Impact of Male Circumcision on Risk of HIV Infection in Men in a Changing Epidemic Context – Systematic Review and Meta-Analysis

Supporting Information

Farley TMM, Samuelson J, Grabowski MK, Ameyan W, Gray RH, Baggaley R. Impact of male circumcision on risk of HIV Infection in men in a changing epidemic context – Systematic review and meta-analysis. J Int AIDS Soc. 2020;23:e25490.

Contents

Table S1: Articles with relevant data excluded after full text review

Reason for exclusion	Details
Further analysis of previous result	1) Quinn 2000 [1] further analysis of Gray 2000 [2] 2) Baeten 2005 [3] further analysis of Lavreys 1999 [4] 3) Gray 2009 [5] further analysis of Gray 2007 [6] 4) Mahiane 2009 [7] further analysis of Auvert 2005 [8] 5) Shaffer 2010 [9] further analysis of Shaffer 2007 [10] 6) Mehta 2012 [11] further analysis of Bailey 2007 [12]
Superseded by more comprehensive analysis	1) Santelli 2015 [13] superseded by Grabowski 2017 [14] 2) Kong 2016 [15] superseded by Grabowski 2017 [14] 3) Tomita 2017 [16] superseded by Vandormael 2019 [17]

Table S2: Risk of bias assessment (observational studies)

First author publication year	1) Confounding	2) Selection of participants into study	3) Classification of intervention or exposure	4) Deviations from intended intervention or exposure	5) Missing data	6) Measurement of outcomes	7) Selection of reported result
B) Extended follow-up of former RCT participants							
Mehta 2013 [18]	Moderate Self-selection to circumcision in control arm after closure of RCT. Adequate control of confounding.	Low Well-defined cohort from RCT. 195 of 1740 (11%) eligible former trial participants did not consent for extended post-trial follow-up.	Low Documented circumcision procedure in study facilities	Low Circumcision provided in study facilities. Actual date of circumcision used as time-varying covariate.	Low Ongoing cohort follow-up, censored at last known HIV negative test	Low Objective laboratory-based outcome (repeat serology)	Low Pre-defined primary endpoint on full study cohort
Gray 2012 [19]	Moderate Self-selection to circumcision after closure of RCT. Adequate control of confounding.	Low Well-defined cohort from RCT control arm. 388/2522 (15%) of former control arm trial participants did not attend first post-trial follow-up.	Low Documented circumcision procedure in study facilities	Low Circumcision provided in study facilities. Actual date of circumcision used as time-varying covariate.	Low Ongoing cohort follow-up, censored at last known HIV negative test	Low Objective laboratory-based outcome (repeat serology)	Low Pre-defined primary endpoint on full study cohort
C) Cohorts of men at high risk of HIV infection							
Cameron 1989 [20]	Moderate Adjustment for genital ulcer disease and frequency of prostitute contact had limited impact on estimated OR. Residual confounding cannot be excluded.	Low STI patients with self-reported recent contact with prostitute cohort (~ 85% HIV seroprevalence) confirmed during three separate interviews and without reference to circumcision status	Low Circumcision status assessed by clinical examination	Low No new circumcisions during follow-up period. Circumcision cannot be reversed.	Low Similar follow-up in circumcised and non-circumcised men	Low Objective laboratory-based outcome (repeat serology)	Low Circumcision a priori risk factor from previous case-control study in STI patients from same setting

