Risk of sexual transmission of human immunodeficiency virus with antiretroviral therapy, suppressed viral load, and condom use: a systematic review

Appendix 4 (as submitted by the authors): Description of included systematic reviews and meta-analyses

Supervie et al., 2014 (1)

The authors of this systematic review sought to estimate the per-act risk of HIV transmission for heterosexual condomless sex in serodiscordant couples with an HIV-positive partner on combination ART in clinical care for more than six months (attending regular check-ups every 3-6 months), and with viral load and CD4 measurement. They searched PubMed/Medline; Embase; Cochrane Library; Web of Science; conference abstracts up-to August 2013; and scanned references of included articles to identify articles that met the inclusion criteria. From the six studies that met all of the inclusion criteria, one randomised controlled trial (RCT), two retrospective cohort studies, and three prospective cohort studies were included. Four studies were set in low- and middle-income countries; one was set in a high-income country; and another set in low-, middle-, and high-income countries. Unpublished data was received from three of the primary study authors. The type of sexual acts and direction of transmission were not considered in the context of ART. The studies included both serodiscordant couples on combination ART with follow-up (1,672) and couples not on ART with follow-up (4,818).

Four studies reported genetically linked HIV transmissions where the index partner was on combination ART that occurred during 2772.8 person years of follow-up, with three of those occurring when the index partner was on combination ART for less than six months. The authors concluded that the available data did not support zero risk of HIV transmission under combination ART. Using Bayesian modelling, the per-act risk of HIV transmission for unprotected sex with HIV infected individuals on combination ART in comprehensive care for more than six months (whether or not virally suppressed) was estimated to be less than 13:100,000 based on approximately one transmission for 113,480 sex acts across the included studies, of which approximately 17% were not condom protected.

The primary limitation of this review was limited generalizability of the results, as the majority of serodiscordant couples included were heterosexual (97%) and reported condom use was high in most studies. Another limitation was the inability to examine HIV transmission in the context of effect modifiers such as HIV genotype, type of intercourse, host genetics or sexually transmitted infections (STIs) on the HIV transmission. The authors assess the quality of included studies using the Cochrane Risk of Bias (ROB) tool and Newcastle-Ottawa Scale. Our assessment of the quality of this review using AMSTAR yielded a score of seven out of 11. The authors declared no conflicts of interest and funding was provided by Sidaction and Agence Nationale de Research sure la SIDA et les Hepatites Virales.

Patel et al., 2014 (2)

The authors of this systematic review aimed to develop updated estimates of HIV transmission risk for various transmission routes (vertical, parenteral, sexual), and determine the effect of various factors that modify transmission (e.g. ART, condom use). The authors performed a multi-step literature search, which began with a comprehensive review of recent systematic reviews and meta-analyses. They searched Medline, Embase, CINAHL, Web of Science, Global Health, and Cochrane Library from 2008-February 2012. They also searched the reference list of a 2005 Centers for Disease Control and Prevention (CDC) summary and the 2011 British Pre-exposure Prophylaxis Guidelines. Subsequently, they searched PubMed from 2008 to May 2013 to identify articles examining factors that modify HIV transmission risk. Studies in both high-income and low- and middle-income settings were identified, although the authors

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attempted to focus on data from high-income areas. A number of estimates for unprotected sexual acts were either obtained from previous meta-analyses or newly calculated.

