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

Running title: Meta-analysis of HIV-1 risk of anal sex

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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%). 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

218 receptive vaginal intercourse (VI): URAI 0.75%,95%CI 0.52-1.03% vs. unprotected receptive VI:
219 0.08%,95%CI 0.06-0.11%[21]. UIAI risk in the ART era is more than four-fold riskier than insertive VI
220 (0.18%,95%CI 0.09-0.31% vs. 0.04%,95%CI 0.01-0.14%[21]).

221 It is unclear why the Leynaert et al URAI risk among females was so high (3.38%, 95%CI 1.85-
222 4.91%[20]). All studies were conducted in industrialised countries, so difference by region is unlikely.
223 Heterosexual study participants reported monogamy and no STIs. However, a large proportion of
224 index cases (65% of the entire sample) were infected by intravenous drug use, so while their sexual
225 partners reported no such use, it is possible that they underreported HIV-1 exposure and acquired
226 HIV-1 via this route. Leynaert et al was a retrospective-partner study, and in multivariate meta-
227 regression, study design explained a larger fraction of the variation across URAI estimates than
228 gender, so the apparent difference by gender may be confounded by study design. HIV risk during
229 URAI is especially uncertain because the only other identified URAI estimate among females, which
230 was excluded for being a pre-2013 abstract, provided a markedly lower estimate than Leynaert et al
231 (0.4% 95%CI 0.08-2.0%): it is in fact lower than all the five included URAI study estimates. This clouds
232 the picture of potential differential risk by gender. The sample sizes of both Leynaert and Halperin
233 were low (n<80), and given heterogeneity in infectiousness between individuals and by stage of HIV-
234 1 infection[25], the widely different estimates may be due to chance (95%CIs are wide and
235 overlapping: 1.85-4.91%[20] and 0.08-2.0%[6]). The lack of study design detail for the Halperin abstract
236 makes it difficult to postulate reasons for the low estimate. However, our main results, based on the
237 a priori exclusion of Halperin et al, mean we cannot exclude the possibility that women have an
238 intrinsically higher URAI HIV-1 acquisition risk than men. This warrants further research, given its
239 implication for HIV-1 prevention. There may exist underlying biological differences between the
240 rectal compartments of males and females, rendering women more susceptible to infection. For
241 example, there may be sex hormone differences, which alter rectal mucosal immunology and
242 enhance susceptibility[26]. However, there has been little research conducted in this area to date, and
243 recent evidence from animal studies suggested an opposite effect (Diane Bolton, person

244 communication). Alternatively, variation in sexual practices by gender may play a role. MSM may be
245 more likely to anticipate receptive AI and therefore prepare to reduce the likelihood of trauma (such
246 as use of lubricants, cleansing the colon). Qualitative research has suggested that heterosexual AI
247 often occurs without the explicit prior consent of women[27, 28].

248 Our meta-regression found the pooled URAI risk among studies conducted in the ART era, when
249 there was likely to be >0% ART use among sexual partners of study participants, was less than half
250 that from pre-ART studies, but this difference failed to reach statistical significance, probably partly
251 because of the small number of estimates and also the variability across estimates in the pre-ART era
252 (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
253 estimates were very similar. Scott et al explained this lack of a significant association by suggesting
254 that a relatively low proportion of infected MSM were on ART and had a suppressed viral load during
255 the years in which data were collected. However, Jin et al[7] URAI estimates were also high, and
256 similar to Baggaley et al[5] 2010's pooled estimate (without ART use), despite the likely high ART use in
257 the Australian study population. In fact, omitting the high heterosexual URAI estimate from Leynaert
258 et al[20] makes pre-ART and ART era URAI estimates more comparable: 1.00% (95%CI 0.22-2.33%) and
259 0.75% (95%CI 0.52-1.03%), respectively.

260

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

267 With ART coverage having continued to increase, now taken at earlier stages of HIV-1 infection and more
268 tolerable regimens increasing levels of adherence, and with the advent of PrEP, it is expected that any

269 future AI HIV-1 infectiousness studies would find further, significant reductions in infectiousness
270 estimates. However, HIV-infected MSM engaging in nondisclosing (not disclosing their HIV status to their
271 partner), condomless AI have been found to be less ART-adherent and more likely to have unsuppressed
272 HIV[31] and so it is important to collect further data to monitor whether these population-level AI HIV-1
273 infectiousness estimates continue to decline over time.

274 There are some limitations to our findings, mainly due to scarcity of data. The few study estimates
275 prevent us exploring the sources of heterogeneity in greater depth. Only one heterosexual study
276 estimate was included, so it is difficult to know if differences in infectiousness by gender are real or
277 confounded by study design. Included estimates were from only two study types: retrospective-
278 partner and prospective studies of individuals. Both have advantages and disadvantages. For
279 example, prospective studies are less likely to experience recall bias and therefore estimating
280 numbers of sex acts may be more precise than retrospective studies. Recruiting individuals is easier
281 than recruiting couples, providing larger sample sizes. Partner studies provide more reliable data on
282 index cases, particularly regarding HIV-1 status, and in theory on their patterns of ART use. Studies of
283 individuals rely on participants' perceptions of the status of their sexual partners. However, couples
284 may be more likely to underreport sexual partners outside the main relationship because of social
285 desirability bias. Leynaert et al only reported from monogamous couples[20], but all other study
286 estimates included participants reporting multiple partners and multiple sexual behaviours. It can be
287 challenging to estimate transmission risks using such data, especially where the HIV-1 infection and
288 ART use status of sexual partners cannot be known with certainty: there are a lot of unknowns which
289 must be accounted for. Different studies have used different statistical techniques to attempt this.
290 All but one study used FTFI to gather sexual behaviour data, which may lead to social desirability
291 bias[32]. These limitations may over- or underestimate per-act risk, and together with the small
292 number of studies identified, and the variation in methods of data analysis, mean we recommend
293 further data gathering using more confidential techniques such as ACASI, and analysis using
294 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.

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Tables

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	✓	✓

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
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] **0.73**[f]	(0.34-1.09) (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] **0.41**[i]	(0.75-1.62) (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 individuals, 2001-2007	**0.16**	(0.05-0.31)	× Data not yet published	✓	✓

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
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] **0.22**[f]	(0.04-0.29) (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] **0.20**[i]	(0.18-0.41) (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, 19c]	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, 8c]	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, 20d]	
>0%	0.75 (0.52-1.03)	0.650	0.0%	2	[7, 8d]	p=0.537
Pooled estimate	**1.25 (0.55-2.23)**	**0.0002**	**87.3%**	**5**	**[7, 8, 19, 20c]**	
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, 8c]	P=0.955
Pooled estimate	**0.17 (0.09-0.26)**	**0.7716**	**0.0%**	**3**	**[7, 8c]**	

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.

Figure legends

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].