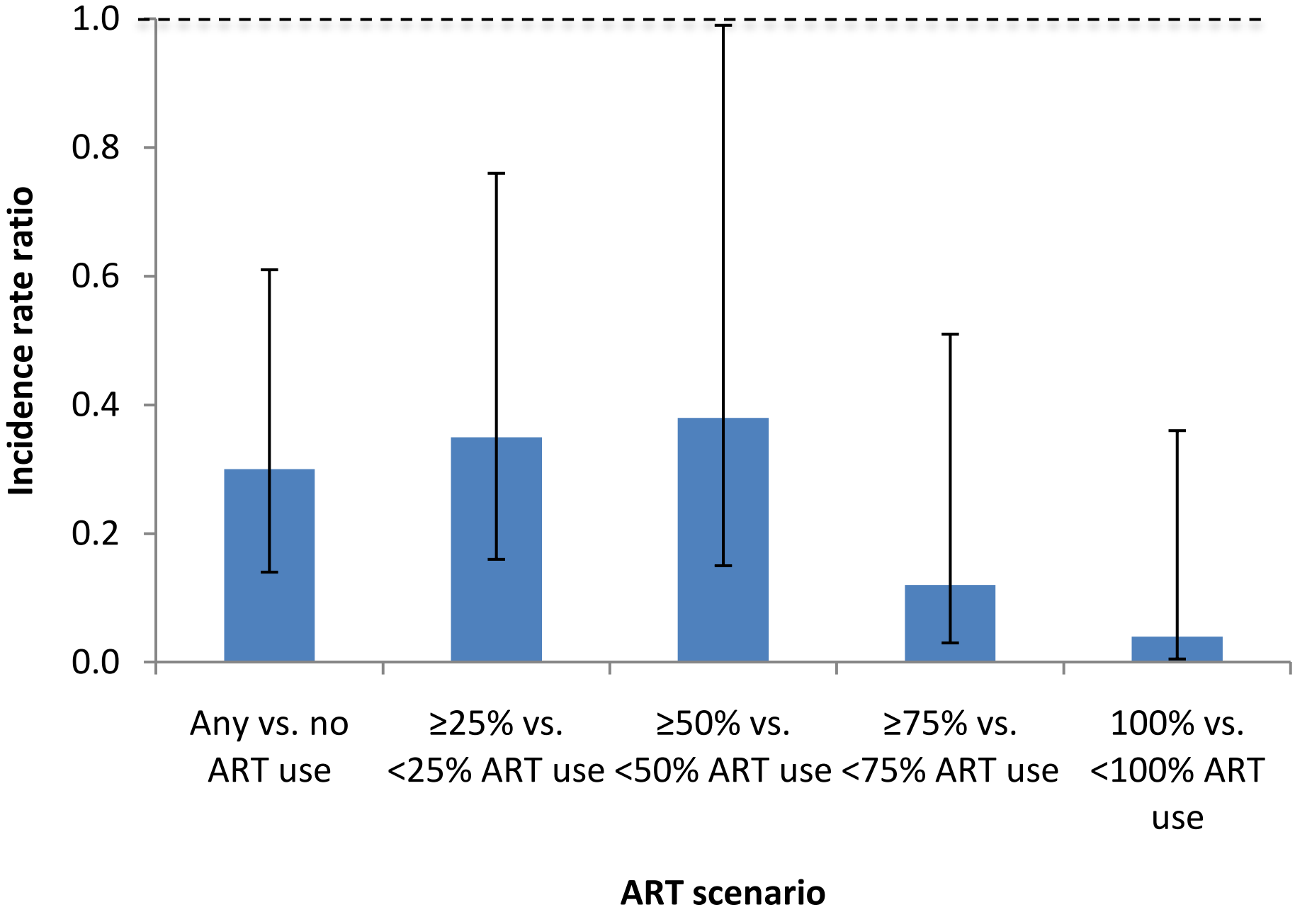


Figure 4


1.0
0.8
0.6
0.4
0.2
0.0
Incidence rate ratio
Any vs. no ART use
≥25% vs. <25% ART use
≥50% vs. <50% ART use
≥75% vs. <75% ART use
100% vs. <100% ART use
ART scenario

Supplemental Digital Content
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