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Bacterial vaginosis and HIV acquisition: A meta-analysis of published studies

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Abstract

Objectives—To assess and summarize the published literature on the extent to which bacterial vaginosis (BV) may increase the risk of HIV acquisition.

Design—Meta-analysis of published studies.

Methods—MEDLINE and other electronic databases were systematically searched for eligible publications. The association between BV and incident HIV was separately analyzed from that between BV and prevalent HIV. The latter were further analyzed stratified by BV diagnostic method, HIV risk profile of the study population and whether or not adjusted estimates were presented.

Results—Twenty-three eligible publications were identified, including a total of 30,739 women. BV was associated with an increased risk of HIV acquisition in HIV-incidence studies (relative risk = 1.6, 95% CI: 1.2, 2.1). All but one of 21 HIV-prevalence studies reported estimates above the null. The latter results were heterogeneous and showed some evidence of funnel plot asymmetry, precluding the estimation of a single summary measure. The association between BV and HIV in prevalence studies appeared stronger for women without high-risk sexual behavior.

Conclusions—BV was consistently associated with an increased risk of HIV infection. High BV prevalence may result in a high number of HIV infections being attributable to BV. More prospective studies are needed to accurately evaluate the role of BV in HIV acquisition in low versus high risk women. Furthermore, randomized clinical trials may be worth considering to determine the effect of BV control measures on HIV acquisition.

Keywords

Bacterial vaginosis; HIV acquisition; meta-analysis

Bacterial vaginosis (BV) is the most frequent type of vaginitis in women of reproductive age [1–3]. BV is an imbalance in the ecology of the normal vaginal flora [4] that is characterized by the depletion of lactobacilli [3], and the proliferation of anaerobic bacteria such as *Gardnerella vaginalis*, *Morbilincus species*, *Prevotella species*, *Mycoplasma hominis* and the recently identified *Atopobium vaginae* [2,5–7]. It most often manifests clinically as a vaginal pH of >4.5, the presence of thin whitish homogenous vaginal discharge, the detection of “clue”

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cells and the presence of an amine odor after the addition of 10 percent potassium hydroxide [8,9]. BV has been shown to increase the risk of adverse gynecological and obstetrical outcomes such as preterm delivery[10,11] pelvic inflammatory disease (PID) and upper genital tract infections [12–14]. However, the effect of BV on the risk of HIV infection in women has not been clearly quantified.

The magnitude of the association between BV and HIV has varied in epidemiological studies, ranging from the absence of any association[15] to a near four-fold odds of being HIV infected among BV-positive women compared to BV-negative women [16]. BV is estimated to be the most prevalent vaginal infection particularly in countries with high HIV prevalence [2]. If BV is confirmed to increase the risk of HIV infection, the treatment of BV could be a meaningful intervention to prevent HIV acquisition. In a 2001 review of the role of sexually transmitted diseases in HIV acquisition, Rottingen et al estimated that BV was associated with a 40% increase in the risk of HIV based on an analysis of two studies[17]. Obtaining a precise and updated estimate of the strength of the association between BV and HIV from published studies could be useful in predicting the potential impact of the control of BV on HIV incidence rates in a population. This prediction could also be more accurate if factors that modify the strength of the BV and HIV association were identified.

This paper aims to systematically review all published studies of the association between BV and HIV infection. Estimates of the association between BV and HIV are presented for both HIV incidence and prevalence studies, and analyzed for potential modification factors, publication bias, and heterogeneity of study results.

METHODS

Search strategy

Medline was searched for peer-reviewed publications on the association between BV and HIV using the following terms: (“Vaginosis, Bacterial”[MeSH] OR “bacterial vaginosis” OR (“Bacterial Infections”[MeSH] AND (“Vaginitis” [MeSH] OR vagina*)) OR “Gardnerella”[MeSH]) AND (HIV OR “HIV Seropositivity”[MeSH] OR “HIV”[MeSH] OR “HIV Infections”[MeSH]). This search yielded 281 published articles. The Web of Science™, Popline™ and NLM Gateway™ databases were further searched using the keywords “bacterial vaginosis and HIV”. These searches yielded 193, 83 and 166 publications, respectively, but no additional articles were located beyond the Medline search. Articles were included in this meta-analysis if the magnitude of the association between BV and HIV was presented or could be calculated from the information provided in the article, and if there was a clear description of the diagnostic methods used for ascertaining both BV and HIV infections. When there was evidence of multiple publications of the same study over time, only the article with the largest sample size was included. Although non-English articles were eligible for inclusion, none were found. Conference abstracts and other unpublished manuscripts were excluded, as these could not be systematically reviewed.