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Lavreys 1999 [4]	Moderate Adjustment for major HIV risk factors increased magnitude of protective effect of circumcision. Further adjustment for incident sexually transmitted infections had little impact. Potential for unmeasured confounding cannot be excluded.	Low Trucking company employees enrolled without reference to circumcision status. 19% did not return for follow-up visits, not related to HIV risk factors.	Low Circumcision status assessed by clinical examination	Low No new circumcisions during follow-up period. Circumcision cannot be reversed.	Low Similar follow-up rates in circumcised and non-circumcised men	Low Objective laboratory-based outcome (repeat serology)	Low Pre-defined endpoint
Gray 2000 [2]	Moderate No adjustment possible	Low Secondary analysis of cohort in cluster-randomized trial of STD intervention. No bias expected between circumcision status and cohort enrolment.	Moderate Self-reported circumcision status	Low Majority of circumcisions performed under age 12 y for traditional or religious reasons. No reported circumcisions during follow-up and none expected in this community. Circumcision cannot be reversed.	Moderate Approx. 75% follow-up rate overall. No information on differences according to HIV risk profile or circumcision status.	Low Objective laboratory-based outcome (repeat serology)	Low Further analysis of cluster randomized trial cohort on a risk factor of major interest from previous studies
Reynolds 2004 [21]	Moderate Limited impact of adjustment for major HIV risk factors. Potential for unmeasured confounding cannot be excluded.	Low Condom use in previous 3 months lower in non-enrolees than enrolees in previous analysis of initial cohort enrolled May-1993 – Mar-1995 [22], though condom use during follow-up not associated with circumcision status.	Low Circumcision status assessed by clinical examination	Low No new circumcisions reported during follow-up period. Circumcision cannot be reversed.	Unclear No information on proportion with incomplete outcome nor differences according to HIV risk profile or circumcision status	Low Objective laboratory-based outcome (repeat serology)	Low Further analysis of prospective STI cohort on endpoint of major interest from previous studies

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Hughes 2012 [23]	Moderate No effect of adjustment for risk factors for HIV infection on estimated impact of circumcision	Low Highly selected group of serodiscordant couples in RCT, but no evidence of any relation to circumcision other than HIV status	Low Circumcision determined by clinical examination	Low Circumcision cannot be reversed	Low Low loss to follow-up rate in RCT	Low Objective laboratory-based outcome (repeat serology)	Low One of 21 factors investigated for potential to modify per-act transmission probability, of primary interest from previous publications and a pre-specified factor for subgroup analysis in the original RCT.
D) Community-based cohorts before circumcision scale-up							
Gray 2000 [2]	Moderate Limited impact of adjustment for potential sociodemographic and behavioural confounders assessed at baseline and during follow-up	Low Secondary analysis of cohort included in cluster-randomized trial of STD intervention. No bias expected between circumcision status and cohort enrolment.	Moderate Self-reported circumcision status	Low Majority of circumcisions performed under age 12 yr for traditional or religious reasons	Moderate Approx. 75% follow-up rate overall. No information on differences according to HIV risk profile or circumcision status.	Low Objective laboratory-based outcome (repeat serology)	Low Further analysis of cluster randomized trial cohort on a risk factor of major interest from previous studies.
Shaffer 2007 [10]	Moderate Limited impact of adjustment for potential sociodemographic and behavioural confounders assessed at baseline on risk estimate	Low Rates of refusal to participate in cohort and information on HIV risk factors between refusers and participants not reported. Not considered likely to be related to circumcision status.	Moderate Self-reported circumcision status	Low Circumcision cannot be reversed. No reported circumcisions during follow-up. 98% of circumcisions performed under age 20 years while mean age of cohort 31 years.	Low 10% of cohort missing outcomes	Low Objective laboratory-based outcome (repeat serology)	Low Risk factor of primary interest given prior publications, and RCT results which motivated the specific analysis

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Kim 2016 [24]	Serious Single multinomial logistic regression model fitted to incident, prevalent and absence of HIV infection in both men and women, together with an age x circumcision interaction term. Impossible to extract adjusted effect of circumcision on HIV incidence or prevalence and assess impact of adjusting for potential confounding factors.	Low High participation rates (80% blood draw of eligible individuals) and no evidence participation rates related to HIV risk and/or circumcision	Moderate Self-reported circumcision status	Low Circumcision cannot be reversed	Low Few missing data and no reason expected for any association with outcome and exposure	Moderate Incidence estimated from cross-sectional Limiting Antigen Avidity Enzyme Immunoassay ("LAg") assay rather than repeat serology. Sensitivity of estimated incidence ratio to different assumptions on recent infection window not explored. Even if misclassification errors non-differential, impact would bias estimate towards the null.	Low Risk factor of a priori interest
Dandona 2013 [25]	Serious Long interval between baseline and follow-up surveys (5-6 years) and long recall period for assessment of behavioural risk factors	Moderate 8,390 of 12,066 (70%) HIV-negative men and women in baseline survey traced and provided follow-up blood for HIV testing. Participation rate 75% for rural and 63% for urban men.	Moderate Self-reported circumcision status	Low Circumcision cannot be reversed	Low Few details provided	Low Objective laboratory-based outcome (repeat serology)	Low One of 16 risk factors investigated for potential impact on HIV incidence, second strongest association after HIV-positive spouse

