Heterosexual HIV-1 infectiousness from prospective discordant couple studies according to antiretroviral use: Supplemental Digital Content

Baggaley et al.

Methods

Search strategy: PubMed, Science Direct and NLM Gateway online databases and bibliographies of relevant articles were initially searched to September 2006 using search terms: "HIV transmission probability" OR "HIV transmission probabilities" OR "HIV infectivity" OR "HIV infectiousness" NOT "perinatal" NOT "mother to child" NOT "mother-to-child" and by replacing "HIV" by the terms, "LAV", "HTLV-III" and "HTLV III". PubMed was searched by titles whereas Science Direct and NLM Gateway were searched by abstracts, titles, keywords and authors. The PubMed search was updated four times (to June 29th 2007, September 6th 2008, August 10th 2010 and 31st July 2011) using more efficient search terms and Boolean operators, for matches under any field: (HIV OR LAV OR HTLV III OR HTLV-III OR AIDS OR human immunodeficiency virus OR human T-lymphotropic virus III OR acquired immunodeficiency) AND (infectiousness OR infectivity OR probability OR contact OR contacts OR partner OR partners OR wives OR spouses OR husbands OR couples OR discordant OR (transmission AND (heterosexual OR homosexual OR risk OR female OR male OR anal))). Search terms aimed to capture publications estimating HIV-1 infectiousness of all types and modes of transmission for use for other HIV-1 infectiousness reviews (6, 8-10). Bibliographies of relevant articles were examined for additional references. Additionally, we searched abstracts from the previous two years of International AIDS Society, Conference on Retroviruses and Opportunistic Infections and International Society of Sexually Transmitted Research on “discordant”.

Data analysis and statistical methods: Cumulative incidence estimate 95%CI were recalculated using the Wilson ‘score’ method (86) as recommended by Newcombe 1998 (87) so that results would be comparable. All calculations were performed using StataSE 10.0 (Stata Corporation, College Station, Texas, USA). Forest plots were created in R version 2.11.1 (88).

Aggregate variables: We created aggregate study-level variables for condom use, STIs and infection stage, due to incomplete and non-comparable reporting of these risk factors between studies.

Infection stage: continuous variable from 0 (low infectiousness) to 1 (highly infectious), weighted by proportion of index cases in the sample at each infection stage. Asymptomatic infection = 0; AIDS, primary, acute infection, WHO stage IV = 1; symptomatic (but not defined as AIDS), "ARC" (AIDS-related complex), WHO stage III = 0.5. "Majority" or "mainly" was estimated to represent 75% e.g. "mainly AIDS and ARC" was assumed to mean 75% fell into these categories, equally divided between them and thus scoring 0.56. For studies reporting patients as either asymptomatic or symptomatic, with no reference to AIDS, "symptomatic" was assumed to consist of 50% AIDS patients, 50% symptomatic without AIDS. Alternatively CD4 count was used: 0-199=1; 200-399=0.5; ≥400 cells/mm^3=0 (studies reporting CD4 ≥250 graded 0.25). The majority of reported CD4 counts were collected at baseline, but where counts were recorded from different time points, the time point producing the largest infection score was used. Where CD4 count was provided as a mean or median with range, no score calculation was attempted. For O'Brien et al (40), there was some exposure to acute HIV-1 infection, but the amount could not be quantified. We added 0.1 to the score to reflect the increase in infectiousness this exposure would cause.

Condom use: continuous variable from 0 (never/rare condom use) to 1 (always/consistent use), weighted by proportion of couples reporting each frequency of use. Always or consistent use=1; often=0.66; sometimes=0.33; rarely or never=0. The majority of reported of condom use were recorded at baseline. Where reports from follow-up were provided, we took the average proportion of couples reporting each frequency, combining all time points. Where a study reported excluding consistent condom users but provided no further information, we did not attempt to calculate a score. "Any use" or "ever used" reported by partners, or reporting unprotected sex in the past month, was coded as "sometimes" i.e. 0.33. Where reporting was phrased as the proportion "ever unprotected sex", the proportion was evenly distributed between often, sometimes and rarely/never categories. Where condom use frequency was not reported, but from the text it was evident that there was some condom use by study participants, again we did not attempt to calculate a score. Where both index cases and partners reported condom use, data from the partners were used.

Sexually transmitted infections (STIs): The non-uniform reporting of STIs (different infections, affecting index or partner, at baseline or during follow-up) makes the formulation of an aggregate score a challenge. A continuous variable from 0 (minimal effect of STIs within partnership) to 1 (maximum level of risk associated with STIs within the partnership) was created. Prevalence/incidence of any STI

among index cases and partners was given equal weight. Genital ulcer disease (including herpes simplex virus (HSV), syphilis and Haemophilus ducreyi) scored twice the risk of non-ulcerative infections including Chlamydia trachomatis and gonorrhoea for incident STIs. Incidence of STIs during follow-up scored twice the risk of prevalent STIs at baseline or history of STIs (assumes participants' infections were treated prior to study entry) with the exception of HSV, where prevalence or history scored three quarters of the risk of incidence (reflecting the incurable condition but also that older infections have less frequent and milder ulcerative outbreaks). Where STIs were not reported, but from the text it was evident that they were present within the study population, we did not attempt to calculate a score. In many instances there was incomplete reporting, particularly reporting only STIs among partners, or only among index cases, which makes this a rather unreliable measure of STI risk. Furthermore, risk associated with STI prevalence at baseline or history of STI is based only on the expectation of STI incidence during follow-up. However our score does provide some measure of STI risk which is useful in exploring the heterogeneity in estimates.

Male circumcision: Where proportion was not reported despite the text of a publication indicating at least some male participants had been circumcised, we did not attempt to estimate the prevalence. For combined man-to-woman and woman-to-man transmission, we used the proportion circumcised of all male study participants, regardless of whether they were partner or index within a couple. This was because some studies reported circumcision prevalence without specifying the direction of HIV-1 transmission and so we kept the measure as consistent as possible.

Male circumcision 2: In view of the restricted data on male circumcision available from the included studies, an ecological analysis was attempted using country-level prevalence data. Prevalence estimates used were as follows:

Country	MC prevalence	Country	MC prevalence	Country	MC prevalence
United States	79.0%	Thailand	12.3%	Haiti	0.1%
United Kingdom	15.8%	France	14.0%	DRC	70.0%
The Netherlands	5.9%	Germany	10.9%	Tanzania	70.0%
Spain	2.0%	Italy	1.1%	Rwanda	10.0%
Zambia	12.0%	Malawi	17.0%	China	11.4%
Uganda	25.0%	Kenya	84.0%	India	8.3%
Brazil	7.4%	Greece	3.0%	Belgium	3.0%
Botswana	25.0%	South Africa	35.0%	Kenya	84.0%

MC – male circumcision. Prevalence estimates from (16).

For study estimates derived from multiple countries, we used the mean male circumcision prevalence from all countries (De Vincenzi et al (29): France, Italy, Greece, The Netherlands, United Kingdom, Belgium, Germany, Spain; Sullivan et al (20): Rwanda and Zambia; and Celum et al (28): Botswana, South Africa, Kenya, Zambia, Rwanda, Tanzania, Uganda). We compared high (≥50%) versus low (<50%) male circumcision prevalence countries.

eFigure legends

eFigure 1 Flowchart summarising the results of the search on HIV-1 cumulative incidence and incidence rate estimates up to July 2011. Where not reported in the publication, incidence rate estimates were calculated using reported information on number of transmission events and mean or median duration of follow-up of couples. Combined: combined man-to-woman and woman-to-man direction of transmission. All ART-stratified studies provided transmission risk estimates for non-ART and ART receiving index cases for combined transmission except for Musicco et al (17) which reported man-to-woman transmission, and Baeten et al reported results stratified by ART use of the initially uninfected partner rather than the index partner (i.e. pre-exposure prophylaxis) (67). Two studies provided man-to-woman and woman-to-man risks for ART-receiving index cases only.

