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Supplementary webappendix

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Appendix

The effect of HSV-2 infection on subsequent HIV acquisition: an updated systematic review and meta-analysis

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FURTHER DETAILS ON THE METHODS

A. Search strategy and selection criteria

Two reviewers (KJL and JARE) performed the searches, screened the articles and extracted the data in an electronic spreadsheet. PubMed/Medline and Embase online bibliographic databases were searched from 01/01/2003 to 25/05/2017 to ensure overlap with the review by Freeman *et al.*(1) which had date of search to June 2004. This simultaneously enabled us to ensure our searches were sufficiently sensitive, i.e., retrieved those publications from 2003 and 2004 found by Freeman *et al.*(1) – about half of their included studies. To this dataset we also added articles published before 2003 taken directly from Freeman *et al.*.

For PubMed, we combined 2 searches: (1) article titles and abstracts were searched using the following keywords: (HIV*, human immunodeficiency virus, human immunedeficiency virus, human immune deficiency virus OR human immuno deficiency virus) AND (HSV*, herpes simplex, herpes virus type 2, herpes virus 2, herpesvirus 2, genital herpes OR herpes genitalis); (2) articles were searched using the following MeSH Terms: (herpes simplex OR simplexvirus) AND (human immunodeficiency virus, HIV infection, HIV antibodies, HIV seronegativity OR HIV seroprevalence). No terms were included for study design; longitudinal study design was identified at the screening stages.

For Embase, the search strategy was as follows: HIV*.ti,ab, human immun#deficiency virus.ti,ab, human immun# deficiency virus.ti,ab (all keywords), exp[loded] human immunodeficiency virus, exp human immunodeficiency virus infection, exp human immunodeficiency virus antibody, human immunodeficiency virus prevalence OR exp HIV test (all mapped terms), AND: HSV*.ti.ab, herpes simplex.ti,ab, herpes virus type 2,ti.ab, herpes virus 2.ti,ab, herpesvirus 2.ti,ab, genital herpes.ti,ab, herpes genitalis.ti,ab (all keywords), simplexvirus, exp[loded] herpes simplex virus 2 OR exp herpes simplex (all mapped terms), AND: inciden*.ti,ab, longitudinal*.ti,ab, prospective*.ti,ab, cohort*.ti,ab, follow up.ti,ab, follow*up.ti,ab, follow* up.ti,ab, case-control.ti,ab, trial.ti,ab, time series*.ti,ab, intent* to treat.ti,ab, clinical trial.ti,ab, seroinciden*.ti,ab, seroconvert*.ti,ab, control group*,ti.ab, time to event*.ti,ab, RCT*.ti,ab, hazard*.ti,ab, retrospective*,ti,ab (all keywords), exp[loded] incidence, exp disease course, exp longitudinal study, exp time, exp prospective study, exp cohort analysis, exp survival, exp follow up, exp case control study, exp retrospective study, exp control group, exp attributable risk, exp risk factor, exp infection risk, exp infection rate, exp virus transmission, exp clinical trial (topic) OR exp randomized controlled trial (topic) (all mapped terms).

Searches were not restricted by language or bibliographic database filters. We excluded cross-sectional studies, studies with no primary data or report of the association between HSV-2 and HIV, studies not diagnosing HSV-2 infection with a type-specific antibody assay, studies relying on self-

reported HIV status, and studies limited to HSV-2-infected and/or HIV-infected individuals only (i.e., no uninfected participants were included). We did not exclude studies on the basis of study quality, which was assessed in detail. Reference lists of retrieved full-text articles and other reviews were also checked to identify additional potential publications(2).

B. Data extraction

Crude cRR and adjusted aRR (and 95%CIs) based on hazard or incidence rate ratios (HR and IRR respectively), or odds ratios (OR), were extracted, or derived from available data. We used the following formulae for calculating cRR (or their 95%CIs) from given numbers in the papers where estimates were not directly reported:

$\log IRR = \ln((d_1/T_1)/(d_0/T_0))$

$selogIRR = sqrt(1/d_1 + 1/d_0)$

$logOR = \ln((d_1/(N_1-d_1))/(d_0/(N_0-d_0)))$

$selogOR = sqrt(1/d_1 + 1/d_0 + 1/(N_1-d_1) + 1/(N_0-d_0))$

where d_0 are d_1 are the number of unexposed and exposed cases, respectively, N_0 and N_1 are the number in the unexposed and exposed population, respectively, and T_0 and T_1 are the total person-years at risk for the unexposed and exposed population, respectively.

For the subsequent meta-analysis, standard errors were calculated from:

$selog\theta = (\ln(95\%UCB)-\ln(95\%LCB))/3{\cdot}92$

where θ is either HRR, IRR or OR, UCB is the upper confidence bound and LCB is the lower confidence bound.

Studies reporting only the significance/non-significance of an association without an estimate, or which could have estimated an association but did not report the results were included. Where multiple publications reported on the same study population, we preferably extracted estimates based on HR from cox regression model or IRR and then on the largest sample size.

We extracted available RR stratified by age, sex, study year, and study arm (for controlled trials). In addition, we extracted information on several participant characteristics (e.g., age, sex, population, and WHO region, the latter subsequently used to define world region) and study characteristics (e.g., study years, study design, sample size, length and rate of follow-up, frequency of sampling, HSV-2 exposure, unexposed comparison group definition, and key potential confounders adjusted for: male circumcision status, condom use, female hormonal contraception use, sexual behaviour (any related variable except condom use), genital ulcer disease (GUD), number of sexual partners and age). We noted if estimates were inappropriately adjusted for GUD, because GUD, which is often caused by HSV-2, is likely to be on the causal pathway to HIV since ulcers can act as a portal of entry for HIV(3, 4). Follow-up rate was defined as the fraction of individuals eligible for inclusion in the study with at least one follow-up visit for HIV. Thus, follow-up rate was a function of (a) the proportion of eligible individuals recruited; (b) the proportion of recruited individuals with subsequent follow-up; and (c) the proportion of followed-up individuals with HSV-2 and HIV testing. The number of individuals at each stage of the study was not always available; therefore we computed the follow-up rate using as

much information as was available, meaning follow-up rate was in some instances overestimated. The follow-up rate for the overarching cohort study or controlled trial was used for nested case-control studies. For those studies included in previous reviews(1, 5) we extracted estimates and information from the original publications rather than from the reviews. The exception was for information and/or estimates obtained through author contact by Freeman *et al.*(1).

RR estimates of HIV following exposure to incident HSV-2 infection were classified in five timing categories reflecting uncertainty in the time sequence between HSV-2 and HIV seroconversion as follows: first, we noted whether the estimate included (a) HSV-2 seroconversion prior to HIV seroconversion (Yes/No/Unknown); (b) HSV-2 seroconversion in the same study interval as HIV seroconversion (Yes/No/Unknown); and (c) HSV-2 seroconversion after HIV seroconversion (Yes/No/Unknown). Second, using these responses we defined: 1=HSV-2 seroconversion observed in previous time interval and thus HSV-2 infection happened before HIV (definitely before); 2=HSV-2 seroconversion observed in same time interval as HIV and thus HSV-2 infection may have happened before or after HIV (indeterminably close); 3=HSV-2 seroconversion observed in previous or in same time interval as HIV (before & indeterminably close); 4a=some HSV-2 seroconversion may have occurred after HIV (maybe after & indeterminably close/before); 4b=some HSV-2 seroconversion observed after HIV (after & indeterminably close/before).

C. Newcastle-Ottawa Quality Assessment Scale assessment

Our criteria for awarding a star in each category of the Newcastle-Ottawa Quality Assessment Scale was as follows:

Case-control studies (including nested case-control studies)

Criteria	Condition required to obtain a star	Bias assessed
Selection 1) Is the Case Definition Adequate (HIV seroconversion)?	Method for confirming HIV positives stated	Misclassification of outcome; selection of cases affected by exposure status
Selection 2) Representativeness of the Cases	Cases were representative of general population individuals in the community (i.e., outside a core risk group), or an epidemiological core group commonly of interest (FSWs, MSM and STI clinic attendees; individuals in a serodiscordant partnership or with other higher-risk sexual behaviour excluded)	Sample representativeness
Selection 3) Selection of Controls (HIV-negative)	Awarded for all studies; considered to be unlikely as a source of bias in this review (studies nested within a cohort study or controlled trial)	Selection of controls affected by exposure status
Selection 4) Definition of Controls	Awarded for all studies; considered to be unlikely as a source of bias in this review because HIV testing was a review inclusion criterion	Misclassification of outcome
Comparability 1a) Comparability of Cases and Controls on the Basis of the Design or Analysis	Adjustment or matching for age was done	Confounding
Comparability 1b) Comparability of Cases and Controls on the Basis of the Design or Analysis	Adjustment or matching for number of sexual partners (any timeframe) was done	Confounding
Exposure 1) Ascertainment of Exposure (HSV-2 infection status)	Unexposed group was defined as HSV-2 seronegative throughout the study (rather than just at baseline)	Misclassification of exposure
Exposure 2) Same Method of Exposure Ascertainment for Cases and Controls	Awarded for all studies; considered to be unlikely as a source of bias in this review (stored or earlier samples used to define exposure status)	Differential measurement of exposure status on basis of outcome

Exposure 3) Non-Response Rate	Follow-up/response rate was at least 80%	Participants drop out for reasons related to the exposure or outcome

Cohort studies and controlled trials (excluding nested case-control studies)

Criteria	Condition required to obtain a star	Bias assessed
Selection 1) Representativeness of the Exposed Cohort (HSV-2 infected)	Exposed individuals were representative of general population individuals in the community (i.e., outside a core risk group), or an epidemiological core group commonly of interest (FSWs, MSM and STI clinic attendees; individuals in a serodiscordant partnership or with other higher-risk sexual behaviour excluded)	Sample representativeness
Selection 2) Selection of the Non-Exposed Cohort	Awarded for all studies; considered to be unlikely as a source of bias in this review (individuals not self-selected on basis of HSV-2 infection status)	Differential selection on basis of exposure
Selection 3) Ascertainment of Exposure	Unexposed group was defined as HSV-2 seronegative throughout the study (rather than just at baseline)	Misclassification of exposure
Selection 4) Demonstration That Outcome of Interest Was Not Present at Start of Study	Awarded for all studies; considered to be unlikely as a source of bias in this review because HIV testing was a review inclusion criterion	Misclassification of outcome; exposure did not precede outcome
Comparability 1a) Comparability of Cohorts on the Basis of the Design or Analysis	Adjustment or matching for age was done	Confounding
Comparability 1a) Comparability of Cohorts on the Basis of the Design or Analysis	Adjustment or matching for number of sexual partners (any timeframe) was done	Confounding
Outcome 1) Assessment of Outcome (HIV seroconversion)	Method for confirming HIV positives stated	Misclassification of outcome
Outcome 2) Was Follow-Up Long Enough for Outcomes to Occur?	Length of follow-up was at least a year	Inadequate identification of outcome
Outcome 3) Adequacy of Follow-Up of Cohorts	Follow-up rate was at least 80%	Participants drop out for reasons related to the exposure or outcome

D. Principal meta-analysis

All estimates within each sub-category for pooling were independent (i.e., for non-overlapping study populations). In some studies, more than one estimate was shown and pooled per sub-category in the main meta-analysis, corresponding to independent estimates from more than one country or city.