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E) Community-based cohorts during circumcision scale-up							
Grabowski 2017 [14]	Moderate Major relevant confounding factors assessed and adjusted for, including time varying circumcision status and risk factors. Potential for unmeasured confounding cannot be excluded.	Moderate Participation rates constant over survey rounds, though evidence that younger persons and those with high-risk sexual behaviours more likely to be lost to follow-up than those with low risk behaviours.	Moderate Self-reported circumcision status	Low Circumcision cannot be reversed	Low Younger men more likely to be lost to follow-up, but no evidence of association with circumcision status. Analysis adjusting for age sufficient to control for differential drop-out rates.	Low Objective laboratory-based outcome (repeat serology)	Low Risk factor of a priori interest
Lissouba 2011 [26]	Moderate Adjustment for potential sociodemographic and behavioural confounders had only moderate impact on risk estimate. Potential for unmeasured confounding cannot be excluded.	Low Survey response rate 74%.	Low Circumcision status determined by clinical examination	Low Circumcision cannot be reversed	Low	Moderate Potential for misclassification as recent infection assessed using HIV-1 Calypte Incidence BED EIA [BED] assay. Sensitivity of estimated incidence ratio to different assumptions on recent infection window not explored. Even if misclassification errors non-differential, impact would be bias towards the null.	Low Pre-defined primary endpoint and subject of the community intervention
Auvert 2013 [27]	Moderate Limited impact of adjustment for major potential confounders, but unmeasured cofounding cannot be excluded	Low Survey response rate 80%	Low Circumcision status assessed by clinical examination	Low Circumcision status assessed by clinical examination	Low	Moderate Potential for misclassification as recent infection assessed using HIV-1 Calypte Incidence BED EIA [BED] assay. Incidence ratio estimates appeared robust to different cutoff values.	Low Predefined primary endpoint