There was a 96% (relative risk of 0.04; 95% CI: 0.01-0.27) and an 80% (relative risk of 0.20; 95% CI: 0.08-0.47) reduction in the risk of transmission for serodiscordant partners where the index partner was taking ART (based on the HIV Prevention Trials Network [HPTN] 052 trial) and using condoms (based on Weller at al., 2002 (3)), respectively. The risk reduction obtained from the combination of ART and condoms was assumed to be 99.2% (95% CI: 0.04-0.20). In the case of receptive anal sex, a meta-analysis of four studies of MSM and heterosexual couples in the US, Europe and Australia, reported the risk of HIV transmission was estimated at 138 transmissions per 10,000 exposures (95% CI: 102-186). With ART, condoms, or a combination of the interventions, the estimates risks were 6.0 (95% CI: 1.0-29), 28 (95% CI: 11-70), and 1.1 (95% CI:0.2-7.3) transmissions per 10,000 exposures, respectively. Insertive anal sex was estimated to carry a risk of 11 transmissions per 10,000 exposures (95% CI: 4-28) based on two studies of MSM and heterosexual couples. With ART, condoms, or both, the estimates risks were 0.4 (95% CI: 0.1-3.0), 2.0 (95% CI: 1.0-8.0), and 0.09 (95% CI: 0.01-0.72) transmissions per 10,000 exposures, respectively. The risk estimate for receptive vaginal sex was adapted from a previous meta-analysis of 10 studies of heterosexual sex partners, and was eight transmissions per 10,000 exposures (95% CI:6-11) (4). Using ART, condoms, or both, led to risk estimates of 0.32 (95% CI: 0.06-1.7), 1.6 (95% CI: 0.63-4.1), and 0.06 (95% CI: 0.01-0.43) transmissions per 10,000 exposures, respectively. Insertive vaginal sex was also adapted from the same previous meta-analysis (with three studies included in this estimate) and estimated to carry a risk of four transmissions per 10,000 exposures (95% CI: 1-14) (4). ART, condoms, or both, led to estimates of 0.16 (95% CI: 0.02-1.3), 0.8 (95% CI: 0.16-3.9), and 0.03 (95% CI: 0.00-0.32) transmissions per 10,000 exposures, respectively. The authors estimated the risk of receptive or insertive oral sex based on two studies of MSM and heterosexual couples to be low but non-zero as they were unable to provide a precise point estimate (95% CI: 0-4 events based on zero events over 8,965 acts) (5,6). They were unable to estimate the effect of ART or condoms on this estimate.

The primary limitation of this review is that relative risks for ART and condoms from previous studies were used and applied to risk estimates from other studies. The relative risk of 0.04 with ART comes from the HPTN 052 trial which primarily enrolled heterosexual couples, and thus it may not be appropriate to apply this estimate to risk estimates for receptive anal sex among MSM, for example. In addition, condom use was high in the HPTN 052 trial (~96%) and thus likely overestimates the effect of treatment. When used simultaneously, condom and ART use could reduce the overall risk of HIV transmission by up to 99.2% (though this reduction may be overestimated). Other elements of the HPTN 052 trial that may influence the relative risk, such as frequent HIV testing and counselling of couples. Furthermore, the estimates in this study do not take into account confounders such as STI, HIV infection stage, and circumcision (the authors did examine the effects of these factors, but not in the context of ART or condoms). Another limitation is the inclusion of cross-sectional or retrospective studies which may be subject to recall bias. Similarly, from a practical perspective, most individuals often do not practice a single sex act exclusively in a given encounter, which complicates estimates of risk for various acts. The authors suggest that their broad and overlapping confidence intervals for transmission risk reflect the imprecision introduced by such limitations. The authors did not assess the quality of included studies. Our assessment of the quality of this review using AMSTAR yielded a score of two out of 11. The authors reported no conflict of interest and are

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affiliated with the US CDC, but the findings/conclusions reported are those of the authors, not necessarily the official position of the CDC.

Loutfy et al., 2013 (7)

The purpose of this systematic review and meta-analysis was to estimate the risk of HIV transmission between heterosexual serodiscordant couples where the index partner was on combination ART and virally suppressed. Searches for this review were conducted using Medline (1950-November 2012), Embase (1980-November 2012), CINAHL (1980-November 2012), and Web of Science (2004-November 2012). Relevant articles were also identified through a hand search of journals (unspecified journals; June 2010-November 2012) and conference proceedings (Conference on Retroviruses and Opportunistic Infections, 2008-2011; International AIDS Conference, 2008 and 2010; and International AIDS Society Conference, 2009 and 2011). Only quantitative observational studies and RCTs were considered. A total of six studies were identified with participants from Brazil, Spain, Thailand, the USA, Thailand, India, Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia, Zimbabwe, and Malawi.

Among the 991 heterosexual couples with confirmed suppressed viral load (below 50-500 copies/mL) at the time of transmission, the pooled estimate of HIV transmission was zero per 100 person-years (95% CI: 0.00-0.05) with zero transmissions over 2,064 person-years of follow-up across three studies and low heterogeneity(I^2: 0%). Conversely, among the 6,070 heterosexual couples with unconfirmed suppression of viral load at the time of sexual encounter, the pooled estimate of HIV transmission was 0.18 per 100 person-years (95% CI: 0.05-0.40) with four transmissions over 8,170 person-years of follow-up across three studies and an I^2 statistic of 0%. Using the upper limit of the sensitivity analysis (0.01) and assuming a life expectancy of 20-50 years, the lifetime risk of HIV transmission to the uninfected partner is 0.2-0.5%.

