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Trichomonas vaginalis and HIV infection acquisition: a systematic review and meta-analysis

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ABSTRACT

Objectives Trichomoniasis is the most prevalent curable STI globally, with the highest incidence and prevalence in sub-Saharan Africa (sSA). STIs have largely been associated with an increase in HIV acquisition. Our objective was to assess the existing literature available in English regarding the association of Trichomoniasis and HIV-1 acquisition.

Methods The review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) under number CRD42018082702. We searched MEDLINE, Embase and Scopus databases to collect articles measuring the association of *Trichomonas vaginalis* infection and HIV acquisition and performed a meta-analysis and qualitative synthesis of the literature.

Results We identified 1806 unduplicated citations, of which 18 papers and 1 conference abstract were eligible for inclusion in the review after applying our inclusion and exclusion criteria. All the studies included in the systematic review had been carried out in sSA. The articles reported various measures of effects, namely: HRs, rate ratios, risk ratios and ORs. In a meta-analysis restricted to 11 studies reporting HR, individuals infected with *T. vaginalis* were 1.5 times more likely to acquire HIV compared with individuals not infected with *T. vaginalis* (95% CI 1.3 to 1.7; p<0.001).

Conclusions *T. vaginalis* is an important factor in HIV acquisition especially in sSA where the prevalence *of* both *T. vaginalis* and HIV-1 are high. This systematic review and meta-analysis confirms the evidence that infection with *T. vaginalis* augments HIV acquisition with 50%. Diagnosis and treatment of *T. vaginalis* infection in both high-risk and low-risk individuals may be a potential tool to reduce new HIV infections.

Trial registration number CRD42018082702

INTRODUCTION

The protozoan *Trichomonas vaginalis* is responsible for trichomoniasis, the most common curable STI.[1] *T. vaginalis* infects both men and women, although this unicellular parasite is more prevalent in women than men. Among people aged 15–49 years, it was estimated that in 2012 the global prevalence of *T. vaginalis* infection among women was 5.0% versus 0.6% among men. These figures correspond to an estimated incidence of 143 million newly infected individuals.[1] Similar to HIV, *T. vaginalis* is more prevalent in sub-Saharan Africa (sSA), as the cumulative prevalence was estimated to be 11.5% among women aged between 15 years and 49 years in sSA in 2012.[1]

According to The Joint United Nations Programme on HIV and AIDS,[2] about 5000 new HIV infections occurred daily in 2016, with a huge proportion, that is, 64%, of new infections occurring in sSA. Already two decades ago, reports suggested that individuals infected with *T. vaginalis* were at an increased risk of HIV acquisition.[3] Some studies have also indicated that *T. vaginalis* and HIV coinfection increases genital shedding of HIV,[4] but opinions differ, especially in the context of antiretroviral therapy.[5] In summary, there is growing evidence that there is a need for special treatment considerations for *T. vaginalis* among women with HIV coinfection.[6]

Better understanding of the association *T. vaginalis* and HIV may provide insights on HIV infections that may be attributed to *T. vaginalis*. Moreover, we may learn how control of *T. vaginalis* may impact HIV transmission as a potentially cost-effective strategy for reducing HIV transmission, particularly in regions where *T. vaginalis* is common.[7] The objective of this systematic review and meta-analysis was to clarify the extent to which *T. vaginalis* infection is associated with HIV infection and acquisition.

METHODS

Protocol and registration

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[8] for carrying out and reporting this systematic review and meta-analysis, using an a priori defined protocol.

Eligibility criteria

We included studies that reported both *T. vaginalis* infection status and HIV status. We only included studies written in English and that documented OR, or risk ratio (RiR), or HRs, or provided the absolute numbers for these parameters to be calculated. There were no restrictions in terms of study design or geographical area where the studies were conducted. We included papers that were published up to 11 March 2018.

Reviews, narrative-only conference abstracts, comments, guidelines, case reports or case series, unpublished articles, multiple reports of the same data and in vitro and animal studies were not considered for inclusion. Infection with *T. vaginalis* was defined as the presence of the pathogen as assessed by culture, wet mount or molecular methods, while HIV status was defined by the presence of HIV antibodies, HIV proteins, HIV RNA or DNA.