[1] One study (Hugonnet et al 2002 (34)) provides two cumulative incidence and incidence rate estimates: one risk for partners of index cases already infected at start of follow-up and one risk for partners of individuals who seroconverted during follow-up. Two studies provided no information on number of discordant couples (19-21).
[2] One study (Cohen et al 2011 (3)) provides results from nine countries, only one of which is high-income, and so it is classed in the figure as low-income.

eFigure 2 Subgroup analysis forest plots displaying random effects summary estimates for various subgroups of potential HIV-1 risk factors within the following no ART use strata: a) combined man-to-woman and woman-to-man transmission, high-income settings; b) combined transmission, low-income settings; c) man-to-woman transmission, low-income settings; d) woman-to-man transmission, low-income settings. * Hugonnet et al (34) provided two estimates.

eFigure 3 Study HIV-1 incidence rate estimates/100 person years by percentage ART use among index cases for combined man-to-woman and woman-to-man transmission, including both high- and low-income settings. Plot a) includes all study estimates where “no ART use” is inferred under the criteria detailed in the Methods, while plot b) only includes study estimates where prevalence of ART use among index cases is explicitly stated. Error bars represent 95% confidence intervals.

eFigure 4 Forest plot summary of HIV-1 cumulative incidence over study follow-up (%) estimates per heterosexual partnership for non-ART-stratified studies reporting combined man-to-woman and woman-to-man transmission, with 95% confidence intervals from a) high-income and b) low-income settings. Random effects model summary values are plotted for no ART use estimates (up to 3% antiretroviral use by study participants – see Methods for classification criteria) and any ART use estimates. Within these two groups, study estimates are plotted in order of increasing ART use and then chronologically. Size of boxes is proportional to number of couples except for Watera et al 2009 (19) and Sullivan et al 2009 (20, 21) which do not provide these data. Hugonnet et al 2002 (34) provides two per partnership estimates: one risk for partners of infected individuals at baseline and one risk for partners of individuals who seroconverted during follow-up. ART – reported percentage ART usage among index cases;

estimate – cumulative incidence (%); n – number of HIV-1 discordant couples; NR – not recorded in publication; x – number of HIV-1 transmitting couples; duration – mean duration of follow-up (years).

eFigure 5 Forest plot summary of HIV-1 cumulative incidence over study follow-up (%) estimates per heterosexual partnership for non-ART-stratified studies reporting man-to-woman and woman-to-man transmission, with 95% confidence intervals: a) man-to-woman and b) woman-to-man transmission from high-income settings; c) man-to-woman and d) woman-to-man transmission from low-income settings. Random effects model summary values are plotted for no ART use estimates (up to 3% antiretroviral use by study participants – see Methods for classification criteria) and any ART use estimates. Within these two groups, study estimates are plotted in order of increasing ART use and then chronologically. Size of boxes is proportional to number of couples. ART – reported percentage ART usage among index cases; estimate – cumulative incidence (%); n – number of HIV-1 discordant couples; NR – not recorded in publication; x – number of HIV-1 transmitting couples; duration – mean duration of follow-up (years, * denotes median rather than mean).

eAppendix Tables

eTable 1 Summary cumulative incidence estimates for ART-stratified studies, relative risk comparing ART-using to non-ART-using index cases.

Setting	Cumulative incidence %, non-ART arm (95%CI)	Cumulative incidence %, ART arm (95%CI)	Relative risk (95%CI)	p-value	n	Studies
All settings	3.3 (2.8-3.8)	1.2 (0.3-5.3)	0.58 (0.41-0.80)	0.001	5	(3, 18, 22-24)
High-income[a]	-	-	-	-	1	(22)
Low-income[a]	3.5 (2.9-4.1)	2.0 (0.5-8.9)	0.89 (0.59-1.32)	0.556	3	(18, 23, 24)

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

eTable 2 Summary of HIV-1 cumulative incidence and incidence rate estimates reported by ART-stratified studies.

Study	Country, direction of transmission, other study details	Risk categories	Cumulative HIV-1 incidence, % (x/n, 95%CI)		Incidence rate per 100 person years (py, 95%CI)	
ANTIRETROVIRAL THERAPY USE BY INDEX CASES						
Musicco et al 1994 (17)	Italy, man-to-woman	With ZDV	NS	(6/NS)	**3.8**	(157.2, 1.8-8.1)
		Without ZDV	NS	(21/NS)	**4.4**	(480.5, 2.9-6.6)
Melo et al[a] 2008 (18)	Brazil, combined man-to-woman and woman-to-man, index patients receiving care and their steady partners 2000-2006. ART initiated because of pregnancy (80%) or CD4 <350 cells/mm^3 (20%). 100% initiating ART achieved viral suppression.	ART (12% partners female)	**0.0**	(0/41, 0.0-8.6)	**0.0**	(90.4, 0.0-4.1)
		No ART (40% partners female)	**12.5**	(6/48, 5.9-24.7)	**5.7**	(106, 2.6-11.8)
		ART (female-to-male)	**0.0**	(0/36, 0.0-9.6)	NS	NS
Watera et al 2009 (abstract) (19)	Uganda, combined man-to-woman and woman-to-man	ART	**0.0**	(0/NS)	**0.0**	(~19.5, 0.0-16.5)
		No ART	NS	(3/NS)	**3.9**	(~76.9, 1.3-10.9)
Sullivan et al 2009 (abstracts) (20, 21)	Rwanda and Zambia, combined man-to-woman and woman-to-man	ART	NS	(4/NS)	**0.7**	(~575, 0.3-1.8)
		No ART	NS	(171/NS)	**3.4**	(~5033, 2.9-3.9)
		ART (man-to-woman)	**0.0**	(0/NS)	**0.0**	(~288, 0.0-1.3)
		ART (woman-to-man)	NS	(4/NS)	**1.4**	(~288, 0.5-3.5)
Del Romero et al 2010 (22)	Spain, combined man-to-woman and woman-to-man. Total cohort: 63% couples reported sexual risk exposure at some point	Combined ART	**0.0**	(0/144, 0.0-2.6)	**0.0**	(417, 0.0-0.9)
		ART mono/dual therapy	**0.0**	(0/47, 0.0-7.6)	**0.0**	(75, 0.0-4.9)
		No ART	**1.5**	(5/341, 0.6-3.4)	**0.6**	(863, 0.2-1.3)
Wang et al 2010 (23)	China, retrospective cohort, combined man-to-woman and woman-to-man (female cases were more likely to be on ART)	ART	**4.8**	(66/1369, 3.8-6.1)	NS	NS
		No ART	**3.2**	(18/558, 2.1-5.0)	NS	NS
Donnell et al 2010 (24)	Africa (14 sites in 7 countries: Botswana, South Africa, Zambia, Kenya, Rwanda, Tanzania, Uganda). Re-analysis of Celum et al 2010 (28) RCT of suppressive therapy for HSV (acyclovir): Partners in Prevention Study). Combined, 32% partners female.	Both arms, ART	**0.3**	(1/349, 0.1-1.6)	**0.4**	(273, 0.1-2.0)
		Both arms, no ART	**3.4**	(102/3032, 2.8-4.1)	**2.2**	(4558, 1.8-2.7)
Reynolds et al 2011 (25)	Combined man-to-woman and woman-to-man	ART	**0.0**	(0/32, 0.0-10.7)	**0.0**	(53.6, 0.0-6.7)
		No ART	NS	(42/NS)	**9.1**	(459.4, 6.8-12.1)

Study	Country, direction of transmission, other study details	Risk categories	Cumulative HIV-1 incidence, % (x/n, 95%CI)		Incidence rate per 100 person years (py, 95%CI)	
Cohen et al 2011 (3)	Nine countries: Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand, United States (HPTN 052 RCT). Combined, 50% partners female.	ART No ART	**0.1** **3.1**	(1/886, 0.0-0.6) (27/877, 2.1-4.4)	**0.1** **1.7**	(1585.3, 0.0-0.4) (1567.3, 1.1-2.5)
ANTIRETROVIRAL THERAPY USE BY PARTNERS – PRE-EXPOSURE PROPHYLAXIS						
Baeten et al 2011 (abstract) (67)	Kenya and Uganda, RCT (Partners PrEP) of pre-exposure prophylaxis; index cases not eligible for ART at enrolment but 19% initiated ART during follow-up, median CD4 at enrolment 495 (IQR 375-662) cells/mL, median plasma viral load 3.9 (IQR 3.2-4.5) $\log_{10}$ copies/mL, 67% monogamy among partners. Combined, 38% partners female	Tenofovir (TDF) Emtricitabine/Tenofovir (FTC/TDF) Placebo	NS NS NS	(18/NS) (13/NS) (47/NS)	**0.7** **0.5** **1.9**	(2441, 0.5-1.2) (2452, 0.3-0.9) (2444, 1.4-2.5)

n – number of followed-up; NS – not stated; initially HIV-1 discordant couples; py – person years; x – number of transmission events during follow-up, RCT – randomised controlled trial, ZDV - zidovudine.

[a] Additional data provided by the authors.

eTable 3 Summary of HIV-1 per partner cumulative incidence (% transmitting over total duration of follow-up) and incidence rate estimates reported by non-ART-stratified studies, stratified by setting, direction of transmission and level of antiretroviral therapy (ART) use.

