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Does per-act HIV-1 transmission risk through anal sex vary by gender? An updated systematic review and meta-analysis

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Abstract

Quantifying HIV-1 transmission risk per act of anal intercourse (AI) is important for HIV-1 prevention. We updated previous reviews by searching Medline and Embase to 02/2018. We derived pooled estimates of receptive AI (URAI) and insertive AI (UIAI) risk unprotected by condoms using random effects models. Subgroup analyses were conducted by gender, study design, and whether antiretroviral treatment (ART) had been introduced by the time of the study.

Two new relevant studies were identified, one of which met inclusion criteria, adding three new cohorts and increasing number of individuals/partnerships included from 1869 to 14,277. Four studies, all from high-income countries, were included. Pooled HIV-1 risk was higher for URAI (1.25%,95%CI 0.55–2.23%,N=5,I^2=87%) than UIAI (0.17%,95%CI 0.09–0.26%,N=3,I^2=0%).

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Conflict of interest statement

We do not have any commercial or other association that might pose a conflict of interest.

The sole heterosexual URAI estimate (3.38%,95%CI 1.85–4.91%), from a study of 72 women published in a peer-reviewed journal, was significantly higher than the MSM pooled estimate (0.75%,95%CI 0.56–0.98%,N=4,p<0.0001) and higher than the only other heterosexual estimate identified (0.4%,95%CI 0.08–2.0%, based on 59 women, excluded for being a pre-2013 abstract). Pooled per-act URAI risk varied by study design (retrospective-partner studies: 2.56%,95%CI 1.20–4.42%,N=2 (one MSM, one heterosexual); prospective studies: 0.71,95%CI 0.51–0.93%,N=3 MSM, p<0.0001). URAI risk was lower for studies conducted in the ART era (0.75%, 95%CI 0.52–1.03%) than pre-ART (1.67%,95%CI 0.44–3.67%) but not significantly so (p=0.537).

Prevention messages must emphasise that HIV-1 infectiousness through AI remains high, even in the ART era. Further studies, particularly among heterosexual populations and in resource-limited settings, are required to elucidate whether AI risk differs by gender, region and following population-level ART scale-up.

Keywords

HIV; anal intercourse; transmission probability; infectivity; review; meta-analysis; heterosexual; MSM; antiretroviral therapy

Introduction

Anal intercourse (AI) drives HIV-1 epidemics among men-who-have-sex-with-men (MSM), and numerous studies have demonstrated that substantial proportions of heterosexual populations also practise AI[1, 2], potentially making it an important source of heterosexual HIV-1 transmission[3]. Quantifying the role of AI in HIV-1 epidemics is important for effective targeting of safe sex messages, for developing and implementing HIV-1 prevention technologies, and to inform mathematical models. Two previously published systematic reviews and meta-analyses have only included four studies providing estimates of the probability of HIV-1 transmission per AI act unprotected by condoms [4, 5].

Baggaley et al derived the first pooled receptive AI unprotected by condoms (URAI) per-act estimates in 2010 (1.37%, 95% confidence interval[95%CI] 0.20–2.54%)[5]. Patel et al[4] updated the review to February 2012, and derived a similar pooled estimate to Baggaley et al despite excluding a study included in Baggaley et al[6] and incorporating one new study (1.38%, 95%CI 1.02–1.86%)[5, 7]. Patel also reported a pooled estimate for insertive AI unprotected by condoms (UIAI): 0.1% (95%CI 0.0–0.3%). However, since their search, additional per-act estimates derived from large HIV-1 cohort datasets have been published[8, 9]. Given the scarce data on per-act AI HIV risk, it is important to update pooled estimates in light of new data, to reduce uncertainty and provide more reliable estimates to address public health questions and for use in models.

Addition of further data may enable evaluation of how HIV-1 infectiousness through AI varies by gender of participants, by ART use in the general population, region and other study characteristics. For example, recent evidence from animal studies suggests increased susceptibility of male rhesus macaques to HIV-1 acquisition following intrarectal challenge, compared to females (Diane Bolton, personal communication).

Our aim was to revise pooled estimates of URAI and insertive AI unprotected by condoms (UIAI) per-act HIV-1 transmission risk through incorporation of new data. We aimed to assess whether the addition of new data leads to significantly different pooled estimates of AI per-act risk; to evaluate the robustness of pooled estimates through sensitivity analysis; and to conduct subgroup analysis to investigate the influence of: 1) ART use among study participants or their partners; 2) gender; 3) region; and 4) study design.

Methods

The systematic review and meta-analysis were conducted in accordance with the PRISMA statement[10].