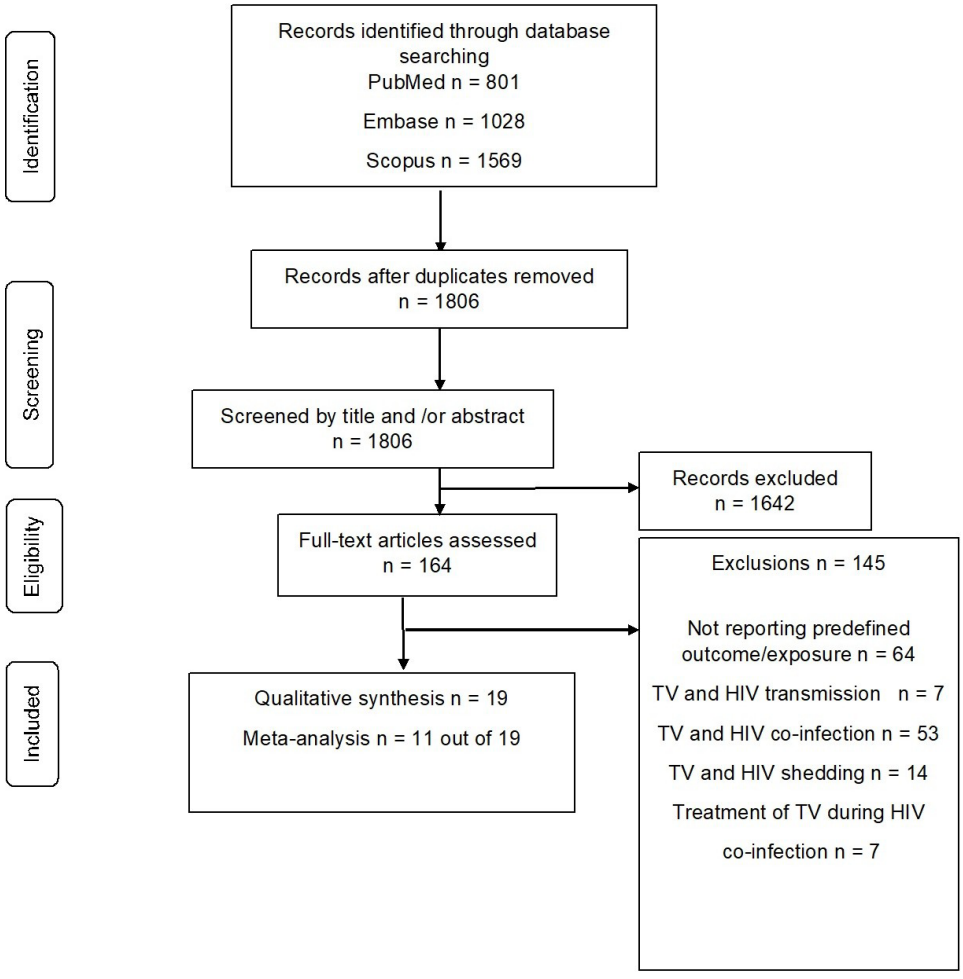

Figure 1 Identification of studies included in the systematic review. HIV, human immunodefeciency virus; TV, *Trichomonas vaginalis*

Search strategy

We searched Embased, MEDLINE (through PubMed) and Scopus. We used the combination of all of the following search terms (*Trichomonas vaginalis, T. vaginalis* and trichomoniasis) with all of the following search terms (AIDS, acquired immunodeficiency syndrome, HIV, HIV, HIV-1 and HIV-2). The bibliographic references of the studies that were considered eligible were also hand searched.

Study selection

Similar to the systematic review by Cools *et al*,[9] studies were selected in a two-stage process (figure 1). First, all bibliographic references were screened to identify studies for full-text evaluation by one reviewer (SCM), on the basis of only the information present in the title and abstract. Subsequently, the full texts of those articles not excluded in the screening process were assessed for eligibility, using the aforementioned criteria, by two authors independently (SCM and PC). Reasons for exclusion were recorded and categorised, and disagreements were resolved by consensus.

Using all search terms, searches were conducted for relevant papers in the preidentified databases (Embase, PubMed and Scopus), and from this, we identified 3398 papers. Once the search was completed, all of the retrieved articles were imported into EndNote X7.8 for removal of duplicates.