	Cumulative incidence, %					Incidence rate, /100py					N	Studies
Setting[a]	Median (min,max)	Summary estimate (95%CI)	Q	p	n	Median (min,max)	Summary estimate (95%CI)	Q	p	n		
Combined transmission												
All settings: No ART	11.5 (0.0,40.6)	12.4 (7.8,19.9)	328	<.001	23	6.3 (0.0,32.5)	7.0 (4.3,11.4)	328	<.001	22	23	(26-34, 38-41, 43, 46-50, 52, 54, 89)[a]
Any ART	2.1 (0.0,6.3)	2.8 (1.9,3.7)[b]	15	.092	10	1.7 (0.0,6.5)	2.2 (1.3,3.8)	33	<.001	10	10	(55-58, 60-65)
High-income: No ART	0.0 (0.0,40.6)	10.6 (2.0,55.0)	36	<.001	7	0.0 (0.0,17.4)	3.6 (0.4,32.6)	9	.110	6	7	(29, 32, 40, 41, 50, 52, 89)
Any ART	3.2 (1.3,5.2)	2.9 (1.1,7.7)	3	.078	2	1.6 (1.3,1.8)	1.6 (0.8,3.1)	<1	.764	2	2	(55, 57)
Low-income: No ART	13.9 (0.0,36.4)	13.1 (8.6,20.1)	288	<.001	16	7.2 (0.0,32.5)	8.1 (5.4,12.1)	282	<.001	16	16	(26-28, 30, 31, 33, 34, 38, 39, 43, 46-49, 54)[a]
Any ART	2.1 (0.0,6.3)	3.3 (2.7,3.9)	9	.288	8	2.1 (0.0,6.5)	2.4 (1.2,4.6)	32	<.001	8	8	(56, 58, 60-65)
Man-to-woman transmission												
All settings: No ART	11.9 (0.0,41.7)	13.9 (9.1,21.1)	249	<.001	25	7.9 (0.0,33.7)	7.9 (5.1,12.4)	133	<.001	20	25	(26-39, 41, 43-51, 53)
Any ART	2.6 (1.2,5.9)	4.2 (1.9,9.5)	10	.006	3	1.5 (0.4,2.7)	1.8 (0.8,4.0)	5	.098	3	3	(57-59)
High-income: No ART	10.8 (0.0,41.7)	13.3 (4.5,39.6)	40	<.001	9	0.7 (0.0,9.7)	2.4 (0.3,16.4)	3	.388	4	9	(29, 32, 35-37, 41, 44, 45, 50)
Any ART	3.5 (1.2,5.9)	4.5 (1.6,12.2)	10	.001	2	1.6 (0.4,2.7)	1.8 (0.7,4.7)	5	.032	2	2	(57, 59)
Low-income: No ART	12.0 (1.0,38.1)	14.2 (9.5,21.2)	200	<.001	16	8.4 (1.0,33.7)	8.9 (6.0,13.2)	89	<.001	16	16	(26-28, 30, 31, 33, 34, 38, 39, 43, 46-49, 51, 53)
Any ART	2.6 (2.6,2.6)	2.6 (0.5,13.5)[c]	0	-	1	1.5 (1.5,1.5)	1.5 (0.3,8.2)[2]	0	-	1	1	(58)
Woman-to-man transmission												
All settings: No ART	8.9 (0.0,21.4)	10.6 (7.1,15.7)	110	<.001	14	5.2 (0.0,11.6)	5.7 (4.0,8.3)	56	<.001	13	14	(26-31, 33, 34, 39, 43, 46-49)
Any ART	12.0 (4.0,16.7)	9.4 (4.3,20.9)	4	.129	3	4.5 (2.1,5.6)	3.7 (2.0,6.6)	<1	.641	3	3	(57, 58, 66)
High-income: No ART	8.5 (8.5,8.5)	8.5 (3.4,19.9)[c]	0	-	1	-	-	-	-	0	1	(29)
Any ART	16.7 (16.7,16.7)	16.7 (7.3,33.6)[c]	0	-	1	5.6 (5.6,5.6)	5.6 (2.4,12.4)[c]	0	-	1	1	(57)

Setting[a]	Cumulative incidence, %					Incidence rate, /100py					N	Studies
	Median (min,max)	Summary estimate (95%CI)	Q	p	n	Median (min,max)	Summary estimate (95%CI)	Q	p	n		
Low-income: No ART	9.1 (0.0,21.4)	10.7 (7.0,16.3)	109	<.001	13	5.2 (0.0,11.6)	5.7 (4.0,8.3)	56	<.001	13	13	(26-28, 30, 31, 33, 34, 39, 43, 46-49)
Any ART	8.0 (4.0,12.0)	6.0 (2.7,13.4)	0	-	2	3.3 (2.1,4.5)	2.9 (1.3,6.3)	<1	.593	2	2	(58, 66)

"No ART" defined as <3% ART use stated in publication, follow-up censored at 1996 or earlier for high-income or 2005 or earlier for low-income countries or, if follow-up not stated, publication pre-1997 for high-income and pre-2005 for low-income countries. All other estimates classed as any ART use.

ART – antiretroviral therapy; combined – combined man-to-woman and woman-to-man transmission; N – number of studies providing an HIV-1 cumulative incidence or incidence rate estimate; n – number of estimates for each outcome (HIV-1 cumulative incidence or incidence rate); p – p-value for heterogeneity; py – person years; Q – heterogeneity statistic.

Summary estimates are random effects estimates from Poisson regression models; fixed effects estimates and estimates from simple pooling of all transmission events and sample sizes are presented in supplementary information available on request. P-values and Q statistics for heterogeneity calculated using the DerSimonian-Laird random effects pooling method (90).

[a] One study (Hugonnet et al 2002 (34)) provides two cumulative incidence and incidence rate estimates: one risk for partners of index cases already infected at start of follow-up and one risk for partners of individuals who seroconverted during follow-up. Sullivan et al's estimate comes from two 2009 conference abstracts (20, 21).

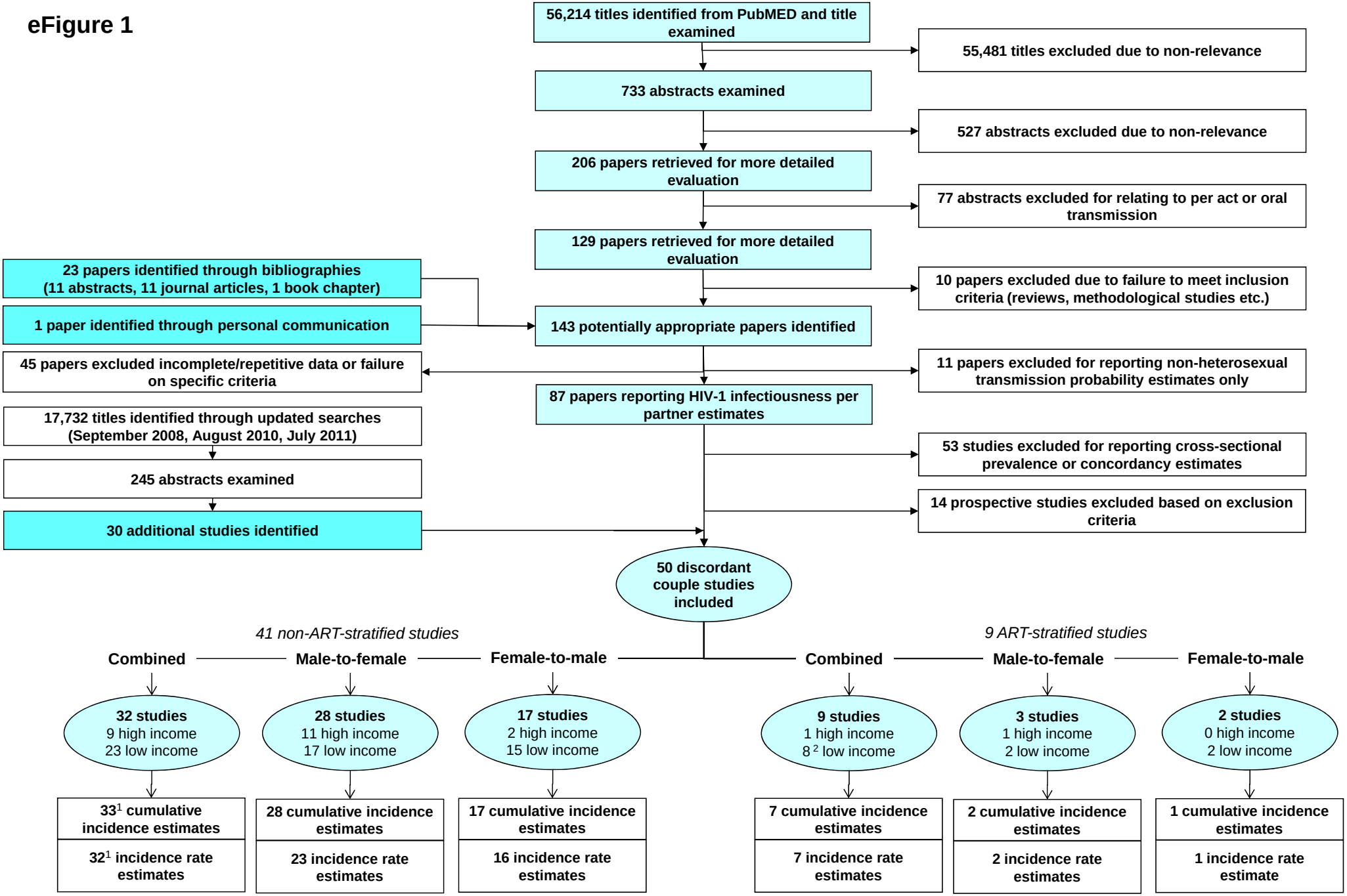
[b] Failure of Poisson model to converge; results produced using the DerSimonian and Laird random effects pooling method (90).