Data abstraction and analysis

For each study, the following information was extracted: author(s), year of publication, study site, year(s) during which study was conducted, study design (HIV incidence or prevalence), HIV risk of study population (low or high), BV diagnosis criteria, HIV ascertainment method, mean or median age of participants, crude and adjusted measures of the association between BV and HIV, and variables for which measures were adjusted. Appropriate measures of association were calculated, when possible, for studies that did not present them.

HIV incidence studies were defined as those that recruited HIV-negative women and prospectively measured incident HIV-infection. HIV prevalence studies were those that assessed BV and HIV status at the same time. Study populations with HIV-risk factors such as female sex workers (FSWs), sexually transmitted infection (STI) clinic attendees and regular partners of HIV infected males were classified as 'High HIV-risk groups'. Women without any of these characteristics were classified as being in a low HIV-risk group. BV diagnostic criteria included the Nugent scoring system[18], Amsel clinical criteria[8] and modifications of Amsel criteria. In the Nugent scoring system (BV when score ≥ 7) Gram stained vaginal smears were assessed for the average number of bacterial morphotypes seen per oil immersion field with Lactobacilli being scored from 0–4, Gardnerella/Bacteroides spp from 0–4 and curved gram-variable rods 0–2. Amsel criteria define BV as the presence of any three of: i. abnormal vaginal discharge, ii. vaginal pH>4.5, iii. presence of clue cells, and/or iv. positive amine test with release of fishy odor on addition of 10 percent KOH to vaginal secretions. Modifications of the Amsel criteria included diagnosing BV only when all four of the above criteria are present or when only two of the four elements are present. BV prevalence at baseline or BV prevalence in controls of case-control studies was recorded as an estimate of BV prevalence in the study population.

All abstracted data were double checked to confirm accuracy. Separate meta-analyses were conducted for HIV incidence studies and HIV prevalence studies (STATA™ version 8). Study estimates, relative risks (RR) or prevalence odds ratios (POR), and corresponding 95 percent confidence intervals were plotted for each analysis. Adjusted estimates, when reported, were preferentially used in analyses. For studies that reported estimates using two different methods of BV diagnosis, the estimate based on the Nugent score was used because the definition of BV using this score was more consistent across studies than the use of Amsel diagnostic criteria. Reported estimates were examined for publication bias graphically, using funnel plots, and statistically using the test of Begg and Mazumdar [19], the test of Egger et al. [19], and Duval and Tweedie's "trim and fill" imputation method [19]. Homogeneity test p-values were computed from Cochran's Q test statistic [19]. To explore sources of heterogeneity, HIV prevalence studies were stratified by HIV risk group, BV diagnostic criteria and whether there was any adjustment for confounders or not. Random effects meta-regression models, using restricted maximum likelihood to estimate the among-study variance [20], were also conducted to assess the association of average study estimates with study characteristics. BV diagnostic method, HIV risk group and a variable indicating the use of adjusted or unadjusted estimates were the independent variables in the models. The impact of each estimate on the summary estimate was explored using influence analyses (14).

RESULTS

Study characteristics

Twenty-three eligible papers were identified altogether including 30,739 women. These reported 29 different estimates of the association between BV and HIV for 25 study populations (two papers each reported estimates for two distinct study populations [16,21], and four other papers each reported estimates using two different methods of BV diagnosis [15,22–24]). Four of the 25 study populations were followed prospectively in Kenya [25], Malawi [21] and South Africa [24] to access incident HIV infection. The remaining 21 studies were studies of prevalent HIV (table 1). Five of these were conducted in the USA, two in Thailand and the remainder in sub-Saharan Africa.