Search strategy

We conducted literature searches to identify new studies reporting data on per-act HIV-1 transmission risk through anal intercourse (AI) published since searches originally performed by Baggaley et al[5] (searched to September 2008), and Patel et al[4] (searched to February 2012). Our search was harmonised to ensure inclusion of terms employed previously[4, 5]. We used the following search string: (HIV OR HIV infections OR human immunodeficiency virus OR AIDS) AND (disease transmission OR infectious OR infectivity OR infectiousness OR transmissibility OR contact OR contacts OR per-contact OR per-act OR effectiveness) AND (sexual OR heterosexual OR homosexual OR coital OR intercourse OR anal). We searched Medline (Ovid), Embase (Ovid), CINAHL (EbscoHost), Web of Science, Global Health, and the Cochrane Library for studies published February 2012 to February 2018 inclusive. See Supplementary Material for further search details.

Unlike Baggaley et al[5], which focused on transmission risk estimates in the absence of ART, we also included studies where ART was likely used by a proportion of study participant partners. This change of inclusion criterion necessitated searching the exclusion lists of Baggaley et al[5] to ensure no studies were excluded based on ART use. We defined ART use to include therapeutic use by index (i.e. initially infected) partners, or pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) use by their (initially uninfected) partners.

Study selection

Inclusion criteria were randomised controlled trials, longitudinal studies (prospective or retrospective) or other empirical observational studies that directly reported estimates of per-act HIV-1 transmission risk through AI. We excluded studies that did not stratify AI risk, receptive versus insertive. Abstracts pre-2013, studies using sample sizes less than 10, and estimates derived from dynamic transmission modelling studies fitted to empirical HIV-1 prevalence curves, were excluded. While we included studies where study populations included individuals using ART, we aimed to include “real life studies” only, and so excluded studies where successful, suppressive ART of index partners was an inclusion criterion. Abstracts and other unpublished data older than five years were excluded because they were unlikely to result in peer-reviewed publication. There was no restriction by study year, region, or language of publication. AI per-act estimates included in previous systematic

reviews[4, 5], which we refer to as "original estimates", were included if they fulfilled the current inclusion criteria.

Data extraction

Study review was conducted independently by two separate authors (RFB and BNO). Data were extracted on the following study and participant characteristics: region, study design, study dates, gender (MSM or heterosexual study population), sample size, statistical method of estimating per-act risk, information on current and history of sexually transmitted infections (STIs), proportion of the study partner population using therapeutic ART and stage of HIV-1 infection of infected partners, condom use, intravenous drug use and ART use (PrEP or PEP). Discrepancies were resolved by consensus.

Statistical methods

We performed random-effects inverse-variance meta-analysis[11] on arcsin-transformed study estimates, which were back-transformed to the original scale to produce pooled estimates for per-act risk of HIV-1 transmission through URAI and UIAI. We presented available study estimates and pooled URAI and UIAI estimates in forest plots.

Meta-regression and subgroup analysis were used to explore potential sources of heterogeneity: gender; study design e.g. retrospective-partner study, prospective cohort of individuals; and ART use among partners. We assessed the robustness of pooled estimates and the influence of each individual study using leave-one-out sensitivity analysis (i.e., an influence analysis[11]). We also assessed the influence of relaxing our inclusion criteria to include Halperin et al (0.4%,95%CI 0.08–2.0%, excluded for being unpublished data pre-2013[6]). Heterogeneity across study estimates was assessed using I^2 statistics. Analysis was performed using R version 3.4.2[12] and the metafor package.

Results

Search results

Of 5336 unique studies published from February 2012 to February 2018 that we identified in our online searches, 4985 were excluded for non-relevance based on title, and 349 excluded based on abstract or full text. Two new articles directly reported per-act HIV-1 transmission probability estimates[8, 9]. No study had been excluded from our previous review based on ART use. Figure 1 illustrates the study selection procedure.

Studies included in each systematic review

Table 1 summarises per-act URAI and UIAI transmission risk estimates and study characteristics for estimates included in Baggaley et al 2010[5], Patel et al[4] and the current analysis. Detailed study characteristics are shown in Table S1, Supplementary Material. Data from 14,227 and 14,000 individuals/partnerships reported in the included studies were used to inform URAI and UIAI pooled estimates, respectively, compared to 1869 individuals/partnerships included in Baggaley et al[5]).

Of the two newly-identified studies[8, 9], Scott et al[8] was preferentially included. Smith et al[9] used data from EXPLORE[13] and VAX 004[14] studies, while Scott et al[8] additionally included Jumpstart[15] and HIVNET Vaccine Preparedness Study (VPS)[16, 17] data. Furthermore, Smith et al[9] did not account for risk factors such as ethnicity and drug use, or for heterogeneity in per-act risk, as Scott did. Scott et al[8] results also superseded and improved upon Vittinghoff et al[18] estimates, which were conducted by the same research group and included the same Jumpstart study data. Vittinghoff et al[18] data are therefore excluded. Halperin et al[6], included by Baggaley et al[5], was excluded for being a pre-2013 abstract. Further details of the advantages of Scott et al methodology, together with further information regarding excluded studies, are provided in Supplementary Material.