E. Assessment of heterogeneity

We investigated the impact of heterogeneity across independent RR using the I^2 statistic(6), which is the percentage variation between effect sizes that is attributable to heterogeneity rather than sampling error. The following guidance for interpretation of the I^2 statistic has been suggested: low: I^2=25-30%; moderate: I^2=50-75%; and high: $I^2 \geq 75\%$(7).

Only independent aRR were included in the meta-regression; we preferentially selected aRR of the association between HIV acquisition following exposure to incident HSV-2 infection over exposure to prevalent HSV-2 infection, where both were available from a study.

The meta-regression did not show the absolute effect of a factor in the association between HSV-2 infection and HIV acquisition. Therefore, sub-group analyses of aRR were conducted separately for the incident and prevalent HSV-2 exposures to produce pooled estimates of the association between HSV-2 infection and HIV acquisition. This was done for factors deemed epidemiologically important *a*

priori (i.e., female sex workers (FSWs), men who have sex with men (MSM), risk group, age, sex, definition of unexposed comparison group, HIV testing frequency and timing sequence for incident HSV-2 infection) and any additional statistically significant factors identified in the univariable meta-regression. The definition of unexposed comparison group and HIV testing frequency were explored because both may introduce misclassification biases and bias RR estimates toward the null. Timing sequence was explored as this may bias RR estimates following exposure to incident HSV-2 infection in either direction. Estimates were added in for the sub-pooling if available by sub-categories, but still ensuring only independent study estimates were included within a sub-category.

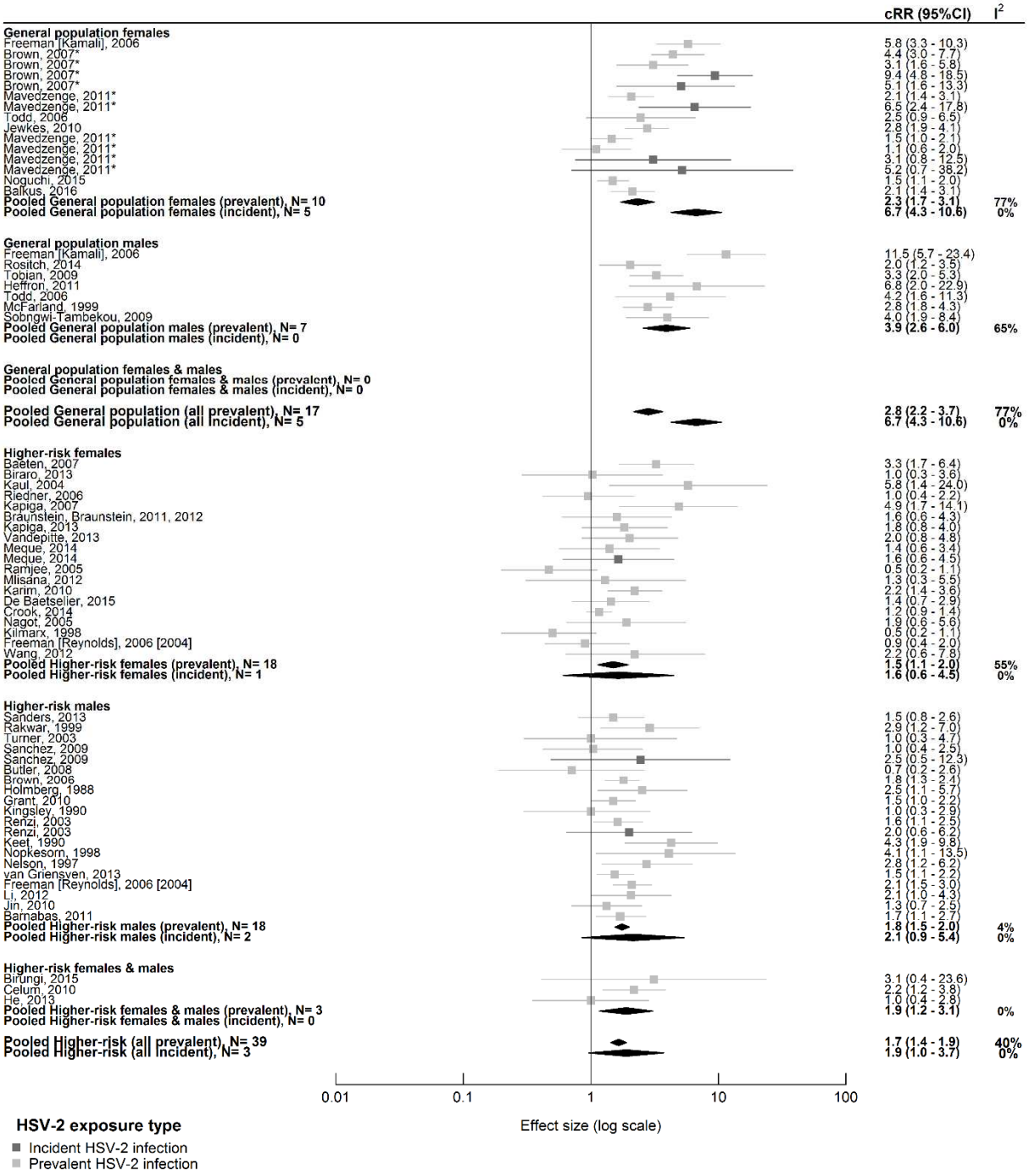
F. Funnel plots

The funnel plots show the log (ln) study estimate and its corresponding standard error (SE), constructed using the "metafunnel" command in Stata(8). The centre line is the fixed-effects pooled estimate with pseudo 95%CI (i.e., summary effect ± 1·96 * SE). This gives the estimated area where 95% of study estimates are expected to fall in in the absence of statistical heterogeneity. The plots also show Egger's test of asymmetry(9). This is a linear regression line through the estimates which aids in the assessment of publication bias.

FURTHER RESULTS

G. Additional forest plots and meta-analyses

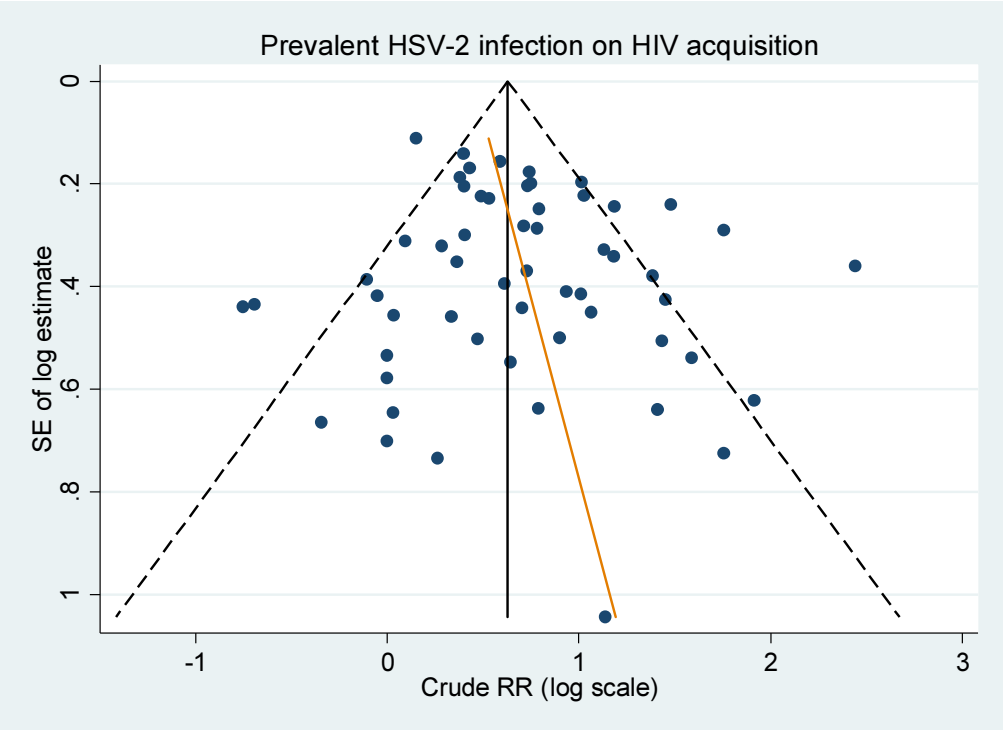
Supplementary Figure S1. Pooled crude cRR estimates of the association between HIV incidence and exposure to HSV-2 infection