BV diagnosis and prevalence

BV was diagnosed either using clinical criteria only (in 13/25 study populations), Nugent's score only (in 8/25 study populations) or both clinical and Nugent's score (in 4/25 study

populations). BV prevalence in these studies ranged from 11.1 percent in women aged 20–35 years in the USA to 70.0 percent in STI symptomatic women in South Africa. The pooled BV prevalence was 33%. BV prevalence was consistently higher using Nugent's criteria as opposed to clinical criteria in all four studies that used both BV diagnostic methods [15,22–24].

BV-HIV association

HIV Incidence studies—There was little evidence of funnel plot asymmetry (Begg p=1.0, Egger p=0.2) or heterogeneity in the study estimates (p=0.7, figure 1). BV was associated with an increased risk of HIV acquisition in HIV incidence studies (figure 1) (RR=1.61; 95 percent CI: 1.21, 2.13).

HIV prevalence studies—Funnel plot tests gave some evidence of asymmetry (Begg p=0.3, Egger p=0.06). In the 'trim and fill' analysis, when a random-effects model was used, one hypothetically missing result was imputed. When a fixed-effect model was used, 9 hypothetically missing results were imputed (Figure 3).

HIV seroprevalence was higher in BV positive women in all but one study (17) (figure 2). The prevalence odds ratios (POR) estimates from these prevalence studies were highly heterogeneous (p<0.0005), and ranged from 0.77 to 3.70. As shown in table 2, this heterogeneity persisted even within strata defined by each of HIV risk group, BV diagnostic method, or estimate adjustment. POR estimates in HIV low-risk groups, tended to be higher than that in HIV high-risk groups. It is worth noting that all but one[35] of the studies classified as low-risk group were studies of pregnant women. In a multivariate meta-regression for prevalence studies, controlling for differences in BV diagnostic method and adjusted versus non adjusted estimates, the POR in the low HIV risk group was still higher, 1.43 fold that in the high HIV-risk group (95 percent CI: 0.94, 2.17). There was little evidence that BV diagnostic criterion (comparing Nugent to clinical criterion) was associated with the magnitude of the association as the ratio of PORs, accounting for variations due to HIV risk groups and adjusted versus non-adjusted estimates, was 0.88 (95 percent CI: 0.61, 1.26). Similarly there was little evidence that estimate adjustment was a substantial source of heterogeneity as the ratio of PORs, comparing adjusted to unadjusted estimates, accounting for variations due to HIV risk groups and BV diagnostic method, was 1.14 (95 percent CI: 0.76, 1.74).

Influence analyses

The impact of each study on the summary estimate was evaluated by successively omitting each of the studies and obtaining a summary for all the other studies. For HIV incidence studies the RR varied little, ranging from 1.58 (after excluding the Taha, 1998 study[21]) to 1.93 (after excluding the Martin, 1999 study[25]). The POR estimate from the study by Greenblatt et al. (1999[23]), by far the most precise of the estimates from the prevalence studies, was highly influential. Although the homogeneity test P-value remained <0.0005 upon removing this result, it substantially influenced the symmetry of the funnel plot. When this result was removed, the symmetry tests produced P=0.2 (Begg) and P=0.6 (Egger); the 'trim and fill' analysis imputed just one hypothetically missing result, regardless of whether a fixed effect or random effects model was used.

Sensitivity analyses

Sensitivity analyses were conducted to determine the impact of the decision to systematically choose Nugent score results over clinical criteria for BV diagnosis for studies with both results available. These sensitivity analyses were conducted by repeating the analyses after replacing, for studies that used two diagnostic methods, estimates based on Nugent scores with those based on Clinical criteria. The sensitivity of the effect estimate to this choice was found to be

robust with an overall RR in HIV incidence studies of 1.47 (95 percent CI: 1.10, 1.95). Heterogeneity in prevalence studies remained unchanged with the POR estimate in low-HIV risk groups of 2.30 (95 percent CI: 1.68, 3.15) still being higher compared to the POR in high-HIV risk groups of 1.53 (95 percent CI: 1.29, 1.82).