Data collection process

A predefined data extraction form was pilot-tested and used for data extraction. From the 19 studies included in the systematic review and meta-analysis, the following information was collected: authors, year of publication, journal, country where the study had been carried out, study design, sample collection period, study population, mean/median age of the participants, total number of study participants, total number of samples included in the analysis, *T. vaginalis* detection method, assessment of HIV status, relevant measures of effects or absolute numbers and statistics. This procedure was performed independently by two authors (SCM and PC), and disagreements were resolved by discussion between both authors.

Risk of bias in individual studies

To assess the quality and risk of bias of the included studies, we developed a quality appraisal tool (online supplementary table 1) based on the Newcastle-Ottawa Scale.[10] We adapted this tool to the content of our meta-analysis. Stars were assigned by SCM for three broad criteria (representativeness of the study groups, comparability of the study groups and quality of the outcome assessment) in order to provide a measure of their quality.

Studies that scored none or one, two or three stars for internal validity of representativeness were classified as having respectively a high, medium or low risk of bias for this criterion.

Studies assigned none, one or two stars for comparability or outcome were considered to have respectively a high, medium or low risk of bias for comparability and outcome.[9]

Data analysis

The meta-analyses was performed using STATA V.13.1. We reported the results of the meta-analyses obtained after pooling individual study estimates with random effects model as HRs with 95% CI. The degree of heterogeneity between the studies was assessed using the I^2 index, with percentages 25%, 50% and 75% being indicative of low, moderate and high heterogeneity, respectively.[11]

To assess publication bias, a funnel plot was created by plotting the natural logarithm of the HRs against the inverse of the SE. The symmetry of the funnel plots was visually inspected and statistically checked using Egger's regression test.[12]

RESULTS

Manuscript and study selection

A total of 1806 unduplicated citations were identified; we selected 164 abstracts for full-text evaluation (figure 1). There were 19 studies that met our inclusion criteria to be included in our systematic review.

Description of selected studies

All studies were conducted in sSA, namely Burkina Faso (n=1), Democratic Republic of Congo (n=2), Ivory Coast (n=1), Kenya (n=5), Malawi (n=1), South Africa (n=4), Uganda (n=4), Zambia (n=1) and Zimbabwe (n=3). Some of the studies were conducted in more than one country. Of the included 19 studies, 17 were cohorts and 2 were nested case–control studies. Generally, all these studies involved a baseline *T. vaginalis* test and additional testing performed at varying intervals depending on the study, with treatment for participants testing positive for *T. vaginalis*.

Thirteen of the studies found a positive association between *T. vaginalis* infection and HIV acquisition.

Eleven studies reported HRs of HIV acquisition in relation to *T. vaginalis* infection, three reported RRs (ie, comparison of incidence rates) of HIV acquisition in relation to *T. vaginalis*, two studies reported RiRs of HIV acquisition in relation to *T. vaginalis* and three reported ORs of HIV acquisition in relation to *T. vaginalis* (table 1).

Most studies (63%) had been carried out among high-risk individuals, that is, female sex workers, and serodiscordant couples. The rest of the studies (37%) had been carried out among low-risk populations, including women attending prenatal or postnatal clinics and family planning clinics and individuals from the general population. Only three studies had male participants. Direct microscopy was the most common method used for detection of *T. vaginalis* (73%) in the studies. Detection of HIV antibodies was the most common method used to determine HIV status (84%) in the studies (table 1).

Treatment of *T. vaginalis* in the studies included in the meta-analysis was mostly on the basis of metronidazole. However, not all participants infected with *T. vaginalis* received treatment. For instance, in the study by Van Der Pol *et al*[13] , participants diagnosed using microscopy received treatment, while those diagnosed using nucleic acid amplification test (NAAT) were not treated. Additionally, in the study by Kleinschmidt *et al*[14] syndromic treatment of STIs was offered.

Risk of bias within studies

Following the critical appraisals of the included studies (online supplementary figure 1). Fourteen studies were assessed as having a high risk of bias for representativeness (high-risk individuals, that is, female sex workers, and serodiscordant couples), three as having a medium risk of bias for representativeness (prenatal care clinic/postnatal care clinic women and family planning clinic attendees) and two studies as having a low risk of bias for representativeness (women from the general population). For the risk of bias for outcome assessment, it was high for 1 study, medium for 16 studies and low for 2 studies. Eight out of the 19 studies were assessed as having a medium risk of bias for comparability, while 11 studies had a low risk of bias for comparability. Individual study appraisals are captured in online supplementary table 2.