Study characteristics

Five URAI per-act study estimates reported by four studies[7, 8, 19, 20] and three UIAI estimates reported by two studies[7, 8] were included in the current analysis (Figure 1). Scott et al[8] provided independent estimates for pre-highly active antiretroviral therapy (HAART, hereafter referred to as ART: study data from 1992–1995) and early ART (study data from 1995–2003) eras, for both URAI and UIAI, because they combined data from four cohorts[13–17].

Data collection occurred between 1987 and 2007, although the earliest included publication did not state study dates[19]. URAI study estimates used data from Australia (N=1[7]), the US (N=3[8, 19]) and one multi-European country study[20] (Table 1). UIAI study estimates used data from Australia (N=1[7]) and the US (N=2[19]). All but one included study estimate (Leynaert et al[20], URAI) used data from MSM populations (Figure 2). Two URAI study estimates were from retrospective-partner studies[19, 20]; the remaining three used data from prospective cohorts of individuals[7, 8].

Three URAI study estimates used face-to-face interview (FTFI) data ([8, 20] and pre-ART[19]), a third used FTFI combined with telephone interviewing[7], and Scott et al's[8] early ART study estimate combined data gathered using FTFI (VAX004[14] and VPS[16, 17]) and audio computer-assisted self-interview (ACASI) (Explore[13]). For UIAI, all three study estimates were from prospective studies and data were collected using FTFI (pre-ART[19]), FTFI plus telephone interview[7] and FTFI plus ACASI combined (early ART[8]).

No studies reported on ART use of index partners. These data were not available from cohorts of individuals because they cannot be collected using this design[7, 8]. Authors discussed plausible ART coverage among infected partners but did not attempt to adjust estimates to account for ART use. Jin et al cited national data that 70% of Australian MSM used ART, and 75% of those had undetectable viral load[7]. For their early ART era estimates, Scott et al cited national data that only around 80% of those infected were aware of their status, and only 30% were virally suppressed, and that these levels were probably even lower during study periods. ART use was also not collected by retrospective-partner studies[19, 20]. Leynaert et al (retrospective-partner) reported that ART use data were not collected, but the study was conducted 1987–1992 and so use was minimal[20]. Similarly, DeGruttola et al (retrospective-partner) was published in 1989[19]. Therefore ART use was minimal, likely 0%, in 3 of 5 ([19, 20] and pre-ART[8]) and 1 (pre-ART[8]) of 3 URAI and UIAI study estimates,

respectively. The remaining two studies were classed as having >0% ART use[7, 8]. Although no included studies reported any information on PEP or PrEP use by study participants, its use is expected to be very low, given the dates of data collection (all before 2007).

Study size varied considerably. Retrospective-partner studies enrolled 155[19] and 72[20] couples, while cohorts followed between 1427[7] and 4581 (EXPLORE[13], included as part of Scott et al[8]) individuals. Number of AI acts with a partner appeared to vary considerably between individuals in the same study, with infectiousness similarly heterogeneous: Jin et al noted that 12 seroconversions in their cohort occurred as a result of <10 unprotected AI acts, while six men did not seroconvert despite reporting a total of 502 URAI acts with ejaculation[7]. Similarly, DeGruttola reported that 12 men reported >100 URAI acts with HIV-1-infected partners without seroconverting, while five men seroconverted after ≤10 such exposures to their infected partner and <3 partners outside the main relationship[19].

Meta-analysis results

The updated pooled estimate of per-act URAI HIV-1 risk of 1.25% (95%CI 0.55–2.23%,N=5, I^2=87%)[7, 8, 19, 20]) was considerably and statistically significantly higher (p=0.0026) and more heterogeneous than the UIAI risk (0.17%, 95%CI 0.09–0.26%, I^2=0%,N=3[7, 8]). Pooled and study estimates are shown in Figure 2.

Subgroup analysis

Table 2 shows the results of the subgroup analysis. The pooled per-act URAI HIV-1 risk was significantly lower for MSM (0.75% 95%CI 0.56–0.98%,N=4) than the sole heterosexual population estimate (3.38% 95%CI 1.85–4.91%,N=1) (p<0.0001). However, relaxing inclusion criteria to include Halperin et al[6] (0.4% 95%CI 0.08–2.0%), one of just two identified estimates from heterosexual populations, excluded for being an abstract pre-2013, reduced the pooled heterosexual URAI estimate to 1.57% (95%CI 0.00–5.87%,N=2,I^2=91%) which was no longer significantly different from the MSM estimate (p=0.370, Figure S1). MSM per-act estimates for both URAI and UIAI showed relatively little heterogeneity (I^2<0.1%).