DISCUSSION

This is an updated systematic review and meta-analysis, of the association between BV and HIV infection. Overall BV prevalence was high in several populations of women studied, with prevalence rates as high as 70 percent. Our analyses of HIV incidence studies indicate that BV increases the risk of HIV acquisition by approximately 60 percent (95 percent CI 21–113 percent). This was slightly higher that the 40% reported in a previous review of 2 studies [17]. Studies of HIV prevalence tended to find higher HIV prevalence in women with BV. However these prevalence study estimates were heterogeneous and had evidence of funnel plot asymmetry.

The BV-HIV association tended to be weaker in high HIV-risk groups, though the few number of prospective studies limited the confirmation of this trend in HIV incidence studies. A weaker association in high risk women may possibly be due to a depletion of susceptibility to HIV resulting from women in high risk groups having a greater risk of acquiring HIV from causes other than BV. Once HIV infected, they are no longer at risk of acquiring HIV attributable to BV, thus reducing the effect of BV in this group. More data from prospective cohorts are needed to better examine the heterogeneity, by HIV risk group, in the effects of BV on the risk of acquiring HIV. This information could be helpful in identifying specific sub-populations, with a stronger association between BV and HIV, in whom to target BV control measures.

BV results in several changes in the vaginal flora that provide biological plausibility for an increased risk of HIV acquisition in BV positive women. BV is associated with a depletion of hydrogen peroxide-producing lactobacilli that may reduce vaginal defense against microorganisms including HIV[26,27]. Higher vaginal pH (>4.5) that occurs with BV may also increase the availability of vaginal HIV target cells by increasing CD4 lymphocyte activation and multiplication[28]. High vaginal pH may also increase the adherence and survival of HIV[21]. BV has also been associated with a reduction in vaginal fluid levels of secretory leukocyte protease inhibitor (SLPI)[5], which has been shown to block HIV infection *in vitro*[29]. Finally, by increasing intravaginal levels of interleukin-10, BV may increase the susceptibility of macrophages to HIV[30]. These changes, combined with the difficulties of successfully eradicating BV[31], may explain the increased risk observed in most epidemiology studies.

Some methodological limitations to this review need to be considered. The first are concerns on whether a meta-analysis of observational studies can effectively control for confounding and bias[19]. An attempt at reducing these was made by the preferential use of adjusted estimates in the estimation of summary measures. Meta-regression also revealed little difference between the adjusted and unadjusted estimates used in the final analysis. The second limitation has to do with the relatively few prospective studies included in this analysis. The restricted number of HIV incidence studies prohibited any sub-group analysis. However, this did not appear to be necessary as there was no heterogeneity among the estimates from these studies. The limited number of studies also prohibited any reliable analysis of other potential sources of heterogeneity such as pregnancy or age. More prospective studies are needed to accurately evaluate the causal association between BV and HIV. Third, this review was limited to that of published studies. This had little impact on the estimate from HIV incidence studies as there was no evidence of funnel plot asymmetry. The impact of publication bias on HIV prevalence studies was however unclear because of the heterogeneity in the estimates and

discrepancies in the results of the various methods of assessing publication bias (Begg's versus Egger's methods; Duval and Tweedie's 'trim and fill' random versus fixed models). The funnel plot of the POR estimates was unusual in that the one estimate that was by far the most precise (Greenblatt et al. 1999[23]) fell well outside the range of the other estimates. Given the pronounced heterogeneity among all POR results, this result was not given a very high weight when the trim and fill analysis was conducted using a random-effects model. With a fixed-effect model, however, the exceedingly high inverse-variance weight assigned to this estimate caused the trim and fill analysis to suggest publication bias so profound that one-third of all prevalence results are unreported, all of them on the reduced-prevalence side of the null. Although some publication bias in that direction might have occurred, we are not inclined to believe that it could have been that great. In any event, the prevalence results were much too heterogeneous to warrant aggregating them to produce a single, summary estimate. We found nothing obvious about the Greenblatt et al. (1999[23]) study that should have caused it to produce an estimate so unlike the remainder of the literature. It was one of five studies conducted in the United States and one of four US studies designed to include sizable proportions of HIV-positive and HIV-negative women. Yet it was the only one to produce an inverse association. We are inclined to consider it's departure from the main thrust of the literature an unexplained anomaly.