[c] Insufficient studies to perform Poisson regression.

References

As for main manuscript.

eFigure 1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55,481 titles excluded due to non-relevance
733 abstracts examined
527 abstracts excluded due to non-relevance
206 papers retrieved for more detailed evaluation
77 abstracts excluded for relating to per act or oral transmission
129 papers retrieved for more detailed evaluation
10 papers excluded due to failure to meet inclusion criteria (reviews, methodological studies etc.)
23 papers identified through bibliographies (11 abstracts, 11 journal articles, 1 book chapter)
1 paper identified through personal communication
143 potentially appropriate papers identified
45 papers excluded incomplete/repetitive data or failure on specific criteria
11 papers excluded for reporting non-heterosexual transmission probability estimates only
17,732 titles identified through updated searches (September 2008, August 2010, July 2011)
87 papers reporting HIV-1 infectiousness per partner estimates
245 abstracts examined
53 studies excluded for reporting cross-sectional prevalence or concordancy estimates
30 additional studies identified
14 prospective studies excluded based on exclusion criteria
50 discordant couple studies included
41 non-ART-stratified studies
9 ART-stratified studies
Combined
Male-to-female
Female-to-male
Combined
Male-to-female
Female-to-male
32 studies
9 high income
23 low income
28 studies
11 high income
17 low income
17 studies
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15 low income
9 studies
1 high income
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3 studies
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32[1] incidence rate estimates
28 cumulative incidence estimates
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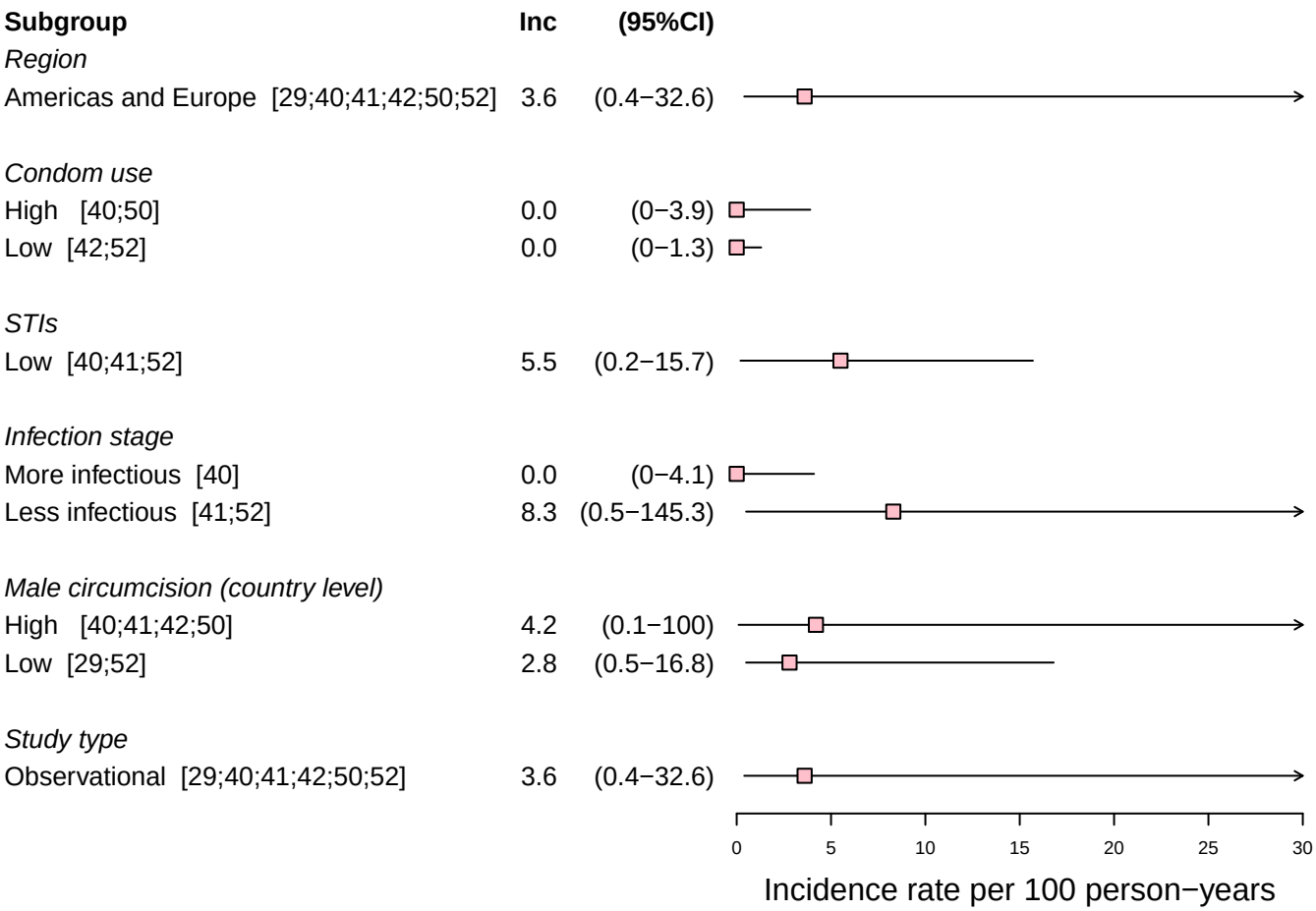
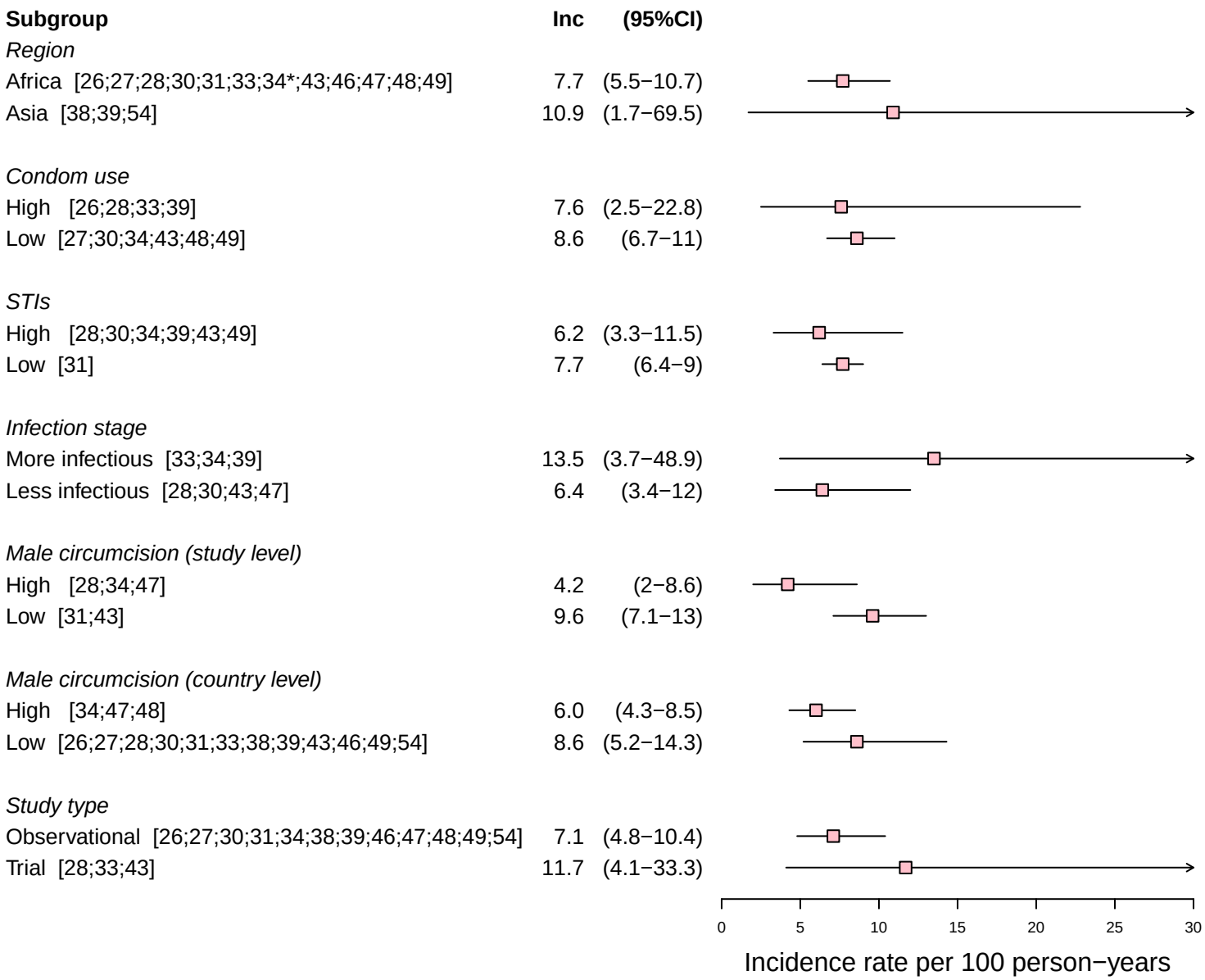
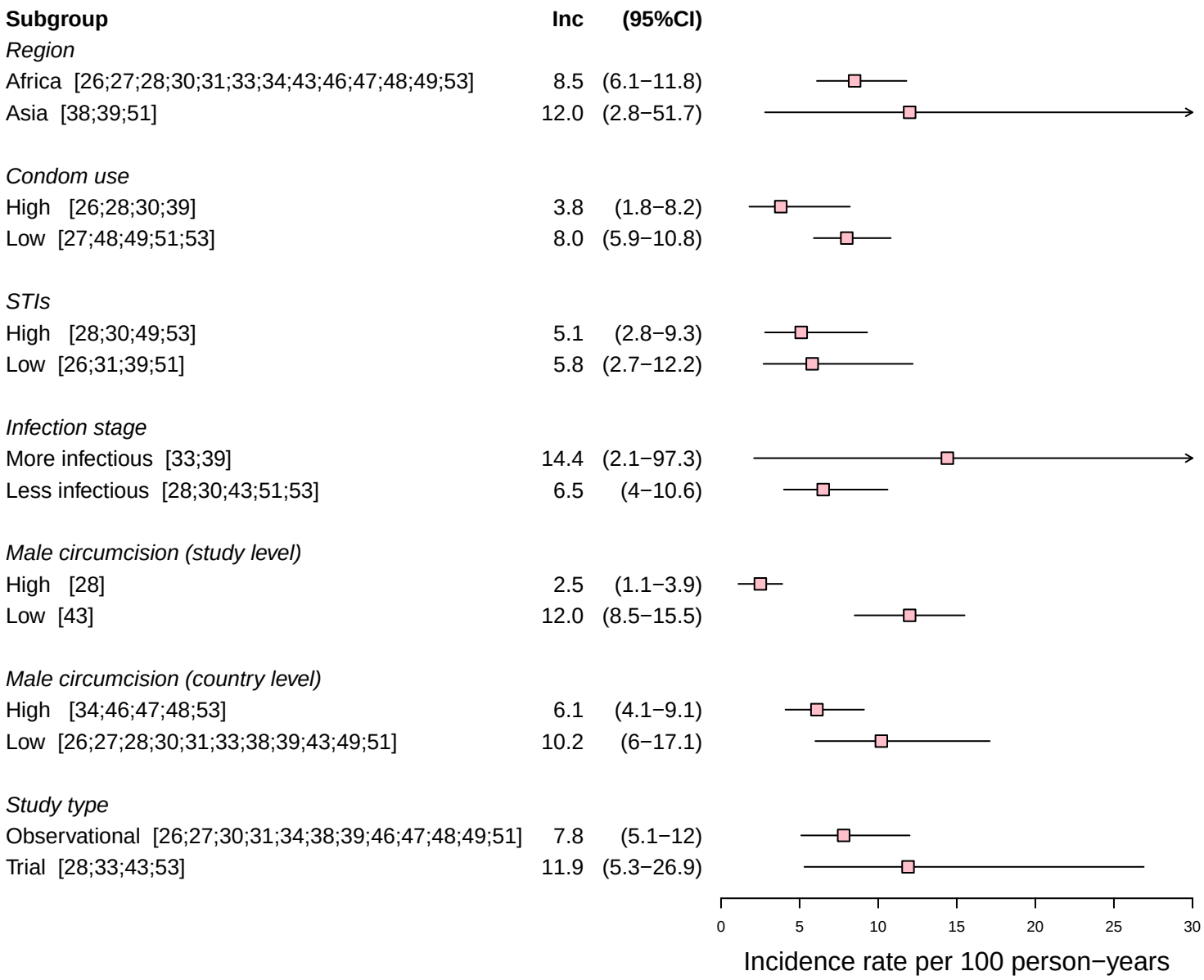
eFigure 2a