Pooled per-act URAI risk from studies where ART was likely to have been used by >0% of sexual partners was lower than half (0.75%,95%CI 0.52–1.03%N=2) that without ART use (1.67%,95%CI 0.44–3.67%,N=3) but this difference was not significant (p=0.537). Per-act UIAI risks were similar by ART use (0.14%,95%CI 0.04–0.29% for 0% use vs. 0.18%, 95%CI 0.09–0.31% for >0% use, p=0.955). When assessed in multivariate meta-regression analysis, only study design was (borderline) significantly associated with magnitude of URAI transmission risk (p=0.055), accounting for >99% of the heterogeneity across study estimates (R^2=99.9%). Meta-regression analysis could not be undertaken for UIAI given the small number of estimates (N=3, all from MSM populations).

Sensitivity analysis

In the leave-one-out sensitivity analysis, only the omission of the heterosexual URAI estimate from Leynaert et al[20] among heterosexual couples substantially reduced heterogeneity (I^2 reduced from 87% to 0%), producing an all-MSM pooled URAI estimate

(0.75%, 95%CI 0.56–0.98%) (Figure S1). Adding the Halperin et al[6] study estimate did not substantially influence the URAI pooled estimate (1.10%,95%CI 0.50–1.94%,I^2=85%, Figure S1). The pooled UIAI estimate was also not affected by any individual study estimate because study estimates were remarkably homogeneous (Figure 2, I^2=0).

Discussion

Our updated review incorporates recently-published study estimates which strengthen the analysis and robustness of pooled per-act risk estimates by greatly increasing the number of included individuals (data from 14,227 individuals/partnerships, compared to 1869 individuals/partnerships in Baggaley et al[5]). Our results highlight that risk of HIV-1 transmission through AI remains high (1.25%,95%CI 0.55–2.23%,N=5 for URAI; 0.17%, 95%CI 0.09–0.26%,N=3 for UIAI), and raises the question of whether HIV risk during URAI is higher for women than MSM, also highlighting the lack of data from resource-limited settings.

Our new pooled estimate is slightly lower than the previous pooled URAI estimates by Baggaley et al[5] and Patel et al[4], and a slight, nonsignificant increase on the previous pooled UIAI estimate reported by Patel et al[4]. We have explored sources of heterogeneity as far as possible, given the few included study estimates. In fact, URAI and UIAI estimates from MSM study populations were remarkably homogeneous (I^2=0%). It is unclear whether gender or study design accounted for the heterogeneity across all URAI study estimates, but even after omitting the highest URAI estimate (i.e., the sole heterosexual estimate[20], see Figure S1), the estimate of HIV-1 transmission risk through URAI remained high (0.75%, 95%CI 0.56–0.98%). Even considering only study estimates which were conducted since the introduction of ART, risk remained nearly 10-fold riskier than unprotected receptive vaginal intercourse (VI): URAI 0.75%,95%CI 0.52–1.03% vs. unprotected receptive VI: 0.08%, 95%CI 0.06–0.11%[21]. UIAI risk in the ART era is more than four-fold riskier than insertive VI (0.18%,95%CI 0.09–0.31% vs. 0.04%,95%CI 0.01–0.14%[21]).

It is unclear why the Leynaert et al URAI risk among females was so high (3.38%, 95%CI 1.85–4.91%[20]). All studies were conducted in industrialised countries, so difference by region is unlikely. Heterosexual study participants reported monogamy and no STIs. However, a large proportion of index cases (65% of the entire sample) were infected by intravenous drug use, so while their sexual partners reported no such use, it is possible that they underreported HIV-1 exposure and acquired HIV-1 via this route. Leynaert et al was a retrospective-partner study, and in multivariate meta-regression, study design explained a larger fraction of the variation across URAI estimates than gender, so the apparent difference by gender may be confounded by study design. HIV risk during URAI is especially uncertain because the only other identified URAI estimate among females, which was excluded for being a pre-2013 abstract, provided a markedly lower estimate than Leynaert et al (0.4% 95%CI 0.08–2.0%): it is in fact lower than all the five included URAI study estimates. This clouds the picture of potential differential risk by gender. The sample sizes of both Leynaert and Halperin were low (n<80), and given heterogeneity in infectiousness between individuals and by stage of HIV-1 infection[25], the widely different estimates may be due to chance (95%CIs are wide and overlapping: 1.85–4.91%[20] and 0.08–2.0%[6]). The lack