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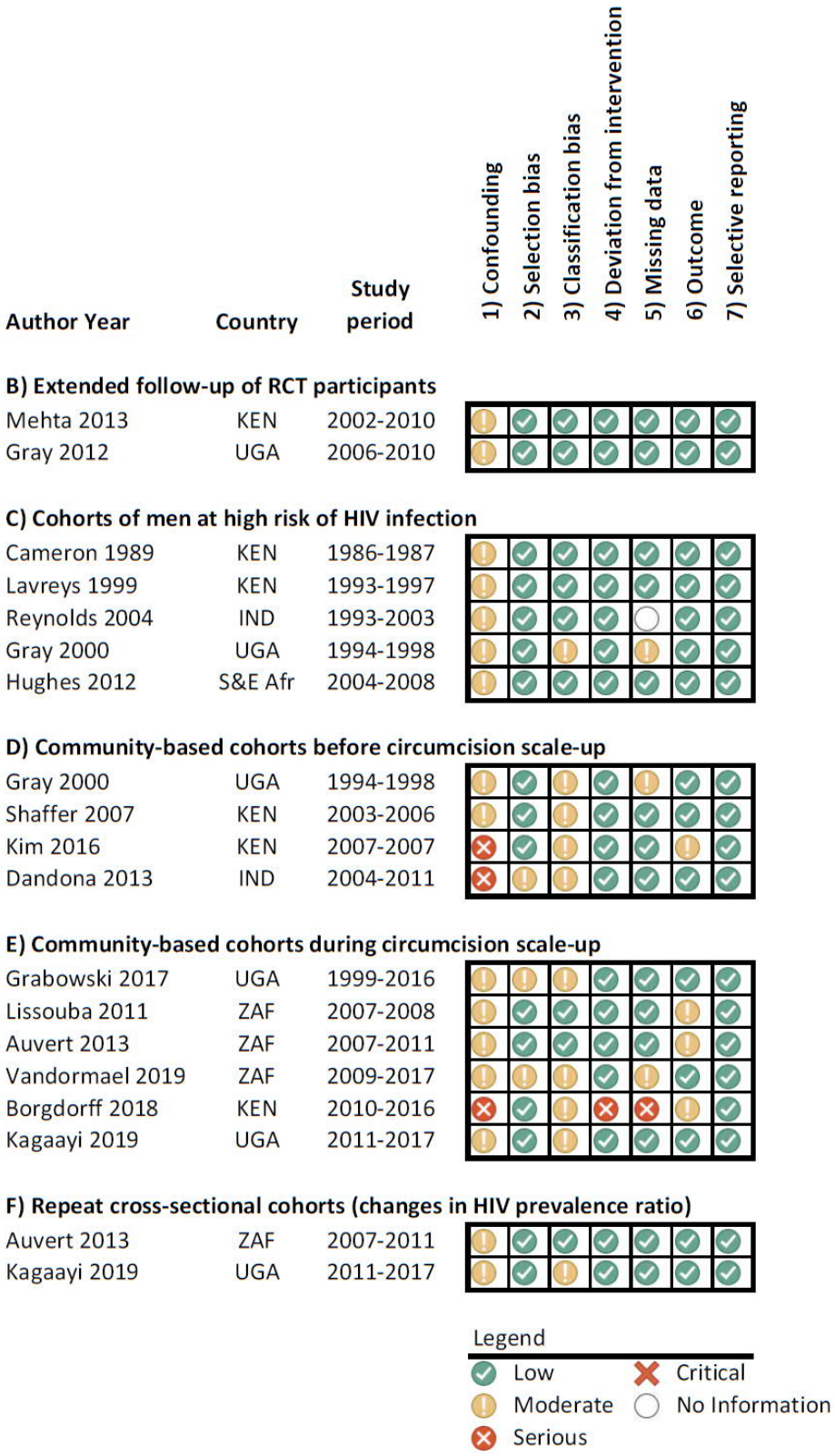
Vandormael 2019 [17]	Moderate No assessment of circumcision-specific confounders, but major risk factors included in model; residual confounding cannot be excluded.	Moderate Average 35% of eligible subjects contacted and tested for HIV. Adjustment for out-migration and not having HIV test using propensity-score weighting.	Moderate Self-reported circumcision status	Low Circumcision cannot be reversed	Moderate Average 35% of eligible subjects contacted and tested for HIV	Low Objective laboratory-based outcome (repeat serology)	Low Risk factor of a priori interest from previous studies
Borgdorff 2018 [28]	Serious Potential for more men at higher risk of HIV infection to choose circumcision within VMMC program. No data presented on impact of potential confounders.	Low	Moderate Self-reported circumcision status	Serious No information on changes in circumcision status during follow-up period. National VMMC programme initiated in 2008 and likely to have included many men in study cohort.	Serious Only 41% of participants HIV-negative in first survey present in a follow-up cohort	Moderate Home-based HIV testing using established and validated serological testing algorithm. Self-reported HIV infection taken as valid endpoint in absence of HIV test, but self-reported HIV-negative test not considered a valid endpoint.	Low Pre-defined outcome and exposure of specific interest given context of VMMC programme expansion in country following results from RCTs.
Kagaayi 2019 [29]	Moderate Limited impact of adjustment for major potential confounders, but unmeasured cofounding cannot be excluded	Low Low refusal rates	Moderate Self-reported circumcision status	Low Circumcision cannot be reversed	Low Low rates of missing data	Low Objective laboratory-based outcome (repeat serology)	Low Exposure of primary interest
F) Repeat cross-sectional cohorts (changes in HIV prevalence ratio)							
Auvert 2013 [27]	Moderate Limited impact of adjustment for major potential confounders after age differences accounted for	Low Survey response rate 80%	Low Circumcision status assessed by clinical examination	Low Circumcision cannot be reversed	Low	Low Objective laboratory-based outcome (serology)	Low Pre-defined primary endpoint

First author publication year	1) Confounding	2) Selection of participants into study	3) Classification of intervention or exposure	4) Deviations from intended intervention or exposure	5) Missing data	6) Measurement of outcomes	7) Selection of reported result
Kagaayi 2019 [29]	Moderate Limited impact of adjustment for major potential confounders	Low Low refusal rates	Moderate Self-reported circumcision status	Low Circumcision cannot be reversed	Low Low rates of missing data	Low Objective laboratory-based outcome (serology)	Low Pre-defined primary endpoint