Limitations in the original studies included in this meta-analysis could also impact our estimates. With BV being a time-dependent condition, prospective studies of HIV incidence are susceptible to misclassification in the definition of BV status resulting from the use of either BV status at enrollment, or BV status at prior visit as indicators of BV status immediately preceding HIV acquisition. Misclassification could also result from false positive or false negative diagnosis of BV using either clinical or bacteriologic criteria. Both of these mechanisms of misclassification are expected to be non-differential and thus lead to more conservative estimates of the effect of BV on HIV acquisition. Original studies of HIV prevalence by BV status (using case-control or cross-sectional designs), in addition to the aforementioned susceptibility to misclassifying BV status, could also be subject to selection bias when HIV cases are enrolled from high sexual-risk populations in whom BV is more frequent. If not controlled, such a bias would result in an overestimate of the association between BV and HIV. However, we do not think this may have been substantial as most studies did control for atleast one indicator of sexual risk thus attenuating the impact of selection bias. Finally, all the observational studies included in this analysis are subject to residual confounding, which could result in an underestimate or overestimate of the magnitude of the association between BV and HIV.

Despite these limitations, this review was strengthened by extensive search of published literature using multiple databases and references of identified publications. Furthermore, by separating HIV incidence studies from HIV prevalence studies, the effect of BV on incident HIV was separately analyzed. This distinction is important as studies of incident HIV are not liable to reverse causation bias that would result from HIV infected women being more likely to acquire bacterial vaginosis. The analysis of sources of heterogeneity also allowed us to identify HIV risk group, and not method of BV diagnosis, as an important source of heterogeneity in prevalence study results. Finally we refrained from using summary estimates in the presence of heterogeneity. It has been argued that even when a random effects model is used to obtain a summary estimate, the latter is not always conservative and is potentially misleading if interpreted as an average effect[32].

The high prevalence of BV in certain populations (particularly those most impacted by the HIV pandemic) implies that notwithstanding the relatively modest effect of BV on HIV infection, a high proportion of HIV infection could be attributable to BV. In a population of women having a BV prevalence of 30 percent, with a relative risk of 1.6, the population attributable

risk proportions (PARP), the proportion of HIV in a population that is attributable to BV, is estimated at 15 percent. Although other sexually transmitted infections (STIs) have been shown to increase the risk of HIV infection with a higher RR in the order of 2–5[33], the relatively lower prevalence of these STIs as seen in some of the studies included in this analysis[34–37] may result in similar proportions of HIV infection being attributable to these STIs as to BV.

The potential impact of BV could also be expressed in the number of women who need to have BV for each additional case of HIV. This depends on the baseline risk of HIV amongst women without BV. For instance, with a 2.0% baseline risk of HIV seroconversion among BV-negative women[21], a relative risk of 1.6 would correspond to an absolute risk increase of approximately 1.2%, or about 1 additional case of HIV for every 80 to 90 women with BV. These data suggest that greater attention needs to be given to BV in the global fight against HIV infection. Randomized clinical trials (RCT) to determine the effect of BV control measures on HIV acquisition may be worth considering. A previous RCT of the effects of mass treatment of STIs on HIV conducted in Rakai (Uganda) used a single dose of oral metronidazole 2g and found no effect on HIV acquisition[38]. However, although 2g of metronidazole can cause short term remission, it is not the recommended treatment[39,40] thus limiting the inference that can be made on the effect of BV treatment from the Rakai study. Future RCTs assessing this effect will need to use the recommended treatment regimen with a longer duration associated with lower recurrence rates. In addition to the need to evaluate the potential of BV treatment to prevent HIV acquisition and transmission, a better understanding of its risk factors and determinants of BV recurrence is required.