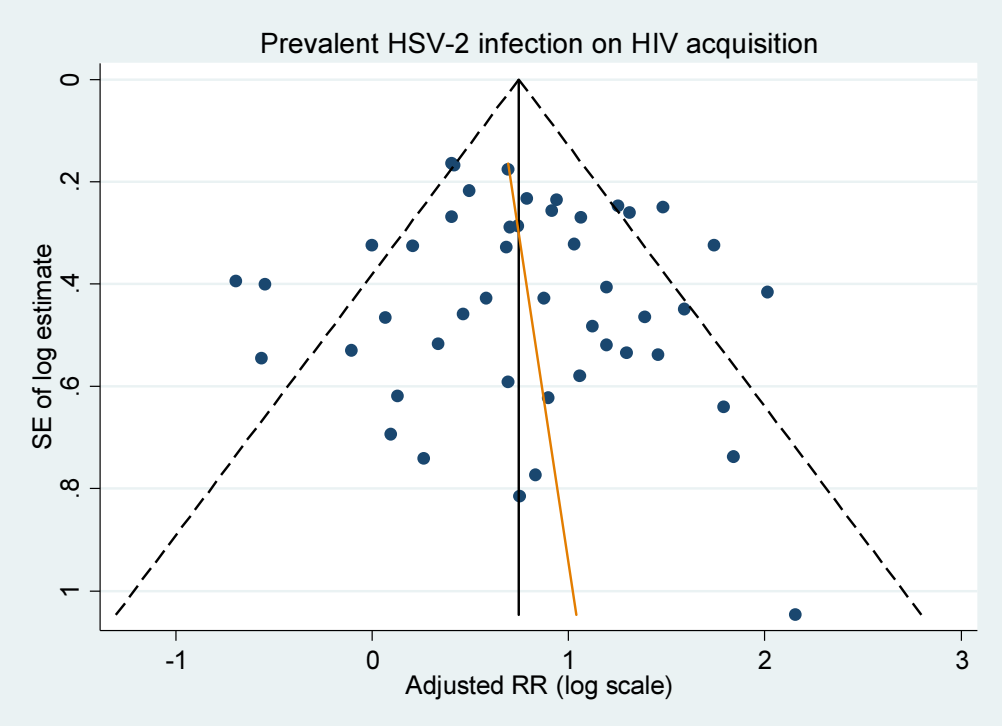
Footnote: Estimates for both prevalent HSV-2 infection on HIV acquisition, and incident HSV-2 infection on HIV acquisition (timing=1; i.e., HSV-2 seroconversion observed in previous time interval and thus *definitely before* HIV), are shown on this plot. Estimates are presented for females and males combined where these could not be obtained separately by sex. Multiple estimates for the same study corresponding to different study countries or areas are presented where these could not be combined or where it was not appropriate to do so (i.e., countries span two sub-regions) (*); however all estimates are independent (i.e., for non-overlapping study populations) within each HSV-2 exposure category. Estimates are ordered by WHO region, UN Population Division African sub-region and then mid-point of study year.

H. Funnel plots to assess publication bias

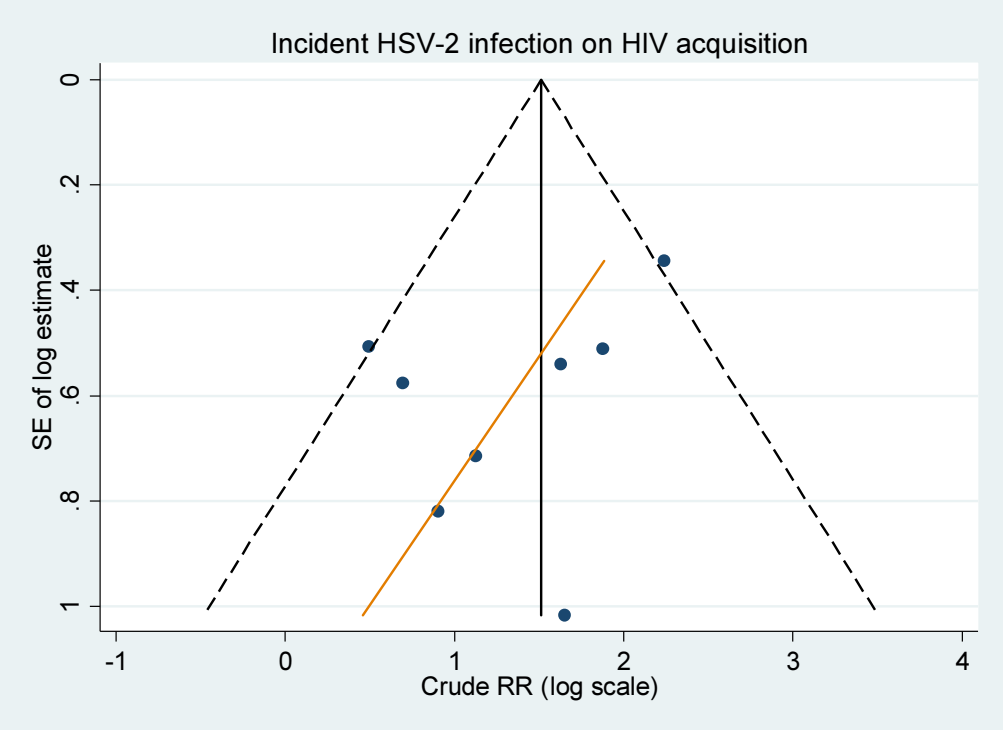
Supplementary Figure S2a. Funnel plot of the log crude cRR estimates of the association between HIV incidence and exposure to prevalent HSV-2 infection



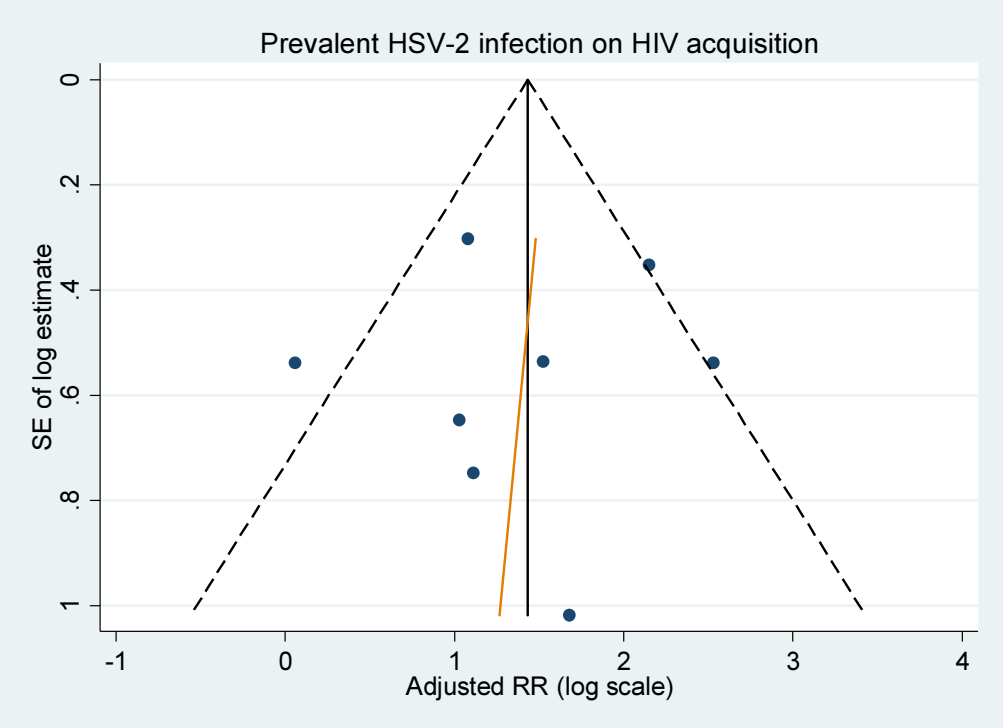
Supplementary Figure S2b. Funnel plot of the log adjusted aRR estimates of the association between HIV incidence and exposure to prevalent HSV-2 infection



Supplementary Figure S3a. Funnel plot of the log crude cRR estimates of the association between HIV incidence and exposure to incident HSV-2 infection (timing=1)



Supplementary Figure S3b. Funnel plot of the log adjusted aRR estimates of the association between HIV incidence and exposure to incident HSV-2 infection (timing=1)



I. Supplementary tables

Table S1. Description of studies and RR estimates of the association between HIV incidence and exposure to prevalent HSV-2 infection by participant and study characteristics, by estimate type

Characteristic	No. of studies (N_s)	No. of estimates (N_e)					
		HR		IRR		OR	
		Crude	Adj	Crude	Adj	Crude	Adj
All	**54**	**31**	**43**	**22**	**11**	**37**	**18**
PARTICIPANT CHARACTERISTICS							
Mean or median age[1,8]							
≤25 years	15	7	13	6	2	5	2
>25 years	39	24	30	16	9	28	15
Not reported	2	0	0	0	0	4	1
Sex[1]							
All females[1]	28	17	23	12	3	12	8
• General population	11	6	7	4	2	7	6
• FSWs	8	7	13	2	0	0	0
• Other higher-risk[5]	10	4	3	6	1	5	2
All males	28	12	16	6	5	19	10
• General population	10	5	8	3	4	6	6
• MSM	13	6	5	1	0	9	4
• Other higher-risk[6]	5	1	3	2	1	4	0
Females and males combined[7]	8	2	4	4	3	6	0
WHO region							
Africa	35	22	32	18	10	24	14
Outside Africa							
• Americas	8	1	1	0	0	10	4
• Europe	1	0	0	0	0	1	0
• Eastern Mediterranean	0	0	0	0	0	0	0
• Southeast Asia	5	2	6	4	1	1	0
• Western Pacific	4	4	2	0	0	0	0
• World (not including Africa)	1	2	2	0	0	1	0
HSV-2 prevalence[1]							
≤30%	13	8	9	3	2	3	1
>30%	42	22	33	19	9	34	17
Not reported	1	1	1	0	0	0	0
STUDY CHARACTERISTICS							
Study year (mid-point)[1]							
Pre-2000	16	7	11	4	5	20	16
2000 onwards	33	22	28	16	4	16	2
Not reported	6	2	4	2	2	1	0
Study design							
Cohort	27	21	27	10	8	3	3
Case-control[9]	7	0	1	0	0	8	3
Controlled trial	20	10	15	12	3	26	12
Study design for analysis of controlled trial data							
• Prospective	17	10	15	12	3	11	0
• Nested case-control[9]	3	0	0	0	0	15	12
Controlled trial intervention arm[1]							
• Intervention	6	0	0	3	0	5	2
• Control	6	1	1	3	0	4	2
• Combined	20	9	14	6	3	17	8
Overall number of participants for study[1]							
≤1000	31	16	18	7	0	26	18
>1000	24	15	25	15	11	11	0
Follow-up duration[1]							
≤1 year	14	9	13	6	2	7	0
>1 year	37	22	29	15	6	27	17
Not reported	4	0	1	1	3	3	1