of study design detail for the Halperin abstract makes it difficult to postulate reasons for the low estimate. However, our main results, based on the a priori exclusion of Halperin et al, mean we cannot exclude the possibility that women have an intrinsically higher URAI HIV-1 acquisition risk than men. This warrants further research, given its implication for HIV-1 prevention. There may exist underlying biological differences between the rectal compartments of males and females, rendering women more susceptible to infection. For example, there may be sex hormone differences, which alter rectal mucosal immunology and enhance susceptibility[26]. However, there has been little research conducted in this area to date, and recent evidence from animal studies suggested an opposite effect (Diane Bolton, person communication). Alternatively, variation in sexual practices by gender may play a role. MSM may be more likely to anticipate receptive AI and therefore prepare to reduce the likelihood of trauma (such as use of lubricants, cleansing the colon). Qualitative research has suggested that heterosexual AI often occurs without the explicit prior consent of women[27, 28].

Our meta-regression found the pooled URAI risk among studies conducted in the ART era, when there was likely to be >0% ART use among sexual partners of study participants, was less than half that from pre-ART studies, but this difference failed to reach statistical significance, probably partly because of the small number of estimates and also the variability across estimates in the pre-ART era (from 0.60%[8] to 3.38%[20]). For both URAI and UIAI, Scott et al pre-ART and early ART era per-act study estimates were very similar. Scott et al explained this lack of a significant association by suggesting that a relatively low proportion of infected MSM were on ART and had a suppressed viral load during the years in which data were collected. However, Jin et al[7] URAI estimates were also high, and similar to Baggaley et al[5] 2010's pooled estimate (without ART use), despite the likely high ART use in the Australian study population. [22, 23]In fact, omitting the high heterosexual URAI estimate from Leynaert et al[20] makes pre-ART and ART era URAI estimates more comparable: 1.00% (95%CI 0.22–2.33%) and 0.75% (95%CI 0.52–1.03%), respectively.

However, as Jin and Scott et al followed individuals rather than couples over time, information on infection status, current ART use and viral load of each sexual partner of each study participant was missing: data that are required to control for ART use adequately. [22, 23,29]While evidence shows that HIV-infected individuals with ART-mediated viral suppression do not transmit HIV-1[22-24], our findings demonstrate that HIV-1 infectiousness through AI remains high, indicating that many HIV-infected individuals practising condomless AI are not on effective ART and remain infectious.

With ART coverage having continued to increase, now taken at earlier stages of HIV-1 infection and more tolerable regimens increasing levels of adherence, and with the advent of PrEP, it is expected that any future AI HIV-1 infectiousness studies would find further, significant reductions in infectiousness estimates. However, [22, 23,29]HIV-infected MSM engaging in nondisclosing (not disclosing their HIV status to their partner), condomless AI have been found to be less ART-adherent and more likely to have unsuppressed HIV[31] and so it is important to collect further data to monitor whether these population-level AI HIV-1 infectiousness estimates continue to decline over time.

There are some limitations to our findings, mainly due to scarcity of data. The few study estimates prevent us exploring the sources of heterogeneity in greater depth. Only one heterosexual study estimate was included, so it is difficult to know if differences in infectiousness by gender are real or confounded by study design. Included estimates were from only two study types: retrospective-partner and prospective studies of individuals. Both have advantages and disadvantages. For example, prospective studies are less likely to experience recall bias and therefore estimating numbers of sex acts may be more precise than retrospective studies. Recruiting individuals is easier than recruiting couples, providing larger sample sizes. Partner studies provide more reliable data on index cases, particularly regarding HIV-1 status, and in theory on their patterns of ART use. Studies of individuals rely on participants' perceptions of the status of their sexual partners. However, couples may be more likely to underreport sexual partners outside the main relationship because of social desirability bias. Leynaert et al only reported from monogamous couples[20], but all other study estimates included participants reporting multiple partners and multiple sexual behaviours. It can be challenging to estimate transmission risks using such data, especially where the HIV-1 infection and ART use status of sexual partners cannot be known with certainty: there are a lot of unknowns which must be accounted for. Different studies have used different statistical techniques to attempt this. All but one study used FTFI to gather sexual behaviour data, which may lead to social desirability bias[32]. These limitations may over- or underestimate per-act risk, and together with the small number of studies identified, and the variation in methods of data analysis, mean we recommend further data gathering using more confidential techniques such as ACASI, and analysis using standardised statistical methods, to increase comparability of studies and robustness of pooled estimates. Publication bias and selective reporting are likely to be low, because these studies are not assessing significance or effectiveness outcomes. This bias could be investigated using funnel plots if more study estimates became available.