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JA, PN, AAA and JSS defined the question and designed the study. JA and JSS abstracted and reviewed the data. JA, CP and JSS conducted the analysis. All authors wrote or reviewed the manuscript.

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References

1. Sobel JD. Vaginitis. N Engl J Med 1997;337:1896–1903. [PubMed: 9407158]
2. Marrazzo J. Bacterial Vaginosis. Current Treatment Options in Infectious Diseases 2003;5:63–68.
3. Hillier, S.; Holmes, K. Bacterial vaginosis. In: Holmes, PSK.; Mardh, P., et al., editors. Sexually Transmitted Diseases. Vol. 3. McGrawHill; NewYork: 1999. p. 563-586.
4. McDonald H, Brocklehurst P, Parsons J, Vigneswaran R. Antibiotics for treating bacterial vaginosis in pregnancy. Cochrane Database Syst Rev 2003:CD000262. [PubMed: 12804393]
5. Hillier, S.; Wiesenfeld, H.; Murray, P.; Busse, B.; Marrazzo, J. Microbicides 2004. London: 2004. Vaginal fluid SLPI is related to vaginal flora and hormonal contraception.
6. Verhelst R, Verstraelen H, Claeys G, Verschraegen G, Delanghe J, Van Simaey L, et al. Cloning of 16S rRNA genes amplified from normal and disturbed vaginal microflora suggests a strong association between Atopobium vaginae, Gardnerella vaginalis and bacterial vaginosis. BMC Microbiol 2004;4:16. [PubMed: 15102329]

7. Verstraelen H, Verhelst R, Claeys G, Temmerman M, Vaneechoutte M. Culture-independent analysis of vaginal microflora: the unrecognized association of Atopobium vaginae with bacterial vaginosis. Am J Obstet Gynecol 2004;191:1130–1132. [PubMed: 15507931]
8. Amsel R, Totten PA, Spiegel CA, Chen KC, Eschenbach D, Holmes KK. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. Am J Med 1983;74:14–22. [PubMed: 6600371]
9. Wang J. Bacterial vaginosis. Prim Care Update Ob Gyns 2000;7:181–185. [PubMed: 11025268]
10. Hillier SL, Nugent RP, Eschenbach DA, Krohn MA, Gibbs RS, Martin DH, et al. Association between Bacterial Vaginosis and Preterm Delivery of a Low-Birth-Weight Infant. N Engl J Med 1995;333:1737–1742. [PubMed: 7491137]
11. Jacobsson B, Pernevi P, Chidekel L, Jorgen Platz-Christensen J. Bacterial vaginosis in early pregnancy may predispose for preterm birth and postpartum endometritis. Acta Obstet Gynecol Scand 2002;81:1006–1010. [PubMed: 12421167]
12. Sweet RL. Gynecologic conditions and bacterial vaginosis: implications for the non-pregnant patient. Infect Dis Obstet Gynecol 2000;8:184–190. [PubMed: 10968604]
13. Ness RB, Kip KE, Hillier SL, Soper DE, Stamm CA, Sweet RL, et al. A cluster analysis of bacterial vaginosis-associated microflora and pelvic inflammatory disease. Am J Epidemiol 2005;162:585–590. [PubMed: 16093289]
14. Ness RB, Kip KE, Soper DE, Hillier S, Stamm CA, Sweet RL, et al. Bacterial vaginosis (BV) and the risk of incident gonococcal or chlamydial genital infection in a predominantly black population. Sex Transm Dis 2005;32:413–417. [PubMed: 15976598]
15. Cohen CR, Duerr A, Pruithithada N, Rugpao S, Hillier S, Garcia P, Nelson K. Bacterial vaginosis and HIV seroprevalence among female commercial sex workers in Chiang Mai, Thailand. AIDS 1995;9:1093–1097. [PubMed: 8527084]
16. Taha TE, Gray RH, Kumwenda NI, Hoover DR, Mtimavalye LA, Liomba GN, et al. HIV infection and disturbances of vaginal flora during pregnancy. J Acquir Immune Defic Syndr Hum Retrovirol 1999;20:52–59. [PubMed: 9928730]
17. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? Sex Transm Dis 2001;28:579–597. [PubMed: 11689757]
18. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. J Clin Microbiol 1991;29:297–301. [PubMed: 1706728]
19. Egger, M.; Smith, G.; Schneider, M. Systematic reviews of observational studies. In: Egger, M.; Smith, G.; Altman, D., editors. Systematic reviews in health care. Meta-analysis in context. London: BMJ Publishing Group; 2001. p. 211-227.
20. Deeks, J.; Altman, D.; Bradburn, M. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger, M.; Smith, G.; Altman, D., editors. Systematic reviews in health care. Meta-analysis in context. London: BMJ Publishing Group; 2001. p. 285-312.
21. Taha TE, Hoover DR, Dallabetta GA, Kumwenda NI, Mtimavalye LA, Yang LP, et al. Bacterial vaginosis and disturbances of vaginal flora: association with increased acquisition of HIV. Aids 1998;12:1699–1706. [PubMed: 9764791]
22. Warren D, Klein RS, Sobel J, Kieke B Jr, Brown W, Schuman P, et al. A multicenter study of bacterial vaginosis in women with or at risk for human immunodeficiency virus infection. Infect Dis Obstet Gynecol 2001;9:133–141. [PubMed: 11516061]
23. Greenblatt RM, Bacchetti P, Barkan S, Augenbraun M, Silver S, Delapenha R, et al. Lower genital tract infections among HIV-infected and high-risk uninfected women: findings of the Women's Interagency HIV Study (WIHS). Sex Transm Dis 1999;26:143–151. [PubMed: 10100771]
24. Myer L, Denny L, Telerant R, Souza M, Wright TC Jr, Kuhn L. Bacterial Vaginosis and Susceptibility to HIV Infection in South African Women: A Nested Case-Control Study. J Infect Dis 2005;192:1372–1380. [PubMed: 16170754]