Characteristic	No. of studies (N_s)	No. of estimates (N_e)					
		HR		IRR		OR	
		Crude	Adj	Crude	Adj	Crude	Adj
Length of time between testing for HIV							
≤6 months	36	19	33	17	5	19	3
>6 months	6	4	2	0	2	13	12
Mixture of short and long intervals between testing	3	0	0	4	4	0	0
Not reported	9	8	8	1	0	5	3
HSV-2 assay cut-off (only those studies with Focus HerpeSelect® as known assay)							
1·1/manufacturer's recommendation/unknown	14	11	12	7	0	4	3
>1·1	9	5	10	2	4	4	0
Definition of prevalent HSV-2 infection exposure[1]							
Baseline	47	28	34	20	11	31	15
Baseline and >60 days prior to HIV seroconversion	1	2	7	0	0	0	0
Baseline or >2 years prior to HIV seroconversion	1	1	1	0	0	0	0
Prior to, or at same visit as, HIV seroconversion	2	0	1	0	0	2	1
Visit prior to HIV seroconversion	1	0	0	2	0	1	0
Same interval as HIV seroconversion	1	0	0	0	0	1	0
At visit 6 months prior to HIV seroconversion	1	0	0	0	0	1	1
Anytime	1	0	0	0	0	1	1
Definition of unexposed group[1]							
HSV-2 negative at baseline	28	15	17	7	2	18	5
HSV-2 negative throughout follow-up	21	10	19	12	9	17	12
Not reported	6	6	7	3	0	2	1
Extraction of crude estimate[1,4]							
Reported	32	31	N/A	8	N/A	6	N/A
Calculated from available data	23	0	N/A	14	N/A	31	N/A
Adjusted for male circumcision status (males, or females and males combined only)[1,2,3]							
Yes	9	N/A	11	N/A	3	N/A	0
No	15	N/A	7	N/A	4	N/A	10
Unknown	3	N/A	2	N/A	1	N/A	0
Adjusted for condom use[1,2,3]							
Yes	15	N/A	18	N/A	4	N/A	3
No	23	N/A	22	N/A	6	N/A	15
Unknown	4	N/A	3	N/A	1	N/A	0
Adjusted for female hormonal contraception use (females, or females and males combined only)[1,2,3]							
Yes	6	N/A	12	N/A	1	N/A	0
No	16	N/A	14	N/A	4	N/A	8
Unknown	2	N/A	1	N/A	1	N/A	0
Adjusted for any sexual behaviour (excl. condom use)[1,2,3]							
Yes	29	N/A	34	N/A	7	N/A	7
No	8	N/A	7	N/A	3	N/A	11
Unknown	3	N/A	2	N/A	1	N/A	0
Adjusted for GUD[1,2,3]							
Yes	9	N/A	15	N/A	2	N/A	1
No	29	N/A	26	N/A	8	N/A	17
Unknown	3	N/A	2	N/A	1	N/A	0
Adjusted for no. of sexual partners[1,3]							
Yes	20	N/A	22	N/A	5	N/A	6
No	16	N/A	14	N/A	6	N/A	12
Unknown	5	N/A	7	N/A	0	N/A	0
Adjusted for age[1,3]							
Yes	34	N/A	38	N/A	9	N/A	16
No	8	N/A	5	N/A	2	N/A	2
Unknown	0	N/A	0	N/A	0	N/A	0

[1]Some overlapping studies; [2]Includes probable adjustment, and variable not included in multivariate model due to statistical non-significance; [3]Studies providing adjusted estimates; [4]Studies providing crude estimates; [5]Women with higher-risk sexual behaviour, women working in food and recreational facilities, STI clinic attendees, bar workers and women in an HIV serodiscordant partnership (grouped with FSW populations in Figures 2 and 3, Appendix Figure S1 and Table 2); [6]Men with higher-risk sexual behaviour (likely to be MSM), STI clinic attendees, male trucking company employees, clients of FSWs and Thai military conscripts (grouped with MSM in Figures 2 and 3, Appendix Figure S1 and Table 2); [7]Estimates by sex could not be obtained; [8]May be estimated from range; [9]All case-control studies

subsequently analysed together; FSWs – Female sex workers; MSM – Men who have sex with men; GUD – Genital ulcer disease; HR – Hazard ratio; IRR – Incidence rate ratio; OR – Odds ratio.

Table S2. Description of studies and RR estimates of the association between HIV incidence and exposure to incident HSV-2 infection by participant and study characteristics, by estimate type

Characteristic	No. of studies (N_s)	No. of estimates (N_e)					
		HR		IRR		OR	
		Crude	Adj	Crude	Adj	Crude	Adj
All	**28**	**13**	**25**	**8**	**9**	**20**	**13**
PARTICIPANT CHARACTERISTICS							
Mean or median age[1,9]							
≤25 years	10	4	7	2	2	3	3
>25 years	20	9	18	6	7	16	10
Not reported	1	0	0	0	0	1	0
Sex[1]							
All females	11	7	15	2	2	5	7
• General population	4	5	5	0	1	5	7
• FSWs	2	0	7	1	0	0	0
• Other higher-risk[6]	5	2	3	1	1	0	0
All males	17	6	8	4	5	13	6
• General population	6	2	3	3	5	6	5
• MSM	9	4	2	1	0	6	1
• Other higher-risk[7]	3	0	3	0	0	1	0
Females and males combined[8]	5	0	2	2	2	2	0
WHO region							
Africa	16	9	18	6	8	12	12
Outside Africa							
Americas	5	2	2	0	0	5	1
Europe	1	0	0	0	0	1	0
Eastern Mediterranean	0	0	0	0	0	0	0
Southeast Asia	4	1	5	2	1	1	0
Western Pacific	2	1	0	0	0	1	0
World (not including Africa)	0	0	0	0	0	0	0
HSV-2 prevalence[1]							
≤30%	8	5	4	2	2	1	0
>30%	21	8	21	6	7	19	13
Not reported	0	0	0	0	0	0	0
STUDY CHARACTERISTICS							
Study year (mid-point)[1]							
Pre-2000	11	0	7	2	2	18	11
2000 onwards	16	13	16	5	7	1	2
Not reported	2	0	2	1	0	1	0
Study design							
Cohort	15	7	17	4	4	3	0
Case-control[10]	6	0	1	0	0	7	1
Controlled trial	7	6	7	4	5	10	12
Study design for analysis of controlled trial data[1]							
• Prospective	6	6	7	4	5	0	0
• Nested case-control[10]	2	0	0	0	0	10	12
Controlled trial intervention arm							
• Intervention	1	0	0	0	0	2	2
• Control	1	0	0	0	0	2	2
• Combined	7	6	7	4	5	6	8
Overall number of participants for study[1]							
≤1000	13	3	4	2	0	18	11
>1000	16	10	21	6	9	2	2
Follow-up duration[1]							
≤1 year	7	5	8	3	1	3	0
>1 year	18	8	16	5	8	13	13
Not reported	4	0	1	0	0	4	0
Length of time between testing for HIV							
≤6 months	17	11	23	4	1	7	3

Characteristic	No. of studies (N_s)	No. of estimates (N_e)					
		HR		IRR		OR	
		Crude	Adj	Crude	Adj	Crude	Adj
>6 months	4	1	0	0	2	11	10
Mixture of short and long intervals between testing	2	0	0	3	5	0	0
Not reported	5	1	2	1	1	2	0
HSV-2 assay cut-off (only those studies with Focus HerpeSelect® as known assay)							
1·1/manufacturer's recommendation/unknown	8	7	10	2	1	0	2
>1·1	4	2	9	1	0	1	0
Definition of incident HSV-2 infection exposure[1]							
≤60 days prior to HIV seroconversion	1	0	1	0	0	0	0
60 days prior to HIV seroconversion	1	0	5	0	0	0	0
≤6 months prior to HIV seroconversion	2	0	1	1	0	1	0
>6 months prior to HIV seroconversion	1	0	1	1	0	0	0
≤2 years prior to HIV seroconversion	1	1	1	0	0	0	0
Prior to, or at same visit as, HIV seroconversion	2	0	1	0	0	2	0
Visit prior to HIV seroconversion	1	1	1	0	0	0	0
Same interval as HIV seroconversion	1	0	0	0	0	1	0
Anytime	21	11	14	6	7	16	13
Not reported	1	0	0	0	2	0	0
Definition of unexposed group[1]							
HSV-2 negative at baseline	0	0	0	0	0	0	0
HSV-2 negative throughout follow-up	28	10	22	8	9	20	13
Not reported	1	3	3	0	0	0	0
Extraction of crude estimate[1,4]							
Reported	14	13	N/A	6	N/A	1	N/A
Calculated from available data	11	0	N/A	2	N/A	19	N/A
Adjusted for male circumcision status (males, or females and males combined only)[1,2,3]							
Yes	5	N/A	2	N/A	4	N/A	0
No	9	N/A	8	N/A	3	N/A	6
Unknown	0	N/A	0	N/A	0	N/A	0
Adjusted for condom use[1,2,3]							
Yes	8	N/A	11	N/A	6	N/A	1
No	12	N/A	14	N/A	3	N/A	10
Unknown	1	N/A	0	N/A	0	N/A	2
Adjusted for female hormonal contraception use (females, or females and males combined only)[1,2,3]							
Yes	4	N/A	9	N/A	1	N/A	0
No	8	N/A	8	N/A	3	N/A	5
Unknown	1	N/A	0	N/A	0	N/A	2
Adjusted for any sexual behaviour (excl. condom use)[1,2,3]							
Yes	16	N/A	23	N/A	9	N/A	1
No	3	N/A	2	N/A	0	N/A	10
Unknown	1	N/A	0	N/A	0	N/A	2
Adjusted for GUD[1,2,3]							
Yes	8	N/A	12	N/A	4	N/A	0
No	11	N/A	12	N/A	5	N/A	13
Unknown	1	N/A	1	N/A	0	N/A	0
Adjusted for no. of sexual partners[1,3]							
Yes	11	N/A	16	N/A	7	N/A	1
No	8	N/A	7	N/A	1	N/A	10
Unknown	3	N/A	2	N/A	1	N/A	2
Adjusted for age[1,3]							
Yes	14	N/A	20	N/A	8	N/A	13
No	5	N/A	5	N/A	0	N/A	0
Unknown	1	N/A	0	N/A	1	N/A	0
Timing of incident HSV-2 infection in relation to HIV acquisition[1,5]							
1 (Definitely before)	7	6	10	0	1	2	3
2 (Indeterminably close)	2	1	0	0	0	1	0
3 (Before & indeterminably close)	12	4	10	3	1	5	0
4a (Maybe after & indeterminably close/before)	8	0	2	2	5	12	10