While the study authors were aware that sexual act frequency, the presence of STIs, and the direction of sexual transmission may modify transmission rate, there was not enough data available to present these results. The authors note that condom use was relatively high in the studies and that confirmed suppressed viral load does not capture the index partner's viral load at the moment of transmission or the level of HIV RNA in their genital secretions. The authors state that the methodological quality of the studies was reasonable. Our assessment of the quality of this review using AMSTAR yielded a score of seven out of 11. The authors note that the first author, Mona R. Loutfy, is a PLOS ONE Editorial Board member. Funding was received from the Canadian Institutes of Health Research.

Anglemyer et al., 2013 (8)

This Cochrane review aimed to evaluate if ART is associated with a lower risk of HIV transmission, especially in patients with ≥350 CD4 cells/μL. The authors searched in PubMed; Embase; Cochrane Central Register of Controlled Trials; Web of Science; LILACS from January 1987 to August 2012; as well as conference abstracts. They also undertook hand searching of the reference lists of included studies for additional references. Ten studies met the inclusion and exclusion criteria, nine observational studies (two in high-income settings and seven in low-and-middle incomes settings) and one RCT (conducted mainly in low- and middle-income settings) in serodiscordant couples. The type of sexual acts and direction of transmission were not considered in the context of ART.

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HIV transmission risk estimates in studies differed between the RCT and the observational studies; however, overall there were 1,016 transmissions among couples with an index partner on ART and 1,096 among couples with an index partner not on ART. A virologically linked HIV incidence of one per 1,000 person-years (95% CI: 0-5) was observed for the RCT. This corresponds to an incidence rate ratio of 0.04 (95% CI: 0.00-0.27) on ART versus not on ART based on 1,750 participants. A pooled HIV incidence of 31 per 1,000 person-years (95% CI: 19-51) was reported for observational studies based on 46,204 participants across nine studies. This corresponds to a summary incidence rate ratio of 0.58 (95% CI: 0.35-0.96 with high heterogeneity [I^2: 64%]) on ART versus not on ART. A sensitivity analysis of the observational studies was undertaken which removed studies with monotherapy or lack of adequate per-time data which resulted in a reported HIV incidence of 17 per 1,000 person-years (95% CI: 8-36) based on 46,560 participants across seven studies. This corresponds to a summary incidence rate ratio of 0.36 (95% CI: 0.17-0.75 with high heterogeneity [I^2: 62%]) on ART versus not on ART. The follow-up period of observational studies used in these estimates was not reported, nor the absolute number of transmissions that occurred in different groups.

An important limitation of this review was that the vast majority of the couples in the included studies were long-term heterosexual partners; therefore, the findings of this review may not be generalizable to all types of sexual relationships or populations, such as MSM. Other limitations that influence the HIV transmission estimates are that observational studies did not report risk of HIV transmission stratified by the index case's baseline CD4 and there was no analysis performed to control for cofactors, such as number of exposures, circumcision, HIV viral load, STIs, condom use, or potency of ART. Despite these limitations, our assessment of the quality of this review using the AMSTAR tool yielded a score of nine out of 11. The authors used GRADE tables to systematically assess the quality of evidence from the included studies. The authors reported no conflicts of interest.

Baggaley et al., 2013 (9)
The aim of this systematic review and meta-analysis was to estimate HIV infectiousness within serodiscordant couples with various levels of ART use. They searched Pubmed, Science Direct and National Library of Medicine Gateway (NLM Gateway) online databases up to July 31, 2011. They also searched abstracts from the 2010 and 2011 IAS, Conference on Retroviruses and Opportunistic Infections (CROI), and International Society of Sexually Transmitted Research (ISSTR) conferences. They identified 50 studies: 17 in high-income settings and 34 in low- and middle-income settings. The first part of the analysis considered studies where the risk of HIV transmission was stratified by whether the index partner was using ART (prospective cohort studies and one RCT) and the second part considered studies reporting any ART use by the index partner (prospective cohort studies). These studies did not specify the risk of HIV incidence by type or frequency of sex acts.