25. Martin HL, Richardson BA, Nyange PM, Lavreys L, Hillier SL, Chohan B, et al. Vaginal lactobacilli, microbial flora, and risk of human immunodeficiency virus type 1 and sexually transmitted disease acquisition. J Infect Dis 1999;180:1863–1868. [PubMed: 10558942]
26. Hillier S. The vaginal microbial ecosystem and resistance to HIV. AIDS Res Hum Retroviruses 1998;14:S17–21. [PubMed: 9581879]
27. Schmid G, Markowitz L, Joesoef R, Koumans E. Bacterial vaginosis and HIV infection. Sex Transm Infect 2000;76:3–4. [PubMed: 10817059]
28. Hill J, Anderson D. Human vaginal leukocytes and the effects of vaginal fluid on lymphocyte and macrophage defense functions. Am J Obstet Gynecol 1992;166(2):720–726. [PubMed: 1536258]
29. Draper D, Donohoe W, Mortimer L, Heine RP. Cysteine proteases of Trichomonas vaginalis degrade secretory leukocyte protease inhibitor. J Infect Dis 1998;178:815–819. [PubMed: 9728551]
30. Cohen CR, Plummer FA, Mugo N, Maclean I, Shen C, Bukusi EA, et al. Increased interleukin-10 in the the endocervical secretions of women with non-ulcerative sexually transmitted diseases: a mechanism for enhanced HIV-1 transmission? Aids 1999;13:327–332. [PubMed: 10199222]
31. Wilson J. Managing recurrent bacterial vaginosis. Sex Transm Infect 2004;80:8–11. [PubMed: 14755028]
32. Poole C, Greenland S. Random-effects meta-analyses are not always conservative. Am J Epidemiol 1999;150:469–475. [PubMed: 10472946]
33. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect 1999;75:3–17. [PubMed: 10448335]
34. Fonck K, Kidula N, Kirui P, Ndinya-Achola J, Bwayo J, Claeys P, Temmerman M. Pattern of sexually transmitted diseases and risk factors among women attending an STD referral clinic in Nairobi, Kenya. Sex Transm Dis 2000;27:417–423. [PubMed: 10949433]
35. Sewankambo N, Gray RH, Wawer MJ, Paxton L, McNaim D, Wabwire-Mangen F, et al. HIV-1 infection associated with abnormal vaginal flora morphology and bacterial vaginosis. Lancet 1997;350:546–550. [PubMed: 9284776]
36. Mbizvo EM, Msuya SE, Stray-Pedersen B, Sundby J, Chirenje MZ, Hussain A. HIV seroprevalence and its associations with the other reproductive tract infections in asymptomatic women in Harare, Zimbabwe. Int J STD AIDS 2001;12:524–531. [PubMed: 11487393]
37. Riedner G, Rusizoka M, Hoffmann O, Nichombe F, Lyamuya E, Mmbando D, et al. Baseline survey of sexually transmitted infections in a cohort of female bar workers in Mbeya Region, Tanzania. Sex Transm Infect 2003;79:382–387. [PubMed: 14573833]
38. Wawer MJ, Sewankambo NK, Serwadda D, Quinn TC, Paxton LA, Kiwanuka N, et al. Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. Rakai Project Study Group. Lancet 1999;353:525–535. [PubMed: 10028980]
39. Sweet RL. New approaches for the treatment of bacterial vaginosis. Am J Obstet Gynecol 1993;169:479–482. [PubMed: 8357050]
40. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. MMWR Recomm Rep 2002;51:1–78.
41. Meda N, Ledru S, Fofana M, Lankoande S, Soula G, Bazie AJ, Chiron JP. Sexually transmitted diseases and human immunodeficiency virus infection among women with genital infections in Burkina Faso. Int J STD AIDS 1995;6:273–277. [PubMed: 7548291]
42. Rugpao S, Nagachinta T, Wanapirak C, Srisomboon J, Suriyanon V, Sirirojn B, et al. Gynaecological conditions associated with HIV infection in women who are partners of HIV-positive Thai blood donors. Int J STD AIDS 1998;9:677–682. [PubMed: 9863581]
43. Royce RA, Thorp J, Granados JL, Savitz DA. Bacterial vaginosis associated with HIV infection in pregnant women from North Carolina. J Acquir Immune Defic Syndr Hum Retrovirol 1999;20:382–386. [PubMed: 10096583]
44. Fonck K, Kaul R, Kimani J, Keli F, MacDonald KS, Ronald AR, et al. A randomized, placebo-controlled trial of monthly azithromycin prophylaxis to prevent sexually transmitted infections and HIV-1 in Kenyan sex workers: study design and baseline findings. Int J STD AIDS 2000;11:804–811. [PubMed: 11138916]