Visual inspection of the funnel plot shows symmetrical distribution of studies, suggesting no publication bias (figure 2), which is supported by Egger's regression intercept (0.6; 95% CI −0.64 to 1.82; p=0.304).

Association of *T. vaginalis* and HIV acquisition

Eleven of the studies that were reporting HR provided data for the meta-analysis. The point estimate for the HR ranged from 0.71 to 4.79 (table 1). Bearing in mind that ORs and RRs measure only the number of events and take not into account when they occur, these two measures are appropriate for measuring dichotomous outcomes but less appropriate for analysing time-to-event outcomes, which is important when relating *T. vaginalis* infection and HIV acquisition. The meta-analysis indicated that individuals infected with *T. vaginalis* were 1.5 times more likely to acquire HIV as compared with individuals not infected with *T. vaginalis* (HR: 1.5; 95% CI 1.3 to 1.7; p<0.001) (figure 3).

DISCUSSION

In this systematic review and meta-analysis, we assessed the extent to which *T. vaginalis* infection is associated with HIV acquisition. There has been a global decline in deaths from HIV/AIDS-related causes, from a peak of 1.9 million in 2005 to 1.0 million in 2016.[2] Despite this, AIDS-related illnesses remain the leading cause of death among women of reproductive age (15–49 years) globally[2] and the second leading cause of death for young women aged 15–24 years in sSA.[2] The prevalence of *T. vaginalis* was estimated to be approximately 11% in 2012 among women in sSA.[1]

Studies included in our meta-analysis had no heterogeneity and thus appropriate to be combined in a meta-analysis where we demonstrate that individuals infected with *T. vaginalis* are at a higher risk of HIV acquisition. *T. vaginalis* augments the likelihood of HIV acquisition by 50% (HR 1.5; 95% CI 1.3 to 1.7); the amount of HIV acquisition attributable to this pathogen (attributable risk) and its contribution to the HIV pandemic may be substantial due to the high prevalence of *T. vaginalis* infection, especially in sSA. Our results are in agreement with a previous systematic review where they also show infection with *T. vaginalis* increased risk of HIV acquisition.[15]

In a study where they included both high-risk individuals and low-risk individuals, the adjusted HR for HIV acquisition for women with *T. vaginalis* were higher in the low-risk individuals, suggesting that for women with less risk from sexual networks, infection with *T. vaginalis* infection is a very important risk factor for HIV acquisition.[13]

Most studies included in this systematic review used direct microscopy for detection of *T. vaginalis*, a diagnostic technique that has been shown to have a low sensitivity.[13] In a study where they included both high-risk individuals and low-risk individuals, the adjusted HR for HIV acquisition for women with *T.*