Subgroup
Inc
(95%CI)
Region
Americas and Europe [29;40;41;42;50;52] 3.6 (0.4−32.6)
Condom use
High [40;50] 0.0 (0−3.9)
Low [42;52] 0.0 (0−1.3)
STIs
Low [40;41;52] 5.5 (0.2−15.7)
Infection stage
More infectious [40] 0.0 (0−4.1)
Less infectious [41;52] 8.3 (0.5−145.3)
Male circumcision (country level)
High [40;41;42;50] 4.2 (0.1−100)
Low [29;52] 2.8 (0.5−16.8)
Study type
Observational [29;40;41;42;50;52] 3.6 (0.4−32.6)
0
5
10
15
20
25
30
Incidence rate per 100 person−years

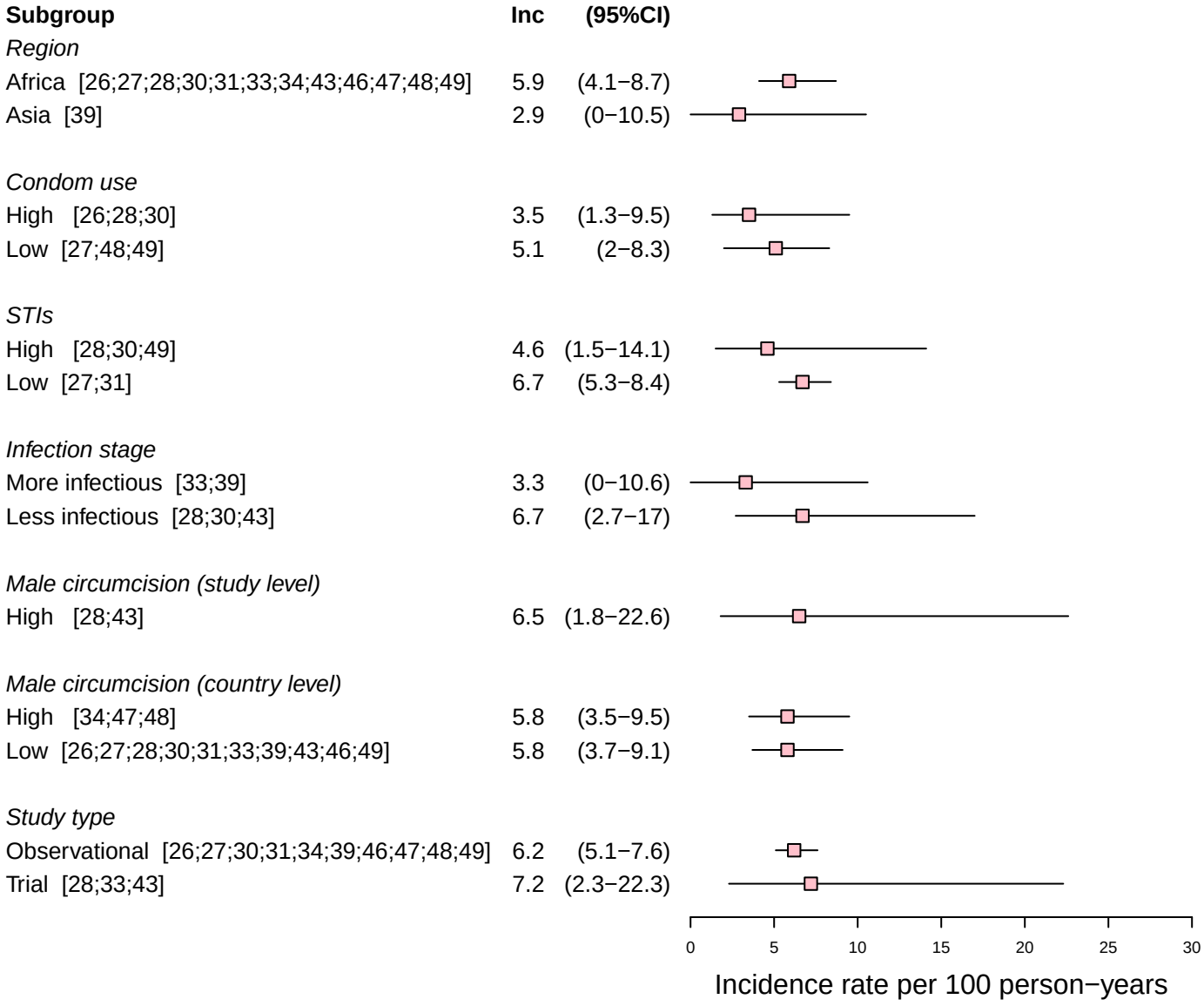
eFigure 2b


Subgroup
Inc
(95%CI)
Region
Africa [26;27;28;30;31;33;34*;43;46;47;48;49] 7.7 (5.5−10.7)
Asia [38;39;54] 10.9 (1.7−69.5)
Condom use
High [26;28;33;39] 7.6 (2.5−22.8)
Low [27;30;34;43;48;49] 8.6 (6.7−11)
STIs
High [28;30;34;39;43;49] 6.2 (3.3−11.5)
Low [31] 7.7 (6.4−9)
Infection stage
More infectious [33;34;39] 13.5 (3.7−48.9)
Less infectious [28;30;43;47] 6.4 (3.4−12)
Male circumcision (study level)
High [28;34;47] 4.2 (2−8.6)
Low [31;43] 9.6 (7.1−13)
Male circumcision (country level)
High [34;47;48] 6.0 (4.3−8.5)
Low [26;27;28;30;31;33;38;39;43;46;49;54] 8.6 (5.2−14.3)
Study type
Observational [26;27;30;31;34;38;39;46;47;48;49;54] 7.1 (4.8−10.4)
Trial [28;33;43] 11.7 (4.1−33.3)
0
5
10
15
20
25
30
Incidence rate per 100 person−years

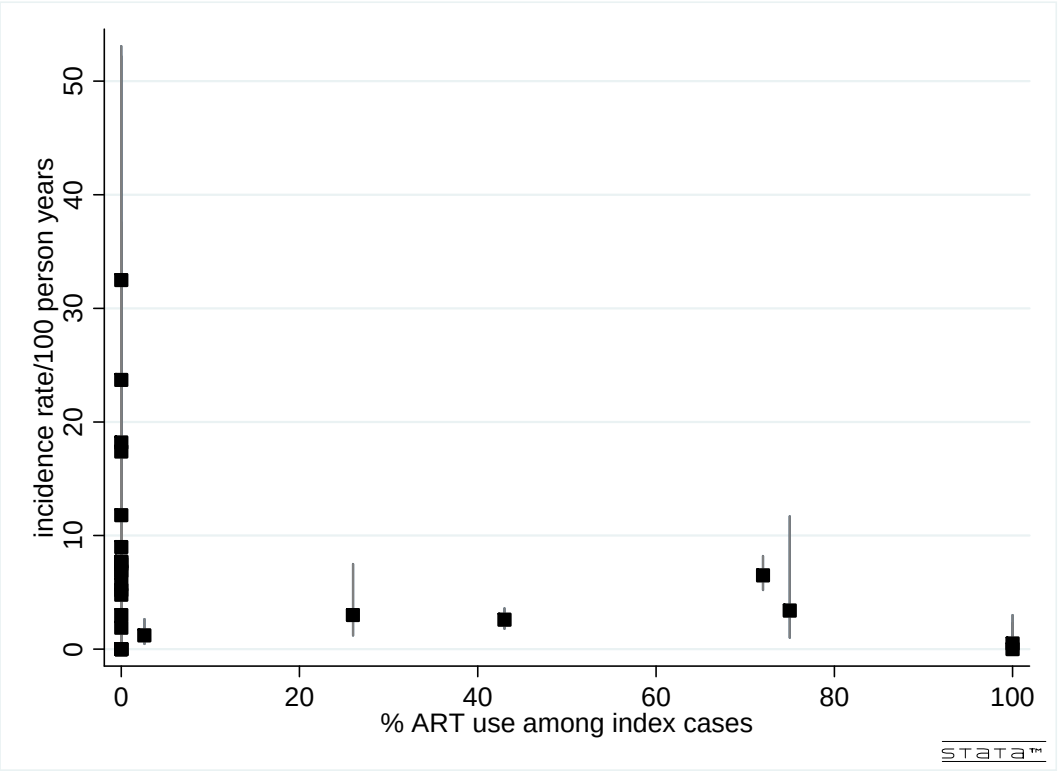
eFigure 2c


Subgroup
Inc
(95%CI)
Region
Africa [26;27;28;30;31;33;34;43;46;47;48;49;53] 8.5 (6.1−11.8)
Asia [38;39;51] 12.0 (2.8−51.7)
Condom use
High [26;28;30;39] 3.8 (1.8−8.2)
Low [27;48;49;51;53] 8.0 (5.9−10.8)
STIs
High [28;30;49;53] 5.1 (2.8−9.3)
Low [26;31;39;51] 5.8 (2.7−12.2)
Infection stage
More infectious [33;39] 14.4 (2.1−97.3)
Less infectious [28;30;43;51;53] 6.5 (4−10.6)
Male circumcision (study level)
High [28] 2.5 (1.1−3.9)
Low [43] 12.0 (8.5−15.5)
Male circumcision (country level)
High [34;46;47;48;53] 6.1 (4.1−9.1)
Low [26;27;28;30;31;33;38;39;43;49;51] 10.2 (6−17.1)
Study type
Observational [26;27;30;31;34;38;39;46;47;48;49;51] 7.8 (5.1−12)
Trial [28;33;43;53] 11.9 (5.3−26.9)
0
5
10
15
20
25
30
Incidence rate per 100 person−years