Characteristic	No. of studies (N_s)	No. of estimates (N_e)					
		HR		IRR		OR	
		Crude	Adj	Crude	Adj	Crude	Adj
4b (After & indeterminably close/before)	5	2	3	3	2	0	0

[1]Some overlapping studies; [2]Includes probable adjustment, and variable not included in multivariate model due to statistical non-significance; [3]Studies providing adjusted estimates; [4]Studies providing crude estimates; [5]1=HSV-2 seroconversion observed in previous time interval and thus HSV-2 infection happened before HIV (definitely before); 2=HSV-2 seroconversion observed in same time interval as HIV and thus HSV-2 infection may have happened before or after HIV (indeterminably close); 3=HSV-2 seroconversion observed in previous or in same time interval as HIV (before & indeterminably close); 4a=some HSV-2 seroconversion may have occurred after HIV (maybe after & indeterminably close/before); 4b=some HSV-2 seroconversion observed after HIV (after & indeterminably close/before); [6]Women with higher-risk sexual behaviour, STI clinic attendees and bar workers (grouped with FSWs in Figures 2 and 3, Appendix Figure S1 and Table 2); [7]Men with higher-risk sexual behaviour (e.g. clients of FSWs), STI clinic attendees and Thai military conscripts (grouped with MSM in Figures 2 and 3, Appendix Figure S1 and Table 2); [8]Estimates by sex could not be obtained; [9]May be estimated from range; [10]All case-control studies subsequently analysed together; FSWs – Female sex workers; MSM – Men who have sex with men; GUD – Genital ulcer disease; HR – Hazard ratio; IRR – Incidence rate ratio; OR – Odds ratio.

Supplementary Table S3. Description of study characteristics relevant to the assessment of study quality for the association between HIV incidence and exposure to HSV-2 infection, and results of the Newcastle-Ottawa scale assessment

Study no.	Multiple population author	Study type	Controlled trial intervention arm (controlled trials only)	Frequency of testing for HSV-2 and HIV infection	Length of fup (yrs)	Prevalent or incident HSV-2 infection exposure	Definition of prevalent/incident HSV-2 infection exposure	Definition of HSV unexposed group	Other variable on which estimate varies, to distinguish it from other estimates in study	Crude estimate reported or could be calculated?	Crude estimate NR but could be calculated??	Adjusted estimate reported?	Adjusted for male circumcision status (males, or females & males combined only)?	Adjusted for condom use?	Adjusted for female hormonal contraception use (females, or females & males combined only)?	Adjusted for (any) sexual behaviour?	Adjusted for genital ulcer disease?	Estimate shown in Figure 2 or Figure S1?	Selection 1)[2]	Selection 2)[2]	Selection 3)[2]	Selection 4)[3]	Comparability 1a)[3]	Comparability 1b)[3]	Outcome (cohorts)/Exposure (case-controls) 1)[4]	Outcome (cohorts)/Exposure (case-controls) 2)[4]	Outcome (cohorts)/Exposure (case-controls) 3)[4]
1	Masese (2015)(10), Baeten (2007)(11), McClelland (2015)(12), Graham (2013)(13)	CT	NA	HSV-2 & HIV: B & mnthly	3·11	P	B & >60 days prior to HIV seroconversion[1]	T	-	NR	NA	Y	NA	Y*	Y	Y	Y	Adjusted only	*	*	*	*	*	*	*	*	*
						I	60 days prior to HIV seroconversion	T	-	NR	NA	Y	NA	Y*	Y	Y	Y	Adjusted only	*	*	*	*	*	*	*	*	*
						P	B & >60 days prior to HIV seroconversion[1]	T	Yr=1993-1997	NR	NA	Y	NA	Y*	Y	Y	Y	N	*	*	*	*	*	*	*	*	*
						I	60 days prior to HIV seroconversion	T	Yr=1993-1997	NR	NA	Y	NA	Y*	Y	Y	Y	N	*	*	*	*	*	*	*	*	*
						P	B & >60 days prior to HIV seroconversion[1]	T	Yr=1998-2002	NR	NA	Y	NA	Y*	Y	Y	Y	N	*	*	*	*	*	*	*	*	*
						I	60 days prior to HIV seroconversion	T	Yr=1998-2002	NR	NA	Y	NA	Y*	Y	Y	Y	N	*	*	*	*	*	*	*	*	*
						P	B & >60 days prior to HIV seroconversion[1]	T	Yr=2003-2007	NR	NA	Y	NA	Y*	Y	Y	Y	N	*	*	*	*	*	*	*	*	*
						I	60 days prior to HIV seroconversion	T	Yr=2003-2007	NR	NA	Y	NA	Y*	Y	Y	Y	N	*	*	*	*	*	*	*	*	*
						P	B & >60 days prior to HIV seroconversion[1]	T	Yr=2008-2012	NR	NA	Y	NA	Y*	Y	Y	Y	N	*	*	*	*	*	*	*	*	*
						I	60 days prior to HIV seroconversion	T	Yr=2008-2012	NR	NA	Y	NA	Y*	Y	Y	Y	N	*	*	*	*	*	*	*	*	*
					1·25	P	B & >60 days prior to HIV seroconversion[1]	T	HSV-2 assay cut-off=1·1	Y	N	Y	NA	Y	Y	Y	Y	Crude only	*	*	*	*	*	*	*	*	*
						I	<60 days prior to HIV seroconversion	T	HSV-2 assay cut-off=1·1; timing=3	NR	NA	Y	NA	Y	Y	Y	Y	N	*	*	*	*	*	*	*	*	*
					1·42	P	B & >60 days prior to HIV seroconversion[1]	T	-	Y	N	Y	NA	Y	Y	Y	Y	N	*	*	*	*	-	*	*	*	-
2	Barnabas (2011)(14)	RCT	CM		1·05	P	B	B	-	Y	N	Y	Y	N	NA	Y	N	Y	*	*	-	*	*	-	*	*	*

			C	HSV-2: B only (day 1 or wks 2 or 4); HIV: B, wk 12 & all subsequent visits except wk 26		P	B	B	-	Y	N	Y	Y	N	NA	Y	N	N	*	*	-	*	*	-	*	*	*
			IV			P	B	B	-	Y	Y	NR	-	-	-	-	-	N	*	*	-	*	-	-	*	*	*
3	Biraro (2013)(15), Biraro (2013)(16)	CT	NA	HSV-2 & HIV: B & 12-mnthly	4·20	P	B	T	General pop'n; F+M	NR	NA	Y	N	N	N	Y	N	N	*	*	*	*	*	*	*	*	-
					4·10	P	B	T	General pop'n; F	NR	NA	Y	NA	N	N	Y	N	Y	*	*	*	*	*	*	*	*	-
					4·60	P	B	T	General pop'n; M	NR	NA	NR	-	-	-	-	-	N	*	*	*	*	-	-	*	*	-
					4·20	I	U	T	General pop'n; F+M	NR	NA	Y	N	N	N	Y	N	N	*	*	*	*	*	*	*	*	-
					4·10	I	U	T	General pop'n; F	NR	NA	Y	NA	N	N	Y	N	N	*	*	*	*	*	*	*	*	-
					4·60	I	U	T	General pop'n; M	NR	NA	NR	-	-	-	-	-	N	*	*	*	*	-	-	*	*	-
					4·20	P	B	T	Serodiscordant couples; F+M	Y	N	Y	N	N	N	Y	N	N	-	*	*	*	*	*	*	*	-
						P	B	T	Serodiscordant couples; F	Y	N	NR	-	-	-	-	-	Y	-	*	*	*	-	-	*	*	-
						P	B	T	Serodiscordant couples; M	NR	NA	NR	-	-	-	-	-	Y	-	*	*	*	-	-	*	*	-
4	Braunstein (2011)(17), Braunstein (2012)(18)	CT	NA	HSV-2: B & at 12 mnths; HIV: quarterly	2·00	P	B	B	-	Y	N	Y	NA	N	N	N	N	Y	*	*	-	*	*	-	*	*	*
5	Brown (2006)(19)	RCT	CM	HSV-2 & HIV: 6-mnthly	3·01	P	B or >2 yrs prior to HIV seroconversion	T	-	Y	N	Y	N	N	NA	Y	N	Y	*	*	*	*	*	*	-	*	*
						I	Within 2 yrs prior to HIV seroconversion	T	-	Y	N	Y	N	N	NA	Y	N	N	*	*	*	*	*	*	-	*	*
						I	Last visit	T	-	Y	N	Y	N	N	NA	Y	N	N	*	*	*	*	*	*	-	*	*
6	Brown (2007)(20), van de Wijgert (2009)(21), Morrison (2007)(22), Van Der Pol (2008)(23), Morrison (2010)(24), Averbach(2010)(25), Mavedzenge (2012)(26)	CT	NA	HSV-2 & HIV: B & every 12 wks for 15-24 mnths	1·83	P	B	T	Zimbabwe	Y	N	Y	NA	Y	Y	Y	Y	Y	*	*	*	*	*	*	*	*	*
						I	A	T	Zimbabwe	Y	N	Y	NA	Y	Y	Y	Y	Y	*	*	*	*	*	*	*	*	*
						P	B	T	Uganda	Y	N	Y	NA	Y	Y	Y	Y	Y	*	*	*	*	*	-	*	*	*
						I	A	T	Uganda	Y	N	Y	NA	Y	Y	Y	Y	Y	*	*	*	*	*	-	*	*	*
7	Jewkes (2010)(27), Jewkes (2008)(28), Christofides (2014)(29)	RCT	CM	HSV-2 & HIV: B & at 1 & 2 yrs	1·90	P	B	B	-	Y	Y	NR	-	-	-	-	-	Y	*	*	-	*	-	-	*	*	*
						I	A	T	-	NS	NA	NS [1]	-	-	-	-	-	N	*	*	*	*	-	-	*	*	*