In conclusion, current evidence suggests that practising unprotected AI continues to confer a high risk of HIV-1 transmission, particularly URAI, even in the ART era. More research is needed as important knowledge gaps regarding HIV-1 risk during AI remain. Given the high HIV-1 transmission risk associated with AI, it is remarkable that more research has not been conducted to evaluate if AI transmissibility differs by gender, high- and low-income countries and following ART scale-up at the population level. Standardised methods should be used to aid comparability between studies, and longitudinal studies reporting HIV transmission rates should be encouraged to use these methods to additionally report per-act estimates. Even today it continues to be important to design safe sex messaging that promotes the use of condoms in addition to interventions such as PrEP and other biotechnologies to prevent HIV-1 transmission through AI for both MSM and heterosexual populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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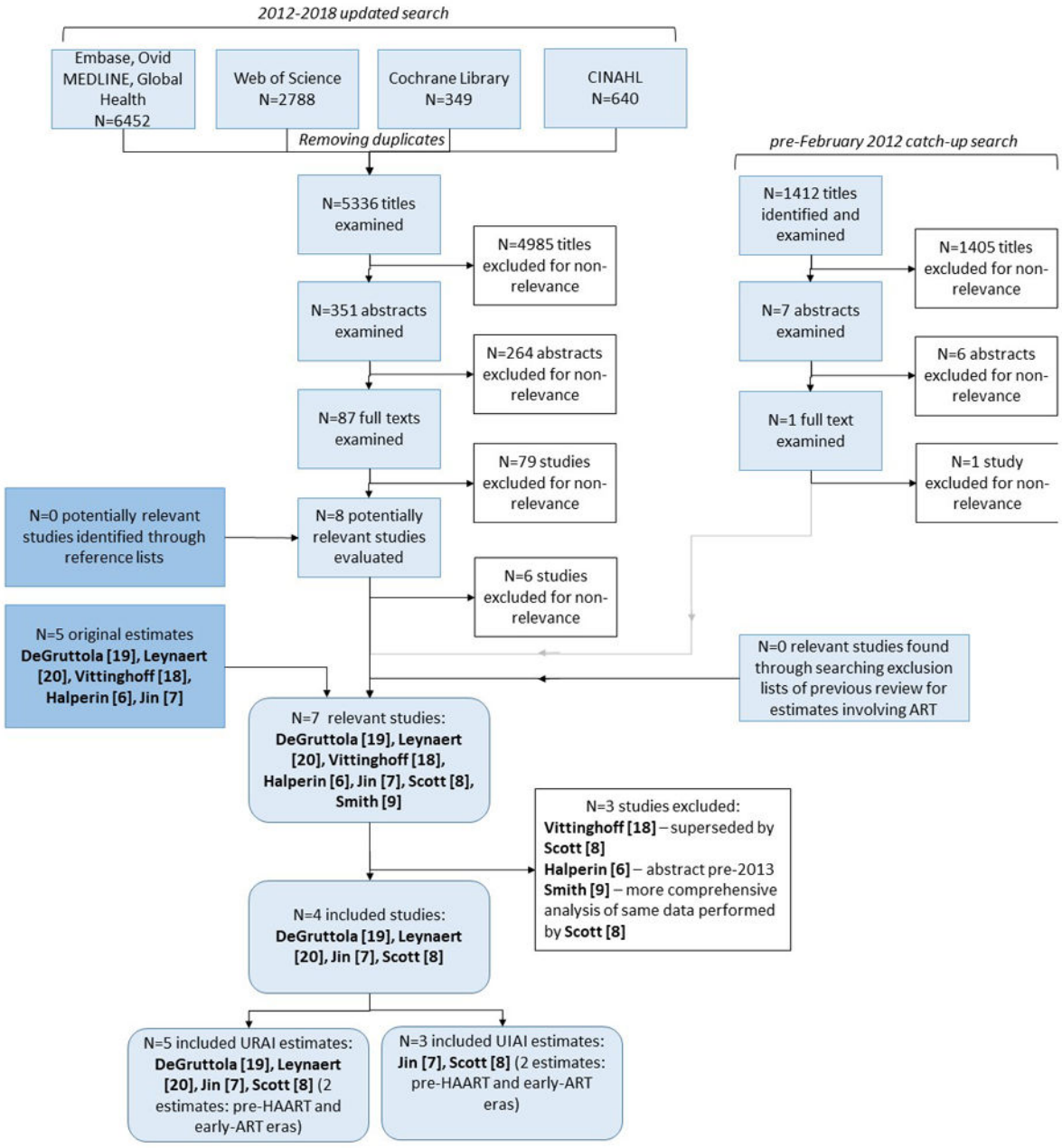

Figure 1.

Flowchart summary of the literature search, comprising an update search from 2012 to February 2018 and a catch-up search to ensure the pre-2012 search included the same search terms as the updated search. “Original estimates” refers to studies included in either previous review[4, 5]. ART – antiretroviral therapy; CINAHL – Cumulative Index to Nursing and Allied Health Literature; UIAI – unprotected insertive anal intercourse; URAI – unprotected receptive anal intercourse.