Table 1 Summary of studies

Authors, year and country	Study population	No of participants/no of HIV seroconversions	HIV detection method	TV detection method	Main finding
Delany-Moretlwe *et al*,[16] 2011, South Africa	HIV-negative women	2451/110	Not stated	Not stated	Baseline TV+ more likely to seroconvert compared with TV–. IRR 2.3 (95% CI 1.1 to 4.9).
Ghys *et al*,[17] 2001, Ivory Coast	FSW HIV negative	284/26	ELISA+WB	Wet prep	TV+ women more likely to seroconvert than TV–. aRR* 2.8 (95% CI 1.3 to 6.2).
Hester and Kennedy,[18], 2003, Zambia	Women (serodiscordant couples)	90/45	Dot-WB	Wet prep	HIV acquisition among TV+ women at baseline compared with TV– women at baseline. OR 0.35 (95% CI 0.16 to 0.76).
Kinuthia *et al*,[19] 2015, Kenya	Women at a prenatal clinic	1304/25	NAATs	Wet prep	HIV acquisition for women with TV. aHR 1.14 (95% CI 0.16 to 8.16).
Kleinschmidt *et al*,[14] 2007, South Africa	Women attending FP clinics	551/23	HIV rapid test	Culture (Daimonds)	TV+ women more likely to acquire HIV-1 than TV– women. aHR 4.79 (95% CI 1.01 to 22.78).
Laga *et al*,[3] 1993, Democratic Republic of Congo	FSW HIV negative	431/68	EIA+WB	Wet prep	TV+ women more likely to seroconvert than TV– women. AOR 1.9 (95% CI 0.9 to 4.1).
Laga *et al*,[20] 1994, Democratic Republic of Congo	FSW HIV negative	531/70	EIA+WB	Wet prep	TV+ women more likely to seroconvert than TV– women. RR 1.7 (95% CI 1.1 to 2.8).
Martin *et al*,[21] 1998, Kenya	FSW HIV negative	799/111	EIA	Wet prep	HIV acquisition for FSW with TV. aHR 1.2 (95% CI 0.7 to 2.2)
Masese *et al*,[22] 2015, Kenya	FSW HIV negative	1964/325	EIA	Wet prep	HIV acquisition for FSW with TV. aHR 1.41 (95% CI 0.99 to 2.02).
Mavedzenge *et al*,[23] 2010, Zimbabwe and South Africa	Women (general population)	4948/309	HIV rapid, EIA	NAATs	HIV acquisition with those with TV. aHR 2.05 (95% CI 1.05 to 4.02)
McClelland *et al*,[24] 2005, Kenya	FSW	1215/238	EIA	Wet prep	HIV acquisition for FSW with TV. HR 1.3 (95% CI 1.0 to 1.7).
McClelland *et al*,[25] 2007, Kenya	FSWs HIV-1–seronegative	1335/261	EIA	Wet prep	HIV acquisition for FSW with TV. aHR 1.52 (95% CI 1.04 to 2.24).
Myer *et al*,[26] 2006, South Africa	Women (general population)	3570/85	Abbott HIV 1/2 Kit	Wet prep	Baseline TV +women more likely to seroconvert than TV– women. cHR 1.84 (95% CI 1.02 to 3.32).
Nagot *et al*,[27] 2005, Burkina Faso	FSW	377/19	EIA	Wet prep	HIV acquisition for FSW with TV. HR 0.71 (95% CI 0.22 to 2.29).
Quinn *et al*,[28] 2000, Uganda	Serodiscodant couples	414/90	EIA+WB	Culture (InPouch)	HIV acquisition when a person has TV. aRR* 1.27 (95% CI 0.65 to 2.35).
Taha *et al*,[29] 1998, Malawi	HIV-negative postnatal women	1196/124	EIA+WB	Wet prep	TV+ women more likely to seroconvert than TV– women. aRR 1.38 (95% CI 0.75 to 2.56).
Van De Wijgert *et al*,[30] 2009, Zimbabwe and Uganda	Women at FP and mother–child health clinics	4439/189	ELISA, confirmed by rapid test or PCR or WB	Wet prep	TV associated with HIV if it is detected in current and previous visit to HIV seroconversion. aHR 1.53 (95% CI 0.21 to 11.01).
Van Der Pol *et al*,[13] 2008, Uganda and Zimbambwe	FP clinic and FSW HIV–	4531/213	NAATs	Wet prep and NAATs	TV+ women at previous visit were more likely to seroconvert than women without TV. AOR 2.74 (95% CI 1.25 to 6.00) FP &FSW AOR 3.3 (95% CI 1.36 to 7.85) FP only.
Vandepitte *et al*,[31] 2013, Uganda	FSW	646/42	HIV rapid, confirmed by ELISA	Culture	TV increase likelihood of HIV acquisition with aHR 2.72 (95% CI 1.27 to 5.84).

All studies were cohort studies, except Hester & Kennedy[18] (2003) and Laga et al.[3] (1993), which were nested case-control studies. Studies are arranged alphabetically according to the name of the first author and then year of publication.
aHR, adjusted HR; AOR, adjusted OR; aRR*, adjusted rate ratio; ARR, adjusted risk ratio; cHR, crude hazard ratio; EIA, enzyme immunoassay; FP, family planning; FSW, female sex workers; IRR, independent risk ratio; NAATs, Nnucleic acid amplification tests; TV, Trichomonas vaginalis; WB, western blot.