8	Gray (2011)(30), Moodie (2015)(31)	RCT	CM	HSV-2: B; HIV: day of first vaccination, wks 12 & 30, & every 6 mnths thereafter, then at unmasking & subsequently every 3 mnths	1·00	P	B	B	F+M	NR	NA	SS	Y	Y[1]	Y	Y	N	N	*	*	-	*	*	-	*	*	-
						P	B	B	F	NR	NA	Y	NA	Y[1]	Y	Y	N	Y	*	*	-	*	*	-	*	*	-
						P	B	B	M	NR	NA	Y	Y	Y[1]	NA	Y	N	Y	*	*	-	*	*	-	*	*	-
9	Guwatudde (2009)(32)	CT	NA	HSV-2 & HIV: B & 6-mnthly	1·00	P	B	B	-	NR	NA	Y	U	U	U	U	U	Y	*	*	-	*	*	-	*	-	*
						I	A	U	-	NR	NA	NR	-	-	-	-	-	N	*	*	-	*	-	-	*	-	*
10	Celum (2010)(33), Hughes (2012)(34), Mackelprang (2012)(35)	RCT	CM	HSV-2: B; HIV: B & quarterly	2·00	P	B	B	-	Y	Y	Y	Y	N	N	N	Y	Y	-	*	-	*	-	-	*	*	-
			IV			P	B	B	OR	Y	Y	NR	-	-	-	-	-	N	-	*	-	*	-	-	*	*	-
			C			P	B	B	OR	Y	Y	NR	-	-	-	-	-	N	-	*	-	*	-	-	*	*	-
			IV			P	B	B	IRR	Y	Y	NR	-	-	-	-	-	N	-	*	-	*	-	-	*	*	-
			C			P	B	B	IRR	Y	Y	NR	-	-	-	-	-	N	-	*	-	*	-	-	*	*	-
11	Heffron (2011)(36)	CT	NA	HIV & HSV-2: B & fup	0·82	P	B	B	-	Y	N	Y	Y	N	NA	N	Y	N	*	*	-	*	*	-	*	-	-
						P	B	B	HSV-2 assay cut-off=3·3	Y	N	Y	Y	N	NA	N	Y	N	*	*	-	*	*	-	*	-	-
						P	B	T	-	Y	N	Y	Y	N	NA	N	Y	Y	*	*	*	*	*	-	*	-	-
						I	A	T	-	Y	N	Y	Y	N	NA	N	Y	N	*	*	*	*	*	-	*	-	-
12	Kaul (2004)(37), Hirbod (2008)(38), Kaul (2007)(39)	RCT	CM	HSV-2: B & 6-mnthly; HIV: B & quarterly	2·14	P	B	B	-	Y	N	Y	NA	Y	N	Y	N	Y	*	*	-	*	*	-	-	*	-
13	Jin (2010)(40)	CT	NA	HSV-2: B & offered annually; HIV: B & annually	3·90	P	B	T	-	Y	N	NS	-	-	-	-	-	Y	*	*	*	*	-	-	*	*	*
						I	A	T	-	Y	N	NS	-	-	-	-	-	N	*	*	*	*	-	-	*	*	*
14	Kapiga (2013)(41)	CT	NA	HSV-2 & HIV: B & quarterly for 12 mnths	0·87	P	B	T	-	Y	Y	Y	NA	Y*	Y*	Y	Y*[1]	Y	*	*	*	*	*	*	*	-	*
						I	A	T	-	Y	Y	Y	NA	Y*	Y*	Y	Y*[1]	N	*	*	*	*	*	*	*	-	*
15	Kapiga (2007)(42)	CT	NA	HSV-2 & HIV: B & quarterly for 12 mnths	1·04	P	B	T	-	Y	N	Y	NA	N	N	Y	Y	Y	*	*	*	*	-	-	*	*	*
						I	A	T	-	Y	N	Y	NA	N	N	Y	Y	N	*	*	*	*	-	-	*	*	*
16	Kebede (2004)(43), Mekonnen (2005)(44)	CT	NA	HSV-2 & HIV: B & 6-mnthly	U	P	B	T	F+M	Y	Y	Y	N	N	N	N	N	N	*	*	*	*	-	-	*	-	*
						P	B	T	F	NR	NA	Y	NA	N	N	N	N	Y	*	*	*	*	*	-	*	-	*
						P	B	T	M	NR	NA	Y	N	N	NA	N	N	Y	*	*	*	*	*	-	*	-	*
						I	A	T	-	Y	Y	-	-	-	-	-	-	N	*	*	*	*	*	-	*	-	*
17	Kjetland (2006)(45)	CT	NA	HSV-2 & HIV: B & at 12 mnths	1·00	P	B	B	-	NS	NA	NS	-	-	-	-	-	N	*	*	-	*	-	-	-	*	-
18	Li (2012)(46)	CT	NA		1·00	P	B	U	-	Y	N	Y	U	U	NA	U	N	Y	*	*	-	*	*	*	*	*	*

				HSV-2 & HIV: B, 6 mnths & 12 mnths		I	A	U	-	NR	NA	NR	-	-	-	-	-	N	*	*	-	*	-	-	*	*	*
19	Mavedzenge (2011)(47), Venkatesh (2011)(48), Padian (2007)(49), Mavedzenge (2010)(50)	RCT	CM	HSV-2 & HIV: B & quarterly	1·00	P	B	U	Zimbabwe	Y	N	Y	NA	N	N	Y*	N	Y	*	*	-	*	*	-	*	*	*
						I	A	U	Zimbabwe	Y	N	Y	NA	N	N	Y*	N	Y	*	*	-	*	*	-	*	*	*
						P	B	U	Durban, South Africa	Y	N	Y	NA	Y	Y	Y	N	Y	*	*	-	*	*	*	*	*	*
						I	A	U	Durban, South Africa	Y	N	Y	NA	Y	Y	Y	N	Y	*	*	-	*	*	*	*	*	*
						P	B	U	Johannesburg, South Africa	Y	N	Y	NA	N	N	Y	N	Y	*	*	-	*	-	-	*	*	*
						I	A	U	Johannesburg, South Africa	Y	N	Y	NA	N	N	Y	N	Y	*	*	-	*	-	-	*	*	*
		CC	CM		1·75	I	A	T	18-24 yrs	NR	NA	Y	NA	U	U	U	N	N	*	*	*	*	*	-	*	*	*
						I	A	T	25-49 yrs	NR	NA	Y	NA	U	U	U	N	N	*	*	*	*	*	-	*	*	*
		RCT	IV			P	B	U	-	Y	Y	NR	-	-	-	-	-	N	*	*	-	*	-	-	*	*	*
			C			P	B	U	-	Y	Y	NR	-	-	-	-	-	N	*	*	-	*	-	-	*	*	*
20	Smith (2010)(51), Mehta (2012)(52), Rositch (2014)(53), Bailey (2007)(54)	RCT	CM	HSV-2: B, 6, 12, 18 & 24 mnths; HIV: B, 1, 3, 6, 12, 18 & 24 mnths	3·50	P	B	B	Smaller N	NR	NA	Y	Y	N	NA	N	N	N	*	*	-	*	*	-	*	*	-
					2·50	P	B	B	Larger N	Y	N	Y	Y	Y	NA	Y	N	Y	*	*	-	*	*	-	*	*	*
			CM (adj.)		2·00	I	A	T	-	Y	N	Y	Y	N	NA	N	Y	N	*	*	*	*	-	-	*	*	*
21	Meque (2014)(55)	CT	NA	HSV-2 & HIV: B & mnthly	1·00	P	B	B	-	Y	N	NI	-	-	-	-	-	Y	-	*	-	*	-	-	*	*	*
						I	A	T	-	Y	N	NI[1]	-	-	-	-	-	Y	-	*	*	*	-	-	*	*	*
22	Muiru (2013)(56)	CT	NA	HSV-2 & HIV: B & quarterly	2·00	P	B	B	-	NR	NA	NR	-	-	-	-	-	N	-	*	-	*	-	-	-	*	*
						I	A	T	-	NR	NA	NR	-	-	-	-	-	N	-	*	*	*	-	-	-	*	*
23	Nagot (2005)(57)	CT	NA	HSV-2 & HIV: B & quarterly	1·95	P	B	B	-	Y	N	Y	NA	N	N	Y	N	Y	*	*	-	*	*	*	*	*	*
						I	A	T	-	NR	NA	NR	-	-	-	-	-	N	*	*	*	*	-	-	*	*	*
24	Karim (2010)(58), Naranbhai (2011)(59), Naranbhai (2012)(60)	RCT	IV	HSV-2: unclear; HIV: B & mnthly	0·83	P	Visit prior to HIV seroconversion	T	-	Y	Y	SS	-	-	-	-	-	N	*	*	*	*	-	-	*	-	-
			C			P		T	-	Y	Y	SS	-	-	-	-	-	N									
			CM			P		T	-	Y	Y	SS	-	-	-	-	-	Y									
25	Sanders (2013)(61), Okuku (2011)(62)	CT	NA	HSV-2 & HIV: B & mnthly (if reported RAI) or quarterly	1·40	P	B	U	Higher-risk F	NR	NA	NR	-	-	-	-	-	N	*	*	-	*	-	-	*	*	-
						I	A	T	Higher-risk F	NR	NA	Y	NA	Y	N	Y	N	N	*	*	*	*	*	-	*	*	-
						P	B	T	MSM	Y	N	NS[1]	-	-	-	-	-	Y	*	*	*	*	*	-	*	*	-
						I	A	T	Higher-risk M	NR	NA	Y	N	Y	NA	Y	N	N	*	*	*	*	*	-	*	*	-
						I	A	T	MSM	Y	N	NS	-	-	-	-	-	N	*	*	*	*	*	-	*	*	-