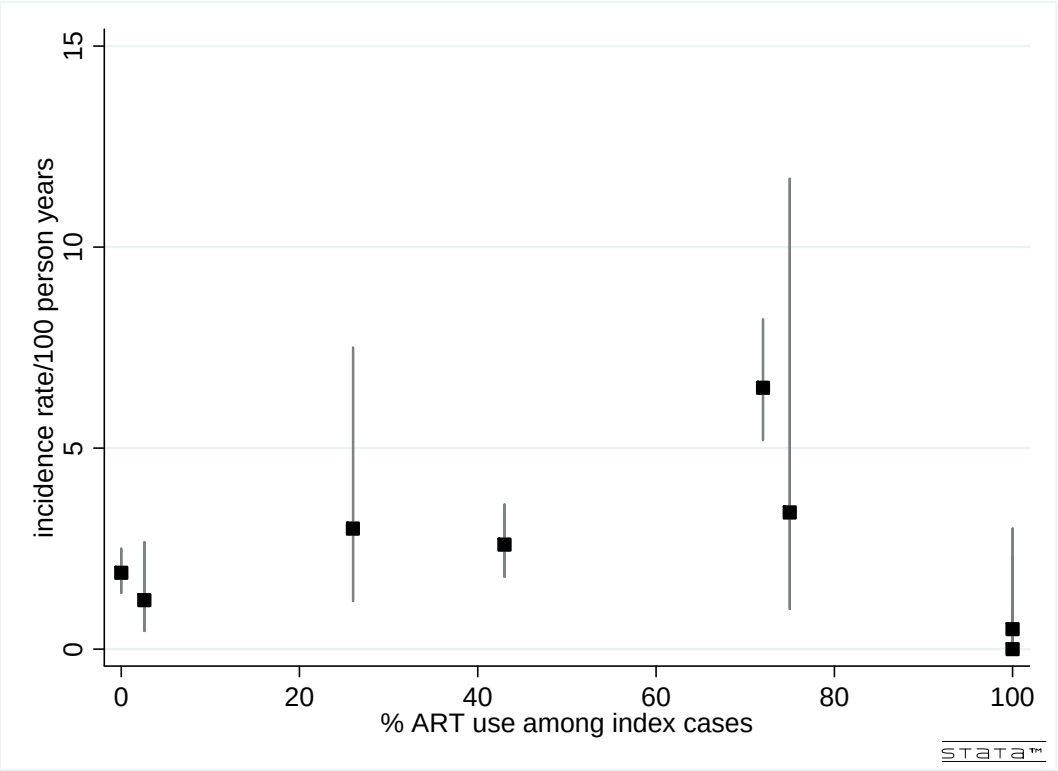
eFigure 2d


Subgroup
Inc
(95%CI)
Region
Africa [26;27;28;30;31;33;34;43;46;47;48;49] 5.9 (4.1−8.7)
Asia [39] 2.9 (0−10.5)
Condom use
High [26;28;30] 3.5 (1.3−9.5)
Low [27;48;49] 5.1 (2−8.3)
STIs
High [28;30;49] 4.6 (1.5−14.1)
Low [27;31] 6.7 (5.3−8.4)
Infection stage
More infectious [33;39] 3.3 (0−10.6)
Less infectious [28;30;43] 6.7 (2.7−17)
Male circumcision (study level)
High [28;43] 6.5 (1.8−22.6)
Male circumcision (country level)
High [34;47;48] 5.8 (3.5−9.5)
Low [26;27;28;30;31;33;39;43;46;49] 5.8 (3.7−9.1)
Study type
Observational [26;27;30;31;34;39;46;47;48;49] 6.2 (5.1−7.6)
Trial [28;33;43] 7.2 (2.3−22.3)
0
5
10
15
20
25
30
Incidence rate per 100 person−years

eFigure 3a

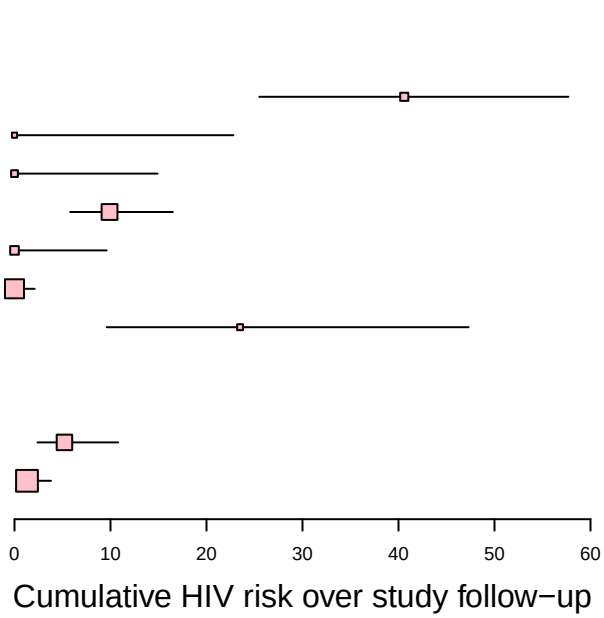

incidence rate/100 person years
0
10
20
30
40
50
0
20
40
60
80
100
% ART use among index cases
Stata™

eFigure 3b


incidence rate/100 person years
0
5
10
15
0
20
40
60
80
100
% ART use among index cases
Stata™

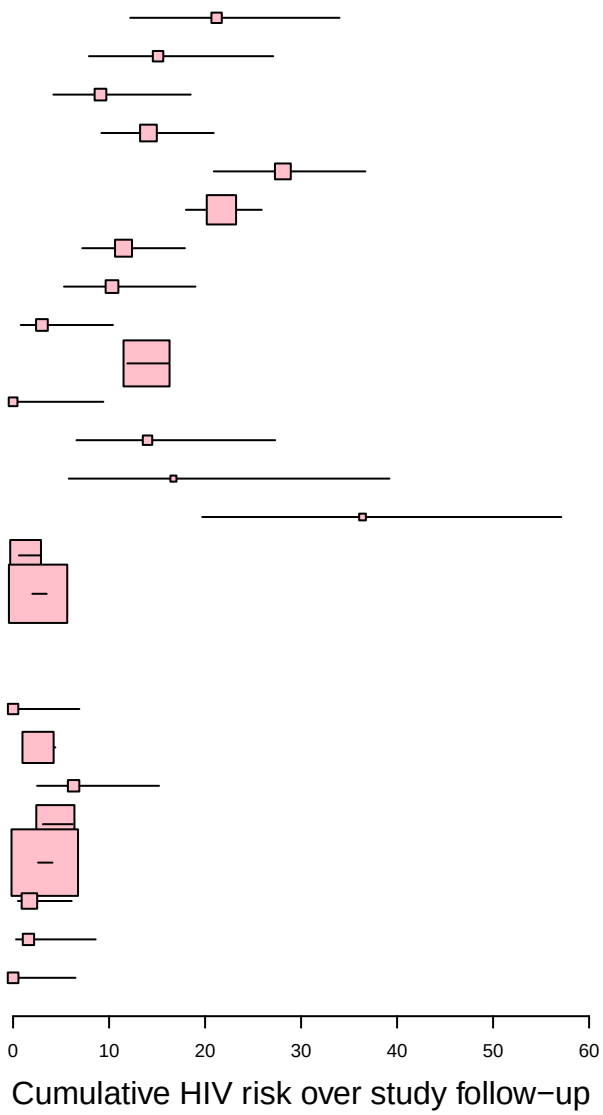
eFigure 4a

Study	ART	x	n	dur	estimate	(95%CI)
No ART use (I^2=81%, p<0.001)						
Fischl et al (1987) [32]	NR	13	32	2.0*	40.6	(25.5−57.7)
van der Ende et al (1988) [52]	NR	0	13	3	0.0	(0−22.8)
Siddiqui et al (1992) [50]	NR	0	22	0.8*	0.0	(0−14.9)
De Vincenzi et al (1994) [29]	NR	12	121	2	9.9	(5.8−16.5)
O'Brien et al (1994) [40]	NR	0	36	2.5	0.0	(0−9.6)
Padian et al (1997) [42]	NR	0	175	1.6	0.0	(0−2.1)
Operskalski et al (1997) [41]	NR	4	17	1.4	23.5	(9.6−47.3)
Any ART use (I^2=33%, p=0.078)						
Robertson et al (1998) [57]	NR	6	116	2.8	5.2	(2.4−10.8)
El−Bassel et al (2010) [55]	NR	3	229	1	1.3	(0.4−3.8)