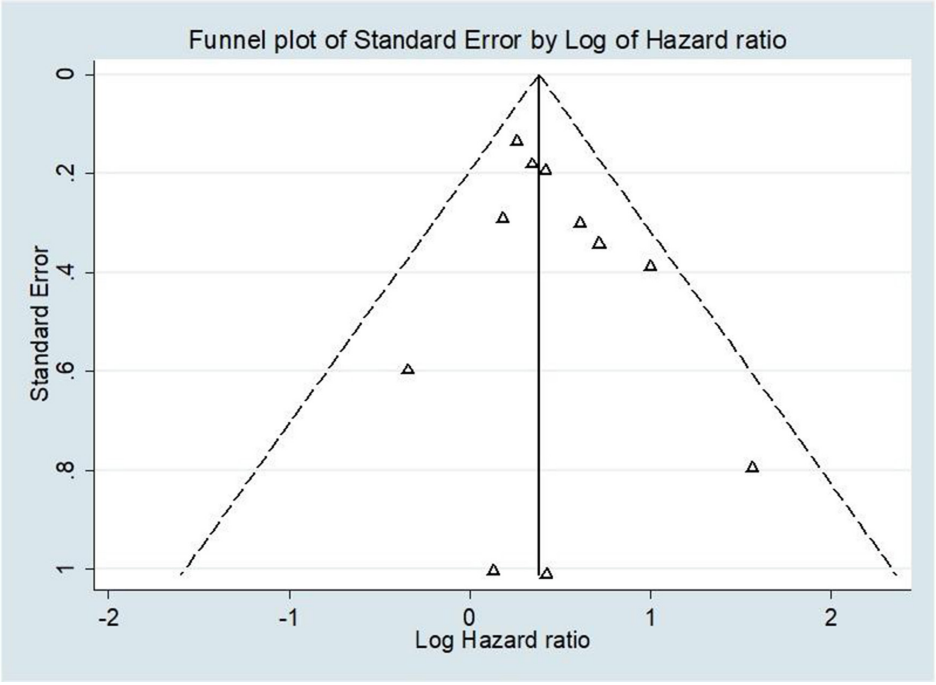

Figure 2 Funnel plot to assess publication bias among studies evaluating the association between *Trichomonas vaginalis* infection and HIV infection acquisition. The triangles represent the estimates of the 11 included studies of the association between *T. vaginalis* infection and HIV infection acquisition. The log of the HR is plotted on the horizontal axis, against the inverse of the SE of the HR on the vertical axis. The vertical line in the funnel plot indicates the fixed-effects summary estimate and the sloping lines indicate the expected 95% CIs for a given SE.

vaginalis were higher in the low-risk individuals, suggesting that for women with less risk from sexual networks, infection with *T. vaginalis* infection is a very important risk factor for HIV.[13]

Several *T. vaginalis* pathogenic mechanisms of *T. vaginalis* may help to explain why individuals infected with *T. vaginalis* may be at a higher risk of HIV acquisition. First, *T. vaginalis* may damage the epithelial membrane[w2], which acts as a barrier to HIV through several pathogenic mechanisms; its cell-to-cell adhesion[w3], haemolysis[w4] and/or excretion of soluble factors[w5]. Second, *T. vaginalis* has been shown to elicit an inflammatory