Among studies with ART and non-ART groups (seven studies comprising 2,821 couples on ART and 4,860 not on ART), the summary incidence rate was 0.2 per 100 person-years (95% CI: 0.07-0.7) among ART-receiving couples based on six total transmissions over 3,013.8 person-years of follow-up. In comparison, the summary incidence rate was 3.6 per 100 person-years (95% CI: 2.0-6.5) for couples not on ART (based on 356 transmissions over 12663.6 person-years of follow-up). This corresponds to a 91% (95% CI: 79-96) per-partner incidence rate reduction with ART use. When the summary incidence rate among ART users was stratified by setting, a single study in high-income setting found a transmission risk of 0.0 per 100 person-

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years (95% CI: 0.0-0.9) over 417 person-years of follow-up, while low- and middle-income studies found an estimate of 0.5 per 100 person-years (95% CI: 0.2-1.2) (5).

Summary estimates were not calculated for studies with 'any' ART use (with no comparison group), but a range of incidence rate estimates were reported. For combined sex acts, two studies in high-income settings found risks of 1.3 per 100 person-years (95% CI: 0.4-3.8) and 5.2 per 100 person-years (95% CI: 2.4-10.8) respectively, although neither study reported on level of ART use (10,11). Studies in low-income settings found risks as low as 0.0 per 100 person-years (95% CI: 0.0-6.5) in one study with 100% reported ART use, and as high as 6.3 per 100 person-years (95% CI: 2.5-15.2) in a study with 26% reported ART use (12,13). Other studies had similar HIV transmission estimates and reported a range of ART use levels (with several not reporting on level of ART use). For male-to-female transmission only, two studies in high-income settings reported estimates of 0.4 per 100 person-years (95%CI 0.1-2.3; with level of ART use not reported) and 2.7 per 100 person-years (95% CI: 1.9-3.6; with 'some' ART use) (11,14). These studies had a combined follow-up of 7.1 years. One study of male-to-female transmission in a low-income setting reported a risk estimate of 1.5 per 100 person-years (95% CI: 0.3-8.2) with a reported level of ART use of 26% over follow-up of 1.7 years (13). For female-to-male transmission, one study in high-income setting reported a risk estimate of 5.6 per 100 person-years (95% CI: 2.4-12.4) but did not report on level of ART use (11). These studies had a combined total follow-up of three years. Two studies examining female-to-male transmission in low-income settings reported risks of 2.1 per 100 person-years (95% CI: 0.7-6.0) without reporting on the level of ART use and 4.6 per 100 person-years (95% CI: 1.5-12.4) with 26% ART use (13,15). These studies had a combined follow-up of 4.6 years.

The studies in low-income settings reporting any or no ART use did not report the frequency of sexual acts and it is unclear how included studies measured level of ART use. Similarly, the authors based their definition of 'any' ART use on inferences from study dates and are therefore unable to confirm which transmitting couples were on ART or not on ART. The estimates from studies without a 'no ART' comparison group should therefore be interpreted with much caution. The authors warn against generalizing estimates across populations due to the potential differences in distribution of risk factors such as stage of infection, viral subtype, STIs, types of sexual acts, and circumcision, in the included studies, which likely confound results. Similarly, meta-analysis results must be interpreted with caution in light of the heterogeneous data included. There are also several limitations due to the reliance on studies of serodiscordant couples. For example, a high proportion of monogamous couples likely resulted in a lower prevalence of concomitant risk factors (e.g. other STIs) and, conversely, there may be confounding because of HIV infection acquisition from outside the partnership (in couples who are not truly monogamous). Studies enrolling serodiscordant couples may have also included varying amounts of risk-reduction counselling and may therefore underestimate true HIV transmission risk. Included studies are also limited by small sample sizes and short follow-ups. The authors did not assess the quality of included studies. Our assessment of the quality of this review using AMSTAR yielded a score three out of 11. The review was funded by the Wellcome Trust, GlaxoSmithKline, UK Medical Research Council, the Bill and Melinda Gates Foundation, the EU FP7, and Imperial College London Junior Research Fellowship Programme. One author was supported by an unrestricted educational grant from GlaxoSmithKline, and the others declared no other conflicts of interest.