26	Ramjee (2005)(63)	RCT	CM	HSV-2 testing done retrospectively; HIV: B & fup	2·20	P	B	T	-	Y	Y	Y	NA	N	N	Y	N	Y	*	*	*	*	*	*	*	*	*
						I	A	T	-	Y	Y	Y	NA	N	N	Y	N	N	*	*	*	*	-	-	*	*	*
27	Renzi (2003)(64)	CC	NA	HSV-2 & HIV: B & 6-mnthly	1·50	P	B	T	-	Y	Y	NR	-	-	-	-	-	Y	*	*	*	*	-	-	*	*	*
						P	A	T	-	Y	N	Y	N	Y	NA	Y	N	N	*	*	*	*	*	*	*	*	*
						I	A	T	-	Y	Y	Y	N	Y	NA	Y	N	Y	*	*	*	*	*	*	*	*	*
28	Freeman (2006) (1)Reynolds (2003)(65), Reynolds (2004)(66)	CT	NA	HSV-2 & HIV: B & 3-mnthly: details from Mehendale 1995(67)	0·89	P	B	T	F+M	Y	N	Y	Y	Y	N	Y	N	N	*	*	*	*	*	*	*	-	*
						I	≤6 mnths prior to HIV seroconversion	T	F+M	Y	N	Y	N	N	N	Y	N	N	*	*	*	*	*	*	*	-	*
						I	>6 mnths prior to HIV seroconversion	T	F+M	Y	N	Y	N	N	N	Y	N	N	*	*	*	*	*	*	*	-	*
						P	B	T	F	Y	N	Y	NA	N	N	Y	N	Y	*	*	*	*	*	*	*	-	*
						I	A[1]	T	F	NR	NA	Y	NA	N	N	Y	N	N	*	*	*	*	*	*	*	-	*
						P	B	T	M	Y	N	Y	N	N	NA	Y	N	Y	*	*	*	*	*	*	*	-	*
						I	A[1]	T	M	NR	NA	Y	N	N	NA	Y	N	N	*	*	*	*	*	*	*	-	*
29	Riedner (2006)(68)	CT	NA	HSV-2 & HIV: B & quarterly	2·25	P	B	B	-	Y	Y	Y	NA	N	N	Y	N	Y	*	*	-	*	-	-	*	*	-
						P	B	B	Adj. for GUD	Y	Y		NA	N	N	Y	Y	N	*	*	-	*	-	-	*	*	-
						I	A	T	-	NR	NA	NR	-	-	-	-	-	N	*	*	*	*	-	-	*	*	-
30	Sanchez (2009)(69)	CC	NA	HSV-2 & HIV: B & 6-mnthly	0·92	P	B	B	-	Y	Y	NR	-	-	-	-	-	Y	*	*	*	*	*	-	-	*	-
						I	A	T	Timing=3	Y	Y	NR	-	-	-	-	-	N	*	*	*	*	*	-	*	*	-
						I	A	T	Timing=1	Y	Y	NR	-	-	-	-	-	Y	*	*	*	*	*	-	*	*	-
31	Sobngwi-Tambekou (2009)(70), Auvert (2010)(71)	RCT	CM	HSV-2 & HIV: B & at 3, 12 & 21 mnths	1·75	P	B	T	-	Y	N	Y	Y	Y	NA	Y	N	Y	*	*	*	*	*	-	-	*	*
						I	A	T	-	Y	N	Y	Y	Y	NA	Y	N	N	*	*	*	*	*	-	-	*	*
32	Tobian (2009)(72), Gray (2009)(73), Tobian (2013)(74)	RCT	CM	HSV-2 & HIV: B & at 6, 12 & 24 mnths	2·00	P	B	T	-	Y	N	Y	Y[1]	Y*	NA	Y*	N	Y	*	*	*	*	*	*	*	*	*
						I	A	T	Timing=4b	Y	N	Y	Y[1]	Y*	NA	Y*	N	N	*	*	*	*	*	*	*	*	*
						P	B	T	Adj. for GUD	Y	N	Y	Y[1]	Y*	NA	Y*	Y	N	*	*	*	*	*	*	*	*	*
						I	A	T	Timing=4b; adj. for GUD	Y	N	Y	Y[1]	Y*	NA	Y*	Y	N	*	*	*	*	*	*	*	*	*
						I	A	T	Timing=3	NR	NA	Y	N[1]	Y*	NA	Y*	Y	N	*	*	*	*	*	*	*	*	*
						I	A	T	Timing=1	NR	NA	Y	N[1]	Y*	NA	Y*	Y	Y	*	*	*	*	*	*	*	*	*
33	Todd (2006)(75), del Mar Pujades Rodriguez (2002)(76)	CC	CM	HSV-2 & HIV: B & at 2 yrs	2·00	P	B	T	F; 15-54 yrs	Y	Y	Y	NA	N	N	N	N	Y	*	*	*	*	*	-	*	*	-
						I	A	T	F; 15-54 yrs	Y	Y	Y	NA	N	N	N	N	N	*	*	*	*	*	-	*	*	-
						P	B	T	M; 15-54 yrs	Y	Y	Y	N	N	NA	N	N	Y	*	*	*	*	*	-	*	*	-
						I	A	T	M; 15-54 yrs	Y	Y	Y	N	N	NA	N	N	N	*	*	*	*	*	-	*	*	-

						P	B	T	F; 15-24 yrs	Y	Y	Y	NA	N	N	N	N	N	*	*	*	*	*	-	*	*	-
						I	A	T	F; 15-24 yrs	Y	Y	Y	NA	N	N	N	N	N	*	*	*	*	*	-	*	*	-
						P	B	T	F; 25-54 yrs	Y	Y	Y	NA	N	N	N	N	N	*	*	*	*	*	-	*	*	-
						I	A	T	F; 25-54 yrs	Y	Y	Y	NA	N	N	N	N	N	*	*	*	*	*	-	*	*	-
						P	B	T	M; 15-24 yrs	Y	Y	Y	N	N	NA	N	N	N	*	*	*	*	*	-	*	*	-
						I	A	T	M; 15-24 yrs	Y	Y	Y	N	N	NA	N	N	N	*	*	*	*	*	-	*	*	-
						P	B	T	M; 25-54 yrs	Y	Y	Y	N	N	NA	N	N	N	*	*	*	*	*	-	*	*	-
						I	A	T	M; 25-54 yrs	Y	Y	Y	N	N	NA	N	N	N	*	*	*	*	*	-	*	*	-
			IV			P	B	T	F	Y	Y	Y	NA	N	N	N	N	N	*	*	*	*	*	-	*	*	-
						I	A	T	F	Y	Y	Y	NA	N	N	N	N	N	*	*	*	*	*	-	*	*	-
			C			P	B	T	F	Y	Y	Y	NA	N	N	N	N	N	*	*	*	*	*	-	*	*	-
						I	A	T	F	Y	Y	Y	NA	N	N	N	N	N	*	*	*	*	*	-	*	*	-
			IV			P	B	T	M	Y	Y	Y	N	N	NA	N	N	N	*	*	*	*	*	-	*	*	-
						I	A	T	M	Y	Y	Y	N	N	NA	N	N	N	*	*	*	*	*	-	*	*	-
			C			P	B	T	M	Y	Y	Y	N	N	NA	N	N	N	*	*	*	*	*	-	*	*	-
						I	A	T	M	Y	Y	Y	N	N	NA	N	N	N	*	*	*	*	*	-	*	*	-
34	Turner (2003)(77)	CT	NA	HSV-2 & HIV: B & repeat visits	2·50	P	B	B	-	Y	N	Y	N	N	NA	Y	N	Y	*	*	-	*	*	*	-	*	*
						I	A	T	-	NR	NA	NR	-	-	-	-	-	N	*	*	*	*	-	-	-	*	*
35	Serwadda (2003)(78)	CC	CM	HSV-2: at 10 mnths; HIV: B & 10-mnthly	2·50	P	B	B	F+M	Y	N	NR	-	-	-	-	-	N	*	*	*	*	*	-	-	*	-
						P	B	B	HSV-2 assay cut-off=3·5	Y	N	NR	-	-	-	-	-	N	*	*	*	*	*	-	-	*	-
						P	B	B	F	NR	NA	Y	NA	Y	N	Y	N	Y	*	*	*	*	*	*	-	*	-
						P	B	B	M	NR	NA	Y	N	Y	NA	Y	N	Y	*	*	*	*	*	*	-	*	-
36	van Griensven (2013)(79), Lam (2017)(80), Thienkrua (2016)(81)	CT	NA	HSV-2: B & 12-mnthly; HIV: B & 4-mnthly	3·00	P	B	B	-	Y	N	Y	U	U	NA	U	N	Y	*	*	-	*	*	-	*	*	-
						I	A	T	-	Y	N	NS	-	-	-	-	-	N	*	*	*	*	-	-	*	*	-
37	Noguchi (2015)(82)	RCT	CM	HSV-2: B & study end; HIV: B & mnthly	1·11	P	B	B	OR	Y	Y	NR	-	-	-	-	-	N	*	*	-	*	-	-	-	*	*
						P	B	B	IRR	Y	Y	NR	-	-	-	-	-	Y	*	*	-	*	-	-	-	*	*
38	Wang (2012)(83)	CT	NA	HSV-2 & HIV: B & fup	1·55	P	B	B	-	Y	N	NS	-	-	-	-	-	Y	*	*	-	*	-	-	*	*	-
39	McFarland (1999)(84)	CT	NA	HSV-2 & HIV: B & 6-mnthly	4·00	P	B	T	-	Y	Y	Y	N	N	NA	Y	Y	Y	*	*	*	*	*	*	*	*	*
						I	A	T	Timing=3	Y	Y	-	-	-	-	-	-	N	*	*	*	*	*	*	*	*	*
						I	A	T	Timing=4b	-	NA	Y	N	N	NA	Y	Y	N	*	*	*	*	*	*	*	*	*