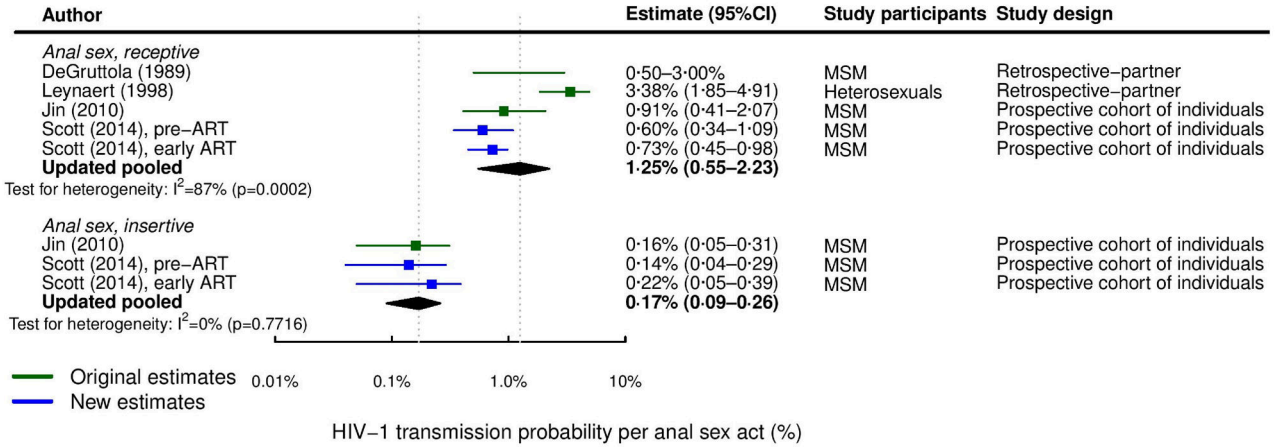

Figure 2.

Forest plot of studies estimating per-act HIV-1 transmission probability through anal intercourse. “Original estimates” refers to studies included in either previous review[4, 5].

Table 1

Summary of per-act anal intercourse HIV-1 transmission probability studies included in meta-analyses reported by Baggaley et al 2010[5], Patel et al[4], and the current analysis.

Reasons for study exclusion are provided, where applicable.

Study	Population, sample size, setting	Design. Study dates	Per-act estimate, % (95%CI)	Included in:		
				Baggaley et al 2010	Patel et al 2014	Current analysis
URAI						
DeGruttola et al 1989[19]	132 MSM (some infected, some uninfected) plus 155 sexual partners, US	Retrospective-partner, study dates not stated	**0.5-3.0**[a]	✓	✓	✓
Leynaert et al 1998[20]	72heterosexual couples (male index) practising AI, Europe	Retrospective-partner, 1987-1992	**3.38** (1.85-4.91)	✓	✓	✓
Vittinghoff et al 1999[18]	1583 MSM, US	Prospective cohort of individuals, 1992-1994	**0.82** (0.24-2.76)	✓	✓	× Superseded[c]
Halperin et al 2002 (abstract)[6] plus S.C. Shiboski (personal communication, 2003)	59 heterosexual couples (male index), US	Retrospective-partner, participants recruited 1985-1986	**0.4** (0.08-2.0)[b]	✓	× Estimate interpreted as a relative risk	× Abstract pre-2013
Jin et al 2010[7]	1427 MSM, Australia	Prospective cohort of individuals, 2001-2007	**0.91**[d] (0.41-2.07)	× Data not yet published	✓	✓
Scott et al 2014[8]	MSM, US Pre-ART N=1813 [c] Early ART N=10,760[f]	Four prospective cohorts of individuals: Jumpstart 1992-1995[15], EXPLORE 1999-2003[13], VAX 004 1998-2002[14], VPS 1995-1999[16, 17]	**0.60**[e] (0.34-1.09) **0.73**[f] (0.45-0.98)	× Data not yet published	× Not included[g]	✓
Smith et al 2015[9]	3490 MSM, US	Two prospective cohorts of individuals: EXPLORE 1999-2003[13], VAX 004 1998-2002[14]	**1.11**[h] (0.75-1.62) **0.41**[i] (0.30-0.55)	× Data not yet published	× Data not yet published	× Study data reported by Scott et al 2014 [8]
UIAI						
Vittinghoff et al 1999[18]	1583 MSM, US	Prospective cohort of individuals, 1992-1994	**0.06** (0.02-0.19)	× Estimate is per partner of HIV-1 positive or unknown serostatus	✓	× Estimate is per partner of HIV-1 positive or unknown serostatus; superseded[c]
Jin et al 2010[7]	1427 MSM, Australia	Prospective cohort of	**0.16** (0.05-0.31)	×	✓	✓