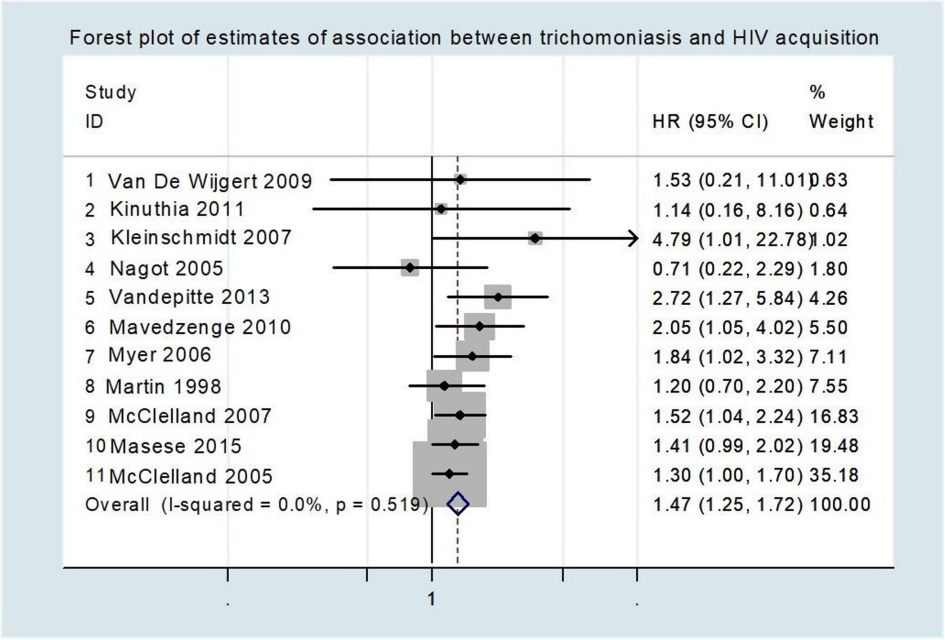

Figure 3 Forest plot of estimates of association between trichomoniasis and HIV acquisition. Studies are plotted to start with the one with the least weight. Each study is represented by a black circle and a horizontal line, which correspond to the HR and 95% CI, respectively. The area of the grey box around each study reflects the weight of the study (determined by random effects analysis) in the meta-analysis. The vertical line in the middle corresponds to an HR of 1.0. The diamond represents the overall HR with the 95% CI given by its width. The arrow indicates the study with the highest confidence interval.There was low heterogeneity of studies included in the meta-analysis as shown by the I^2=0.0%, p=0.510.

response among infected individuals this may lead to an increase in the appearance of HIV target cells[w6,w7]. Third, infection with *T. vaginalis* has been associated with bacterial vaginosis[w8] which, in turn, can increase the risk of HIV acquisition[w9]. All these consequences may facilitate HIV in *T. vaginalis*-infected individuals.

In cases of HIV and *T. vaginalis* coinfection, *T. vaginalis* has been associated with increased genital shedding of HIV[w10]. A previous study showed high prevalence of *T. vaginalis* among HIV serodiscordant African couples[w11]. *T. vaginalis* may be an important factor for HIV transmission in HIV discordant couples. Moreover, if both individuals are infected with *T. vaginalis* as there is potential for synergistic effect, that is, increased genital shedding of HIV, combined with pathogenic mechanisms of *T. vaginalis*, which potentially make individuals infected with *T. vaginalis* be at a higher risk of HIV acquisition. Theoretically, this would increase the likelihood of HIV acquisition than when only one the individuals is infected with *T. vaginalis*.

Regarding the limitations of this review, first, most studies included in the review were conducted among high-risk individuals, that is, female sex workers, and serodiscordant couples. Thus, our result may not reflect the situation in the general population. Second, only a couple of studies included in the review had male participants, but all the studies in our meta-analysis were based on women; our results are biased towards high-risk females. Third, most of the studies in the review used direct microscopy to detect *T. vaginalis* infection. Direct microscopy is characterised by low sensitivity, and samples detected through this technique usually have high parasitaemia. Although the few studies that used culture or NAATs for *T. vaginalis* detection reported positive association of *T. vaginalis* infection and increased likelihood of HIV acquisition, they also signal the need for further longitudinal research on this topic, evaluating if *T. vaginalis* detection techniques have an impact of this association Fourth, we did not assess the risk of bias that might be due to missing data or loss to follow-up. Finally, all studies included in the review were done in sSA, and thus our results may only apply to the sSA population.

CONCLUSION

T. vaginalis may be used as a biological marker for enhanced risk for HIV acquisition for both high-risk and moderate-risk women. *T. vaginalis* may be an important factor in HIV acquisition especially in sSA where the prevalence of both *T. vaginalis* and HIV is high, and this systematic review and meta-analysis provides consolidated evidence that infection with *T. vaginalis* augments HIV acquisition. Diagnosis and treatment of *T. vaginalis* in both individuals at high risk and low risk for HIV may perhaps be a potential tool to reduce new HIV infections.

Additional references can be found in the online supplementary file 2.

Key messages

- Trichomoniasis augments the likelihood of HIV acquisition by 50%.
- Trichomoniasis may be an important factor in HIV acquisition especially in sub-Saharan Africa where the prevalence of both are high.
- Screening and treatment of trichomoniasis may be a potential means of curbing new HIV infections among women with high-risk or moderate-risk behaviour.

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Contributors SCM, PC and TC designed the study. SCM and PC searched for literature, reviewed titles and abstracts for inclusion in the review, performed data extraction and conducted the analysis. SCM wrote the first draft of the manuscript. All authors contributed to data interpretation, reviewed successive drafts and approved the final version of the manuscript.

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