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Baggaley et al., 2010 (16)
Baggaley et al. set out to determine estimates of HIV transmission risk associated with unprotected anal intercourse (UAI) in the context of ART. The search strategy, which involved searches in PubMed, Science Direct, and NLM Gateway is as reported in Boily et al., 2009 (4). The authors estimated per-act sexual transmission risk using retrospective partner, and simple prospective studies, and derived per-partner risk estimates from retrospective partner, prospective serodiscordant couple, and simple prospective studies. The authors then developed two functions to model transmission risk with successful ART for various sex acts, based on data from a cohort study in Rakai, Uganda (Function 1), and a cohort study in Zambia (Function 2) (17,18).

The overall summary incidence rates were 1.4% per act of receptive UAI (95% CI: 0.2-2.5) and 40.4% per partner (95% CI: 6.0-74.9) with no significant differences between opposite sex and same sex couples. The summary incidence rate for insertive UAI was 21.7% per partner (95% CI: 0.2-43.3) and the rate for combined and insertive UAI was 39.9% (95% CI: 22.5-57.4). This estimate is lower after adjusting for potential exposures from outside the partnerships and other exposures. Based on function 1, the per-act risk of HIV transmission for unprotected receptive vaginal or insertive anal intercourse with successful ART is approximately 0.013%, while receptive UAI yields an approximate per-act risk of 0.061% (a 96% risk reduction due to ART). The per-partner risk over 1,000 sex acts ranges from 12.2-20.2% as the proportion of those sex acts that are anal intercourse goes from 0-20%. Alternatively, using function 2, the per-act risk of HIV transmission for unprotected receptive vaginal or insertive anal intercourse with successful ART is approximately 0.0002%, while receptive UAI yields an approximate per-act risk of 0.0011% (a 99.9% risk reduction). It is important to note that function 1 assumes a linear relationship between infectiousness and log serum viral load. Based on function 2, the per-partner risk over 1000 sex acts is less than 0.5% even if UAI represents 20% of the acts, and becomes less than 1% for men who have sex with men (MSM) practicing receptive and insertive UAI with equal frequency, or 1.1% for MSM practicing receptive UAI exclusively. This function two assumes a logistic relationship between viral load and infectiousness.

An important caveat to these models is that transmission risk becomes much larger if there is viral rebound due to treatment failure. It is also important to note that the authors concede that "drawing conclusions on the use of [highly active ART] for HIV prevention is beyond the scope of this article." They suggest that the results for ART be interpreted with caution in light of the contrasting results obtained using function 1 versus function 2, and that this modelling data (which varies substantially depending on assumptions of the model) cannot substitute for empirical data. Another important limitation is that this modelling is not able to take into account other confounding factors (e.g. co-infection with STIs, other risk factors). The authors did not assess the quality of included studies. Our assessment of the quality of this review using AMSTAR yielded a score of three out of 11. The study was funded by the Wellcome Trust, UK Medical Research Council, and Bill and Melinda Gates Foundation, and the authors reported no conflicts of interest.

Attia et al., 2009 (19)
The authors of this systematic review and meta-analysis sought to estimate the HIV transmission risk associated with sexual intercourse when combination ART is used or by viral load. They searched the Medline and Embase databases from 1996-2009, as well as conference abstracts from the International AIDS Society (IAS) conference (2001-2008) and CROI (1997-2009). They identified 16 studies (longitudinal cohort studies of heterosexual

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serodiscordant couples) that met their criteria and encompassed 5,021 couples in 11 cohorts with the majority (8/11) in low- and middle-income countries.

Overall, HIV transmission risk when the index partner was on ART (regardless of viral load) was 0.46 per 100 person-years (95% CI: 0.19-1.09) based on five studies in which five transmissions occurred over 1,098 person-years of follow-up. Two studies showed zero transmissions after 291 person-years of follow-up in participants with viral loads less than 400 copies/mL on ART with a HIV transmission risk of zero per 100 person-years (95% CI: 0-1.27). Although there were zero transmissions, the authors suggest that the data is compatible with one infection every 79 person-years of follow-up (one per 7,900 sex acts at an average of 100 contacts per year). When viral load was greater than 400 copies/mL on ART, transmission risk was zero (95% CI: 0-5.79) based on one study with 52 person-years of follow-up in which no transmissions occurred. In couples where the index partners was not on ART, the rate of transmission was 0.16 (per 100-person years (95% CI: 0.02-1.13) based on one transmission event in five studies. An included cohort from Rakai, Uganda provided further evidence through reporting a per-act estimate stratified by viral load (79). This study found that HIV risk when the index partner's viral load was less than 1,700 copies/mL was 0.0001 per sexual act, and when viral load was greater than 38,500 copies/mL the risk increased to 0.0023 per sexual act. Conversely, when a seropositive partner is not adhering to ART, the overall estimate of risk of transmission between the serodiscordant partners was 5.64 per 100 person-years (95% CI: 3.28-9.70) based on 10 studies with 456 transmissions over 9,998 person-years of follow-up; however, the risk of transmission varied by viral load. For example, transmission risk was 9.03 per 100 person-years (95% CI: 3.87-21.09) when viral load was greater than 50,000 copies/mL, and 2.06 per 100 person-years (95% CI: 0.57-7.47) when viral load was between 400-3,499 copies/mL.