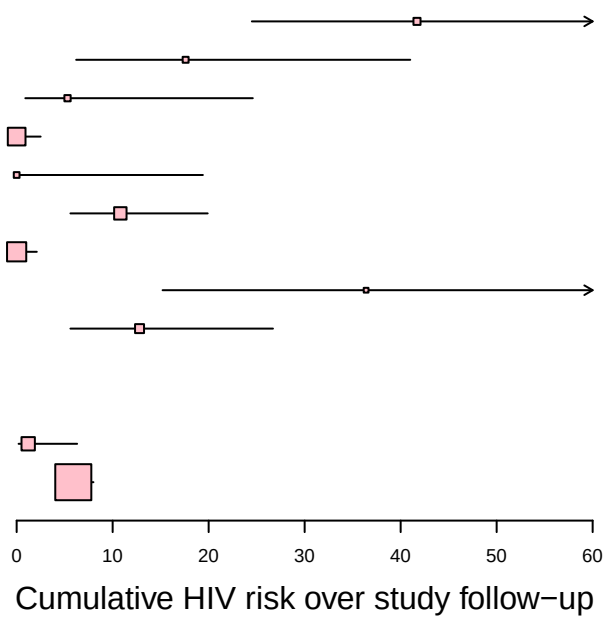
eFigure 4b

Study	ART	x	n	dur	estimate	(95%CI)
No ART use (I^2=94%, p<0.001)						
Hira et al (1990) [33]	NR	11	52	0.9	21.2	(12.2−34)
Allen et al (1992) [26]	NR	8	53	2.2	15.1	(7.9−27.1)
Serwadda et al (1995) [49]	NR	6	66	1.0	9.1	(4.2−18.5)
Deschamps et al (1996) [30]	NR	19	135	2.1	14.1	(9.2−20.9)
Carpenter et al (1999) [27]	NR	34	121	3.6	28.1	(20.9−36.7)
Quinn et al (2000) [43]	NR	90	415	1.8	21.7	(18−25.9)
Ryder et al (2000) [47]	NR	16	139	2.2	11.5	(7.2−17.9)
Senkoro et al (2000) [48]	NR	8	78	1.8	10.3	(5.3−19)
Roth et al (2001) [46]	NR	2	66	1.0	3.0	(0.8−10.4)
Fideli et al (2001) [31]	NR	142	1022	1.8	13.9	(11.9−16.2)
Zhang et al (2001) [54]	NR	0	37	0.5	0.0	(0−9.4)
Hugonnet et al (2002a) [34]	NR	6	43	1.9	14.0	(6.6−27.3)
Hugonnet et al (2002b) [34]	NR	3	18	0.9	16.7	(5.8−39.2)
Mao et al (2004) [38]	NR	8	22	1.1	36.4	(19.7−57.1)
Mehendale et al (2006) [39]	2.60%	6	457	1.1	1.3	(0.6−2.8)
Celum et al (2010) [28]	0%	43	1640	1.4	2.6	(2−3.5)
Any ART use (I^2=11%, p=0.288)						
Li et al (2006) [64]	NR	0	52	1.3	0.0	(0−6.9)
Guthrie et al (2011) [62]	NR	12	469	1.7	2.6	(1.5−4.4)
Rojanawiwat et al (2009) [58]	26%	4	63	2.1	6.3	(2.5−15.2)
Duan et al (2010) [65]	43%	31	702	1.7	4.4	(3.1−6.2)
Kumarasamy et al (2010) [56]	72%	70	2135	0.5	3.3	(2.6−4.1)
Muwonge et al (2011) [61]	75%	2	116	0.5	1.7	(0.5−6.1)
Apondi et al (2011) [63]	100%	1	62	3.0	1.6	(0.3−8.6)
Glynn et al (2011) [60]	100%	0	55	3.0	0.0	(0−6.5)



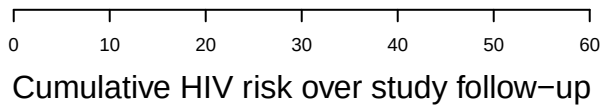
eFigure 5a

Study	ART	x	n	dur	estimate	(95%CI)
No ART use (I^2=78%, p<0.001)						
Fischl et al (1987) [32]	NR	10	24	1.7*	41.7	(24.5−61.2)
Laurian et al (1989) [35]	NR	3	17	2	17.6	(6.2−41)
Lawrence et al (1989) [36]	NR	1	19	1	5.3	(0.9−24.6)
Lusher et al (1991) [37]	NR	0	151	2.3	0.0	(0−2.5)
Siddiqui et al (1992) [50]	NR	0	16	0.8*	0.0	(0−19.4)
De Vincenzi et al (1994) [29]	NR	8	74	1.9	10.8	(5.6−19.9)
Rockstroh et al (1995) [45]	NR	0	178	5	0.0	(0−2.1)
Operskalski et al (1997) [41]	NR	4	11	1.4	36.4	(15.2−64.6)
Ragni et al (1998) [44]	0%	5	39	10	12.8	(5.6−26.7)
Any ART use (I^2=80%, p=0.001)						
Robertson et al (1998) [57]	NR	1	86	2.8	1.2	(0.2−6.3)
Saracco et al (1997) [59]	Some	37	627	2.2	5.9	(4.3−8)



eFigure 5b

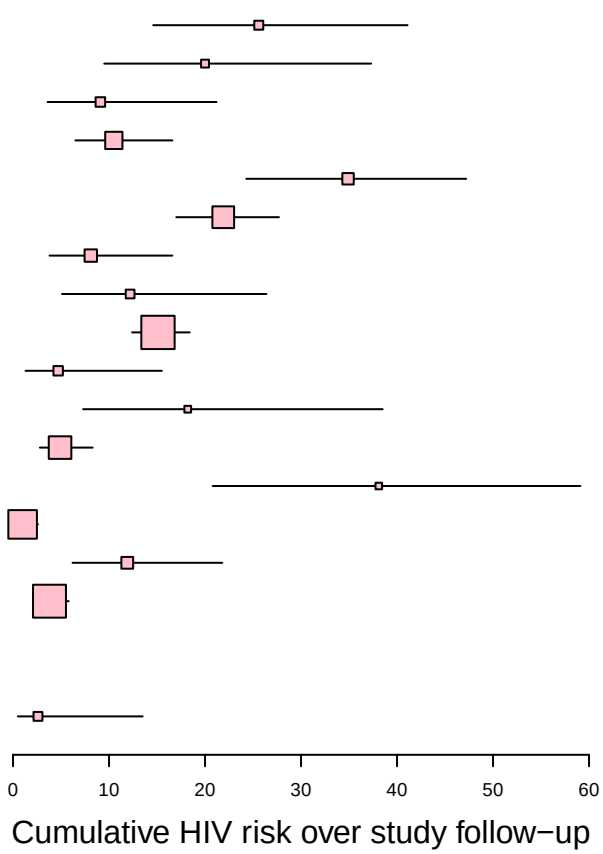
Study	ART	x	n	dur	estimate	(95%CI)
No ART use (I^2 – insufficient estimates)						
De Vincenzi et al (1994) [29]	NR	4	47	1.9	8.5	(3.4−19.9)
Any ART use (I^2 – insufficient estimates)						
Robertson et al (1998) [57]	NR	5	30	3.0	16.7	(7.3−33.6)



Cumulative HIV risk over study follow−up

eFigure 5c

Study	ART	x	n	dur	estimate	(95%CI)
No ART use (I^2=92%, p<0.001)						
Hira et al (1990) [33]	NR	10.0	39	0.9	25.6	(14.6−41.1)
Allen et al (1992) [26]	NR	6.0	30	2.1	20.0	(9.5−37.3)
Serwadda et al (1995) [49]	NR	4.0	44	1.0	9.1	(3.6−21.2)
Deschamps et al (1996) [30]	NR	15.0	143	2.2	10.5	(6.5−16.6)
Carpenter et al (1999) [27]	NR	22.0	63	3.3	34.9	(24.3−47.2)
Quinn et al (2000) [43]	NR	50.0	228	1.8	21.9	(17−27.7)
Ryder et al (2000) [47]	NR	6.0	74	2.2	8.1	(3.8−16.6)
Senkoro et al (2000) [48]	NR	4.5	37	1.6	12.2	(5.1−26.4)
Fideli et al (2001) [31]	NR	81.0	535	1.8	15.1	(12.4−18.4)
Roth et al (2001) [46]	NR	2.0	43	1.0	4.7	(1.3−15.5)
Hugonnet et al (2002) [34]	NR	4.0	22	1.8	18.2	(7.3−38.5)
Tovanabutra et al (2002) [51]	0%	12.0	246	0.9	4.9	(2.8−8.3)
Mao et al (2004) [38]	NR	8.0	21	1.1	38.1	(20.8−59.1)
Mehendale et al (2006) [39]	2.60%	4.0	394	1.1	1.0	(0.4−2.6)
Wawer et al (2009) [53]	0%	8.0	67	1.4	11.9	(6.2−21.8)
Celum et al (2010) [28]	0%	20.0	523	1.5	3.8	(2.5−5.8)
Any ART use (I^2 – insufficient estimates)						
Rojanawiwat et al (2009) [58]	26%	1.0	38	1.7	2.6	(0.5−13.5)



eFigure 5d

Study	ART	x	n	dur	estimate	(95%CI)
No ART use (I^2=88%, p<0.001)						
Hira et al (1990) [33]	NR	1.0	13	1.0	7.7	(1.4−33.3)
Allen et al (1992) [26]	NR	2.0	23	2.3	8.7	(2.4−26.8)
Serwadda et al (1995) [49]	NR	2.0	22	1.0	9.1	(2.5−27.8)
Deschamps et al (1996) [30]	NR	5.0	34	1.9	14.7	(6.4−30.1)
Carpenter et al (1999) [27]	NR	12.0	58	4.0	20.7	(12.3−32.8)
Quinn et al (2000) [43]	NR	40.0	187	1.8	21.4	(16.1−27.8)
Ryder et al (2000) [47]	NR	10.0	65	2.3	15.4	(8.6−26.1)
Senkoro et al (2000) [48]	NR	3.5	41	2.0	8.5	(3.2−21)
Fideli et al (2001) [31]	NR	61.0	487	1.8	12.5	(9.9−15.8)
Roth et al (2001) [46]	NR	0.0	23	1.0	0.0	(0−14.3)
Hugonnet et al (2002) [34]	NR	2.0	21	1.9	9.5	(2.7−28.9)
Celum et al (2010) [28]	0%	23.0	1117	1.3	2.1	(1.4−3.1)
Mehendale et al (2006) [39]	2.60%	2.0	63	1.1	3.2	(0.9−10.9)
Any ART use (I^2=0%, p=incalculable)						
Pan et al (2011) [66]	NR	3.0	75	1.9	4.0	(1.4−11.1)
Rojanawiwat et al (2009) [58]	26%	3.0	25	2.7	12.0	(4.2−30)