Figure S1: Risk of bias assessment (observational studies)



Note:
'S&E Afr' = Seven countries in southern and eastern Africa (BWA, KEN, RWA, TZA, UGA, ZAF, ZMB)

Figure S2: Incidence ratios in community-based studies in Africa without serious risk of bias during circumcision scale-up with studies ordered by A) time period, B) HIV incidence in uncircumcised men, C) average circumcision prevalence during scale-up, and D) average ART prevalence in women during scale-up

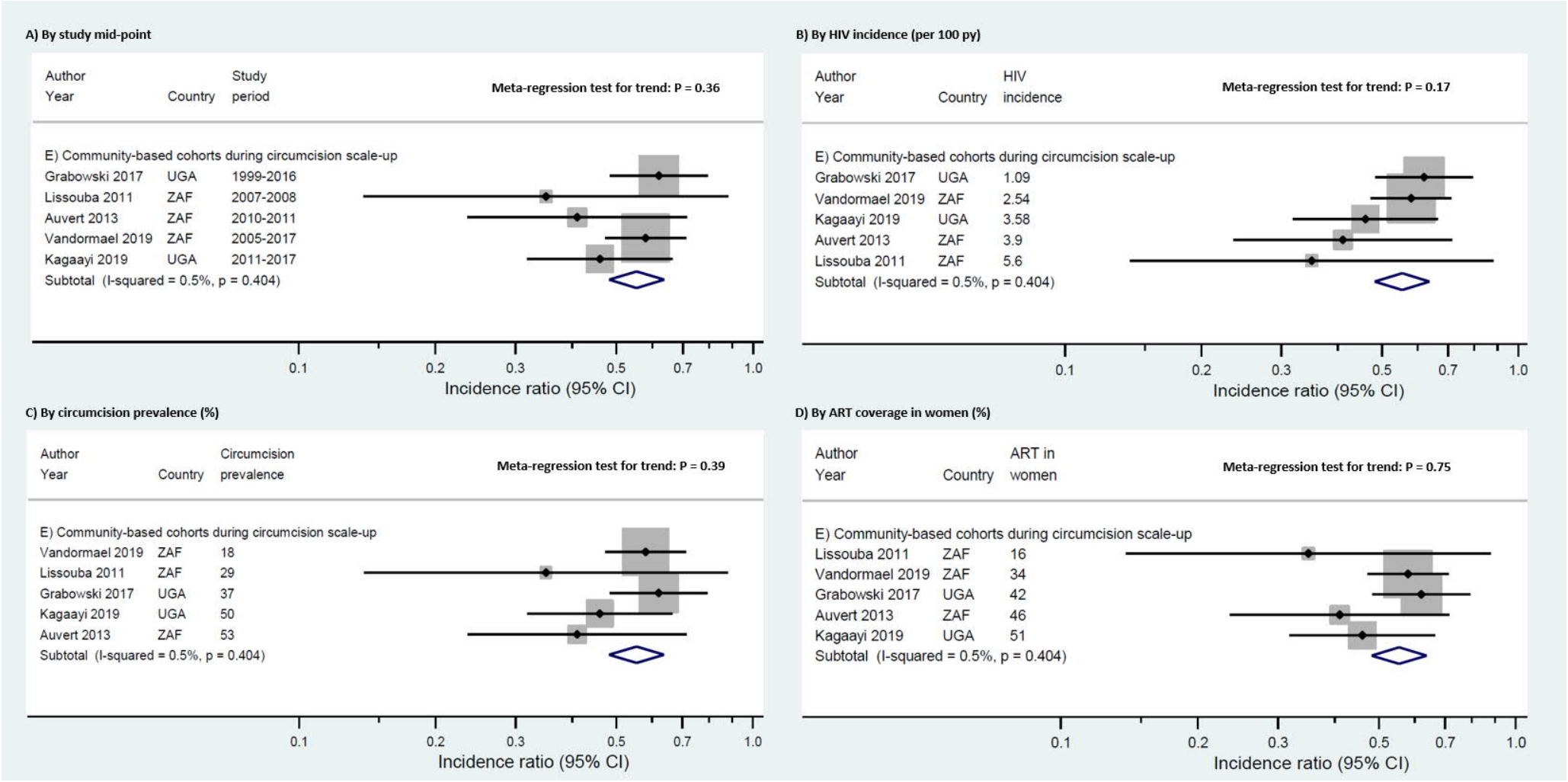
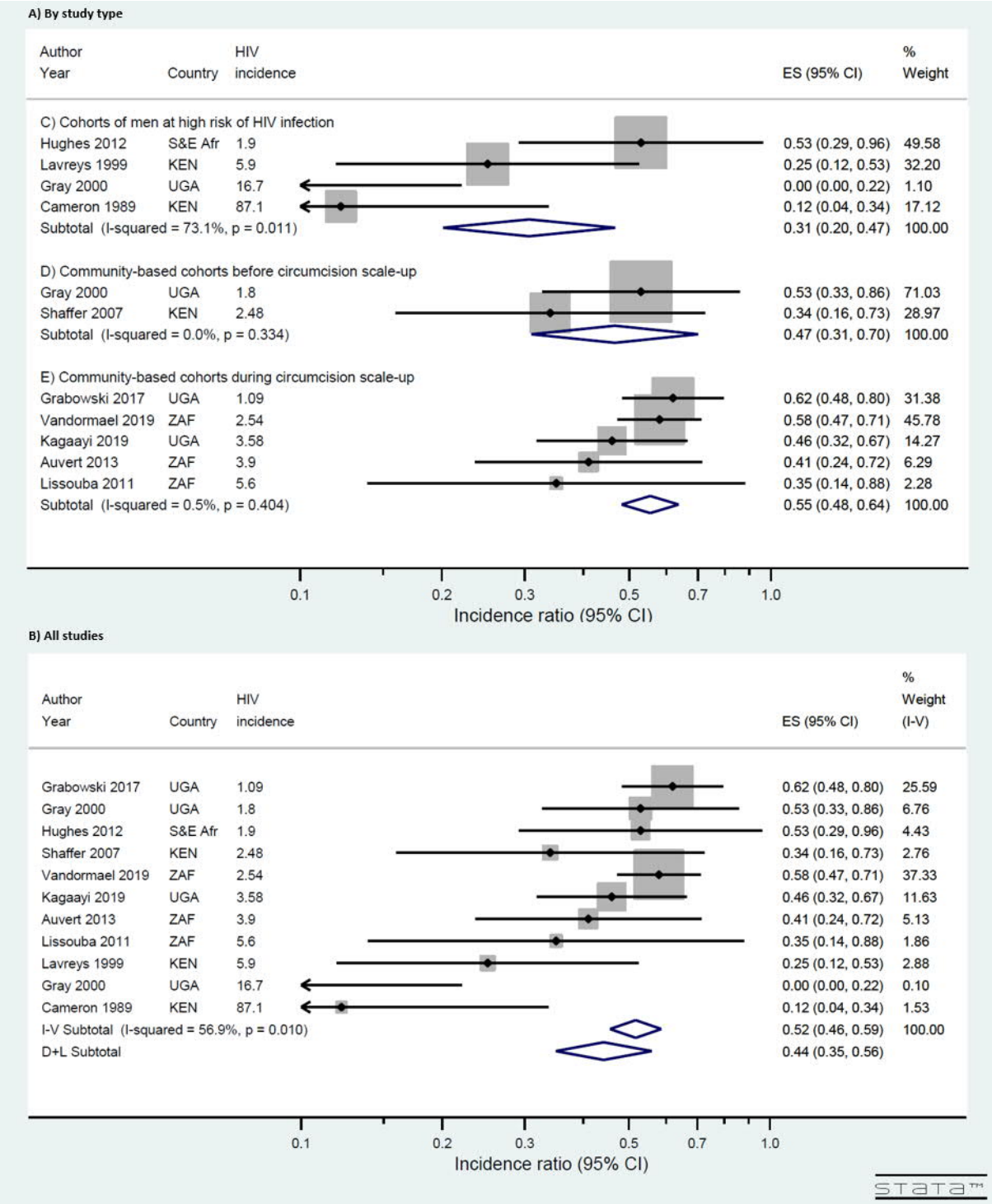


Figure S3: Incidence ratios in observational studies in Africa without serious risk of bias by HIV incidence A) by study type and B) as a single group



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