A limitation to these findings is that the authors were unable to provide an estimate for sexual intercourse without condoms, and thus, the generated estimates are confounded by condom use to an unknown extent. In addition, there was insufficient data to examine the effects of concomitant STIs, sexual practices (e.g. vaginal versus anal intercourse), or direction of transmission. The authors also point out that four studies were available only as conference abstracts with limited detail. Moreover, they encountered challenges in calculating confidence intervals for outcomes for which there were zero events. The authors did not systematically assess the quality of the included studies. Our assessment of the quality of this review using AMSTAR yielded a score of four out of 11. Two of the authors were members of the Swiss Federal AIDS Commission, but the authors state that the views contained in their manuscript are their own.

Boily et al., 2009 (4)
This systematic review and meta-analysis aimed to estimate the probability of HIV transmission, investigate the variance between established estimates, and analyse the influence of selected risk factors on infectivity. The authors performed two searches: a search of PubMed, Science Direct, and NLM Gateway from inception to September 2006 and an updated search of PubMed to September 2008. Additional references from bibliographies of relevant articles were also manually selected. Forty-three publications on 25 different study populations were identified to provide crude estimates or estimates stratified by risk factors and 35 of these publications were included in the univariate meta-analysis. The main meta-analysis focused on serodiscordant heterosexual partners and couples (including female sex workers and their male clients) in low-, middle-, and high-income settings. The included studies were retrospective partner studies;

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prospective discordant couple studies; or non-partner prospective (longitudinal cohort) and retrospective (cross-sectional) studies.

The pooled female-to-male and male-to-female transmission rates per sexual act in high-income settings were 0.0004 (95% CI: 0.0001-0.0014) and 0.0008 (95% CI: 0.0006-0.0011), respectively. The per act risk estimates were higher in low- and middle-income countries at 0.0038 (95% CI: 0.0013-0.0110) in female-to-male couples and 0.0030 (95% CI: 0.0014) in male-to-female couples when commercial sex exposure was not considered. The risk of HIV transmission per act of receptive anal intercourse in high-income settings at 0.017 (95% CI: 0.003-0.089).

The direction of transmission and type of sexual act were not considered in the context of condom use. HIV transmission risk in studies that controlled for condom use was 0.0015 (95%CI: 0.0010-0.0023) per sexual act across all settings and 0.0028 per sexual act in studies set in low- and middle-income countries. Higher risk of transmission was seen from univariate meta-regression analyses in studies that did not control for condom use (per act risk of 0.013 (95%CI: 0.0034 - 0.0498), though the condom use covariate was no longer significant after excluding estimates with commercial sex exposure.

A key limitation of this review was that an estimate was considered to have been controlled for condom use if *any* attempt was made to reduce the number of exposed sex acts to account for frequent condom use, or if condom use was reported to be very low. This limitation may inflate the HIV transmission estimate as levels of condom use varied between the studies. Further bias was introduced in the HIV transmission risk due to a small number of included studies and because many of the studies in low- and middle-income countries included a counselling component as part of the intervention. Other aspects of bias that limit the robustness of the estimates are publication bias and bias introduced due to frailty selection. Frailty selection could result in under-estimation of transmission rates if the studies of serodiscordant couples attract participants who are less susceptible to seroconversion/transmission and therefore remain serodiscordant for longer than the average serodiscordant couple. A final limitation is that the authors did not assess the quality of primary studies. Despite these limitations, our assessment of the quality of this review using the AMSTAR tool yielded a score of five out of 11. The authors reported no conflicts of interest.