Study	Population, sample size, setting	Design. Study dates	Per-act estimate, % (95%CI)	Included in:		
				Baggaley et al 2010	Patel et al 2014	Current analysis
		individuals, 2001-2007		Data not yet published		
Scott et al 2014[8]	MSM, US Pre-ART N=1813[c] Early ART N=10,760[f]	Four prospective cohorts of individuals: Jumpstart 1992-1995[15], EXPLORE 1999-2003[13], VAX 004 1998-2002[14], VPS 1995-1999[16, 17]	**0.14**[e] (0.04-0.29) **0.22**[f] (0.05-0.39)	× Data not yet published	× Not included[g]	✓
Smith et al 2015[9]	3490 MSM, US	Two prospective cohorts of individuals: EXPLORE 1999-2003[13], VAX 004 1998-2002[14]	**0.27**[h] (0.18-0.41) **0.20**[i] (0.15-0.27)	× Data not yet published	× Data not yet published	× Study data reported by Scott et al 2014 [8]

NS – not stated.

[a]Range rather than 95%CI reported by publication.

[b]Range rather than 95%CI.

[c]Estimate superseded by reanalysis of the dataset reported in Scott et al 2014[8].

[d]Jin et al[7] published per-act risk with ejaculation taking place inside the rectum (1.43%, 95%CI 0.48-2.85%) and with withdrawal prior to ejaculation (0.65%, 95%CI 0.15-1.53%). Per-act estimate regardless of when ejaculation occurred was reported in Patel et al[4], obtained from study authors (James Jansson, personal communication).

[e]Data taken from the pre-ART era (estimates use data from the Jumpstart study[15]).

[f]Data taken from the early ART era (estimates use data from the EXPLORE[13], VAX 004[14], and VPS[16, 17] studies).

[g]Data mentioned in text but not included in meta-analysis

[h]Data taken from the EXPLORE study[13], restricted to study participants reporting never using condoms.

[i]Data taken from the VAX 004 study[14], restricted to study participants reporting never using condoms.

Table 2

Subgroup analysis: meta-analytic pooled per-act HIV-1 transmission probability estimates for URAI and UIAI stratified by population subgroup (heterosexual and MSM), study design (retrospective-partner and prospective cohort of individuals) and plausible extent of ART use by sexual partners (0% versus >0%).

Estimate type	Pooled estimate, % (95%CI)	P[a]	$I^{2,b}$, (%)	N	References	p-value[a]
URAI						
Gender						
Women	3.38 (1.85-4.91)	1.000	0.0%	1	[20]	
MSM	0.75 (0.56-0.98)	0.278	<0.1%	4	[7, 8, 19][c]	p<0.0001
Study design						
Retrospective-partner	2.56 (1.20-4.42)	0.1296	56.5%	2	[19, 20]	
Prospective cohort of individuals	0.71 (0.51-0.93)	0.722	0.0%	3	[7, 8][c]	p<0.0001
Plausible extent of ART use by sexual partners						
0%	1.67 (0.44-3.67)	<0.0001	87.6%	3	[8, 19, 20][d]	
>0%	0.75 (0.52–1.03)	0.650	0.0%	2	[7, 8][d]	p=0.537
Pooled estimate	**1.25 (0.55-2.23)**	**0.0002**	**87.3%**	**5**	**[7, 8, 19, 20][c]**	
UIAI[e]						
Plausible extent of ART use by sexual partners						
0%	0.14 (0.04-0.29)	1.000	0.0%	1	[8]	
>0%	0.18 (0.09-0.31)	0.604	0.0%	2	[7, 8][c]	P=0.955
Pooled estimate	**0.17 (0.09-0.26)**	**0.7716**	**0.0%**	**3**	**[7, 8][c]**	

ART – antiretroviral treatment; N – number of study estimates; NA – not applicable; P – P-value; Q – heterogeneity statistic; UIAI – unprotected insertive anal intercourse; URAI – unprotected receptive anal intercourse.

[a] "P" is the p-value for heterogeneity of the pooled estimate; "p-value" is the metaregression p-value defining the significance of the difference in pooled estimates between the two subgroups.

[b] I^2 is calculated as described in Higgins et al[33]. I^2 lies between 0 and 100%; 0% indicates no observed heterogeneity and larger values show increasing heterogeneity.

[c] Two URAI and UIAI estimates were provided by Scott et al[8], using data from studies conducted in the pre-ART and early ART eras.

[d] Scott et al's[8] pre-ART estimates are classed as likely 0% ART use; its early ART estimates are classed as >0% use.

[e] All UIAI study estimates used data from prospective cohorts of individuals from MSM populations and so subgroup analysis could not be conducted gender or design.