40	Kilmarx (1998)(85)	CT	NA	HSV-2 & HIV: B & 3-mnthly plus routine STD clinic attendances	2·47	P	B	B	-	Y	N	Y	NA	N	N	N	N	Y	*	*	-	*	*	-	*	*	*
41	Rakwar (1999)(86)	CT	NA	HSV-2: B only[1]; HIV: B & 3-mnthly	1·67	P	B	B	-	Y	N	Y	Y	Y	NA	Y	N	Y	*	*	-	*	*	-	*	*	-
42	Kingsley (1990)(87)	CC	NA	HSV-2 & HIV: B & fup (6 visits)	2·00	P	At visit 6 mnths prior to HIV seroconversion	T	-	Y	N	Y	N	N	NA	N	N	Y	*	*	*	*	*	*	*	*	*
						I	<6 mnths prior to HIV seroconversion	T	-	Y	Y	NR	-	-	-	-	-	N	*	*	*	*	-	*	*	*	*
43	Nopkesorn (1998)(88)	CT	NA	HSV-2 & HIV: B & at 6, 17 & 23 mnths	1·92	P	B	B	-	Y	N	Y	N	N	NA	Y	N	Y	-	*	-	*	-	-	*	*	*
44	Keet (1990)(89)	CC	NA	HSV-2: B only but stored sera used; HIV: B & 3-mnthly	U	P	Same interval as HIV seroconversion	T	-	Y	Y	NR	-	-	-	-	-	Y	*	*	*	*	-	-	*	*	*
						I	Same interval as HIV seroconversion	T	-	Y	Y	NR	-	-	-	-	-	N	*	*	*	*	-	-	*	*	*
45	Holmberg (1998)(90)	CC	NA	U; HSV-2 samples drawn from before date of HIV seroconversion	U	P	Prior to, or at same visit as, HIV seroconversion	U	-	Y	Y	Y	N	N	NA	Y	N	Y	*	*	*	*	*	*	-	*	*
						I	Prior to, or at same visit as, HIV seroconversion	T	-	Y	Y	NR	-	-	-	-	-	N	*	*	*	*	-	-	*	*	*
46	Nelson (1997)(91)	CC	NA	HSV-2 & HIV: B & 6-mnthly	U	P	Prior to HIV seroconversion	T	-	Y	N	Y	N	N	NA	Y	U	Y	*	*	*	*	-	*	*	*	-
						I	Prior to, or at same visit as, HIV seroconversion	T	-	Y	N	Y	N	N	NA	Y	U	N	*	*	*	*	-	*	*	*	-
47	Vandepitte (2013)(92), Vandepitte (2014)(93)	CT	NA	HSV-2 & HIV: B, 3 mnths, 6 mnths, 9 mnths, 12 mnths then 6-mnthly	2·10	P	B[1]	U	-	Y	Y	Y	NA	Y	Y*[1]	Y	N	Y	*	*	-	*	*	*	*	*	-
48	Balkus (2016)(94)	RCT	CM	HSV-2: B & study end; HIV: B & 3-mnthly	1·75	P	B	B	-	Y	Y	NR	-	-	-	-	-	Y	*	*	-	*	-	-	*	*	-
49	Mlisana (2012)(95), Pellett Madan (2015)(96)	CT	NA	HSV-2: B & mnthly; HIV: B & mnthly	2·00	P	B	B	-	Y	N	Y	NA	U	U	Y[1]	U	Y	*	*	-	*	*	-	-	*	*
						I	A	T	-	NR	NA	NR	-	-	-	-	-	N	*	*	*	*	-	-	-	*	*
50	He (2013)(97), Ding (2015)(98)	CT	NA	HSV-2 & HIV: B & at 12 mnths	1·00	P	B	B	-	Y	N	Y	N	Y*[1]	N	Y	N	Y	-	*	-	*	*	-	*	*	-
						I	A	T	-	Y	Y	NR	-	-	-	-	-	N	-	*	*	*	-	-	*	*	-
51	Hochberg (2015)(99)	CT	NA	HSV-2 & HIV: B & fup (approx. 6 yrs later)	5·63	I	A	T	-	NR	NA	Y	Y*[1]	N	N	Y	N	N	*	*	*	*	-	-	-	*	-
52	Grant (2010)(100)	RCT	CM	HSV-2: testing at B & every scheduled visit & screening every 24 wks; HIV: B & 4-wkly	1·20	P	B	B	-	Y	Y	NR	-	-	-	-	-	Y	*	*	-	*	-	-	*	*	*
			IV		1·20	P	B	B	-	Y	Y	NR	-	-	-	-	-	N	*	*	-	*	-	-	*	*	*
			C		1·20	P	B	B	-	Y	Y	NR	-	-	-	-	-	N	*	*	-	*	-	-	*	*	*
53		RCT	CM		5·00	P	B	U	F	Y	N	Y	NA	N	N	Y	N	Y	*	*	-	*	*	*	*	*	-

	Freeman (2006) (1)[Kamali (unpublished; study information taken from Kamali (2003)(101)]			HSV-2 & HIV: B & subsequent study rounds 2 & 3		P	B	U	M	Y	N	Y	N	N	NA	Y	N	Y	*	*	-	*	*	*	*	*	-
54	De Baetselier (2015)(102)	CC	CM	HSV-2 & HIV: B & at wks 4, 12, 24, 36, 52 & 56 & when clinically indicated	1·00	P	B	B	-	Y	Y	NR	-	-	-	-	-	Y	-	*	*	*	-	-	-	*	*
						P	B	B	HSV-2 assay cut-off=0·66	Y	Y	NR	-	-	-	-	-	N	-	*	*	*	-	-	-	*	*
						P	B	B	HSV-2 assay=Focus	Y	Y	NR	-	-	-	-	-	N	-	*	*	*	-	-	-	*	*
55	Butler (2008)(103)	CC	NA	HSV-2: B & fup[1]; HIV: B & fup	0·50	P	B[1]	U	-	Y	Y	NR	-	-	-	-	-	Y	-	-	*	*	-	-	-	*	*
56	Crook (2014)(104), Daniels (2016)(105)	RCT	CM	HSV-2 testing in wks 0, 40, 52; HIV testing at B & in wks 12, 24, 40, 52	1·00	P	B	B	-	Y	Y	NR	-	-	-	-	-	Y	-	*	-	*	-	-	*	*	*
						I	A	T	-	NR	NA	NR	-	-	-	-	-	N	-	*	*	*	-	-	*	*	*
57	Birungi (2015)(106)	CT	NA	HSV-2 & HIV: B & 6-monthly	1.50	P	B	B	-	Y	Y	NR	-	-	-	-	-	Y	-	*	-	*	-	-	*	*	*
						I	A	B	-	NR	NA	NR	-	-	-	-	-	N	-	*	-	*	-	-	*	*	*

Fup=follow-up; NA=Not applicable; NR=Not reported; NI=not investigated because univariate findings not significant; CT=Cohort; CC=Case-control; RCT=Randomised controlled trial; IV=Intervention; C=Control; CM=Combined; P=Prevalent; I=Incident; B=Baseline; T=Throughout follow-up; A=Anytime during follow-up; U=Unclear or Unknown; OR=Odds ratio; IRR=Incidence rate ratio; MSM=Men who have sex with men; NS=Not statistically significant; SS=Statistically significant; Y*=not included in final model but not SS in univariate model. Timing=1: HSV-2 seroconversion observed in previous time interval and thus HSV-2 infection happened before HIV (definitely before); Timing=2: HSV-2 seroconversion observed in same time interval as HIV and thus HSV-2 infection may have happened before or after HIV (indeterminably close); Timing=3: HSV-2 seroconversion observed in previous or in same time interval as HIV (before & indeterminably close); Timing=4a: some HSV-2 seroconversion may have occurred after HIV (maybe after & indeterminably close/before); Timing=4b: some HSV-2 seroconversion observed after HIV (after & indeterminably close/before). [1]Not certain; [2]For cohort studies and controlled trials: (1) Representativeness of exposed cohort; (2) Selection of unexposed cohort; (3) Ascertainment of exposure; (4) Demonstration that outcome did not occur before exposure. For case-control studies: (1) Adequacy of case definition; (2) Representativeness of cases; (3) Selection of controls; (4) Demonstration that outcome did not occur before exposure; [3]For cohort studies and controlled trials: (1) Comparability of exposed and unexposed. For case-control studies: (1) Comparability of cases and controls; [4]For cohort studies and controlled trials: (1) Assessment of outcome; (2) Length of follow-up; (3) Adequacy of follow-up. For case-control studies: (1) Assessment of exposure; (2) Same method of ascertainment for cases and controls; (3) Non-response rate. For detailed explanation of condition for awarding a star see Appendix C. Follow-up rate defined as the percentage with at least one follow-up visit for HIV among those eligible for enrolment in the study: the rate closest to this was used where information on study enrolment and retention was incomplete which means that the rate presented may be inaccurate. The follow-up rate for the overarching study was used for nested case-control studies.

APPENDIX REFERENCES

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