Powers et al., 2008 (20)
The objective of this systematic review and meta-analysis was to estimate heterosexual HIV infectivity and assess the effect of various factors on this infectivity (e.g. condom use). The authors searched PubMed/Medline, and Web of Science databases from inception to April 27, 2008. They also manually reviewed the text and bibliographies of included studies to identify additional articles that might have been relevant. The authors identified five studies that examined the risk of HIV transmission where there were some condom-protected acts and eight studies that examined the risk of HIV transmission where condoms were rarely used or where condom use was adjusted for. The studies included populations from the US, Thailand, Europe, and Africa. The included studies were longitudinal cohorts and cross-sectional studies examining either serodiscordant heterosexual couples or at risk individuals (e.g. female sex workers, clients of female sex workers). The direction of transmission and type of sexual acts were not considered.

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In their meta-regression, which used modelling to control for some confounding variables, the risk of HIV transmission was 0.7 per 1,000 sexual exposures (95% CI: 0.57-0.83) in studies with at least some condom use. Conversely, in studies where condom use was rare or adjusted for, the risk of transmission was 0.62 per 1,000 exposures (95% CI: 0.53-0.70). The absolute number of transmissions, the frequency of sex acts, and the length of follow-up used to calculate these estimates were not reported. Moreover, included longitudinal studies had intervals between HIV tests varying from two weeks to 10 months.

While HIV incidence rates by condom use were presented, an important limitation of this study is that actual levels of consistent condom use were not specified. This may have inflated the risk of transmission associated with condom use. In addition, studies involving female sex workers or their clients may be confounded by additional risk factors. There was insufficient data available to account for potentially confounding factors including viral load, viral subtype, and ART in the meta-regression analysis. It is also difficult to disaggregate the effect of various modifiers of transmission such as other STIs (although the meta-regression modelling attempts to take this into consideration). The authors did not systematically assess the quality of the included studies. Our assessment of the quality of this review using AMSTAR yielded a score of three out of 11. The authors reported no conflicts of interest.

Weller et al., 2002 (3)
In this Cochrane review, the authors sought to estimate the effectiveness of condoms in reducing heterosexual transmission of HIV. Searches were carried out on the AIDSLINE, CINAHL, Embase, and Medline databases up to the year 2000. Fourteen studies met their inclusion/exclusion criteria, encompassing serodiscordant heterosexual couples from the US, as well as African and European countries (10 of 14 studies were conducted in low- and middle-income countries, while four of 14 were conducted in high-income countries). The studies included in this review were prospective and retrospective cohort studies, as well as a single case study. In this review, the direction of transmission (male-to-female or female-to-male) and the types of sexual acts involved were not considered.

The risk of HIV transmission for couples who self-report always using condoms for vaginal penetrative intercourse acts was found to be 1.14 per 100 person-years (95% CI: 0.56-2.04), over total follow-up period of 946.3 person-years across 13 cohorts in which 11 total transmissions occurred. Conversely, the risk of HIV transmission for couples who self-report never using condoms for vaginal penetrative intercourse acts was found to be 6.68 per 100 person-years, over total follow-up of 598.61 person-years across 10 cohorts in which 40 transmissions occurred. When compared to no condom use, consistent condom use reduced HIV incidence by approximately 80.2%, though this approximation could be as low as 35.4% or as high as 94.2%.

The authors point out that there was a lack of detail in the included studies regarding the true level of condom usage and how condom use was measured in the included studies, which may have led to over-reporting of condom use. Similarly, the authors were unable to estimate if there was disease-free exposure time for each of the couples so they relied on the average person-years of follow-up to calculate transmission incidence. This may have resulted in underestimations of incidence. Moreover, the authors did not appear to systematically assess the quality of the included studies. Correspondingly, our assessment of the quality of this review using the AMSTAR tool yielded a score of four out of 11. The authors reported no conflicts of interest.

Risk of sexual transmission of human immunodeficiency virus with antiretroviral therapy, suppressed viral load, and condom use: a systematic review

Liu et al, 2014 (21)

The objective of this systematic review and meta-analysis was to estimate the relative effectiveness of ART and consistent condom use in reducing HIV transmission in heterosexual serodiscordant couples in China. Searches were conducted in English using PubMed and in Chinese using Wanfang Data, China National Knowledge Infrastructure, and Chinese Biomedical Literature Database from database inception to March 31, 2014. A total of 11 prospective cohort studies (with a combined 45,615 HIV serodiscordant couples followed over 116,332.375 person-years) met the authors' inclusion and exclusion criteria. The direction of HIV transmission and specific sex acts involved were not considered.

In a meta-analysis, the pooled seroconversion incidence rate when the index partner was on ART was 0.92 per 100 person-years (95% CI: 0.48-1.35) across six studies; though, the dispersion of effect sizes suggests that the sample is heterogeneous (I^2: 87.4%). Conversely, when the index partner was not on ART, the pooled seroconversion incidence rate was 2.45 (95% CI: 1.79-3.12) across nine studies; again, the sample is heterogeneous (I^2: 48.8%). When condoms were consistently used, the pooled seroconversion incidence rate was 0.16 per 100 person-years (95% CI: 0.02-0.3) across three studies. The pooled seroconversion incidence rate when condoms were not used consistently was 9.01 (95% CI: 5.90-12.11) per 100 person-years across two studies. The pooled crude incidence risk ratio between couples where ART was used and those where it was not used was 0.47 (95% CI: 0.43-0.52) with 1,013 transmission events over 85,684 person-years of follow-up when ART was used and 766 transmission events over 29,612 person-years of follow-up when ART was not used. The pooled incidence risk ratio between couples where condoms were used consistently and those where condoms were not used consistently was 0.01 (95% CI: 0.00-0.04) with 21 transmissions over 10,949 person-years of follow up when condoms were used consistently and 37 transmissions over 409 person-years of follow-up when condoms were not used consistently.

The authors acknowledge that the true risks of transmission are likely to be lower than the reported estimates because only longitudinal studies were included in this review, which are likely biased to including long-term partners past the early "riskier" phases of their partnership. It is also noted that the sex of the index partner, frequency of sexual activity, route of HIV transmission, and presence of STIs were not accounted for in their estimates. It does not appear that the quality of included studies was systematically assessed. Our assessment of the quality of this review using AMSTAR yielded a score of three out of 11. The authors declared that they have no competing interests and received financial support from the 12th Five-Year Plan of China.

Cambiano et al., 2013 (22)

The aim of this narrative systematic review was to understand the impact of ART use on HIV incidence at a population level and the potential implications of ART recommendations in Europe. Searches for key terms were carried out in Web of Science; Medline; BIOSIS Citation Index; BIOSIS Previews; Journal Citation Report for articles published between January 2006 and November 2013. Hand searches of references of included studies and identification of papers from before 2006 known to the authors were also undertaken. Sixty-two studies were identified that met the authors' inclusion and exclusion criteria, of which 11 included estimates of absolute risk of transmission. The studies included populations from: high-income (two); low- and middle-income (five); and unspecified (four) settings.

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This review provided evidence of HIV transmission risk on ART for different sexual acts and by viral load. For condomless vaginal or condomless insertive anal intercourse with successful ART, studies found that the predicted probability of HIV transmission was 0.013. In the case of receptive condomless anal intercourse with successful ART, this was augmented to a predicted probability of 0.061% (16). In the context of participants treated with ART and virally supressed (defined as viral loads from 50 to 500 copies/mL depending on the study), an absolute risk of transmission of zero per 100 person-years (95% CI: 0-0.05) was observed when viral load was confirmed at the time of transmission and 0.14 per 100 person-years (95% CI: 0.04-0.31) when the viral load was not confirmed (6). Similar results were found in a meta-analysis of studies with participant's viral loads less than 400 copies/mL (zero per 100 person-years; 95% CI: 0-1.27) (19). Evidence from a multi-national long term observational study showed one genetically linked transmission from an individual on ART, which corresponded to an absolute risk of transmission of 0.37 per 100 person-years (95% CI: 0.09-2.04) (23).

The authors identified a gap in the literature as they determined no direct quantitative evidence regarding the risk of HIV transmission among MSM in the context of ART was available at the time of the review. The follow-up periods of observational studies used in these estimates were not reported, nor in most cases the absolute number of transmissions that occurred in different groups. Major limitations within this overview were related to the study design of the primary studies and meta-analysis. Ecological studies use proxy estimates (HIV diagnosis) because the empirical HIV incidence is rarely known and there can often be high levels of confounding. While mathematical models often produce robust estimates, in this context they were unable to capture important parameters related to ART and sex acts due to limited information. The authors did not assess the quality of the studies included in their review. Our assessment of the quality of this review using the AMSTAR tool yielded a score of two out of 11. The authors reported no conflicts of interest.

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