45. Fonck K, Kaul R, Keli F, Bwayo JJ, Ngugi EN, Moses S, Temmerman M. Sexually transmitted infections and vaginal douching in a population of female sex workers in Nairobi, Kenya. Sex Transm Infect 2001;77:271–275. [PubMed: 11463927]

46. Kapiga SH, Sam NE, Shao JF, Renjifo B, Masenga EJ, Kiwelu IE, et al. HIV-1 epidemic among female bar and hotel workers in northern Tanzania: risk factors and opportunities for prevention. J Acquir Immune Defic Syndr 2002;29:409–417. [PubMed: 11917247]

47. Moodley P, Connolly C, Sturm AW. Interrelationships among human immunodeficiency virus type 1 infection, bacterial vaginosis, trichomoniasis, and the presence of yeasts. J Infect Dis 2002;185:69–73. [PubMed: 11756983]

48. Msuya SE, Mbizvo E, Stray-Pedersen B, Sundby J, Sam NE, Hussain A. Reproductive tract infections and the risk of HIV among women in Moshi, Tanzania. Acta Obstet Gynecol Scand 2002;81:886–893. [PubMed: 12225308]

49. Sagay AS, Kapiga SH, Imade GE, Sankale JL, Idoko J, Kanki P. HIV infection among pregnant women in Nigeria. Int J Gynaecol Obstet 2005;90:61–67. [PubMed: 15907849]

50. Demba E, Morison L, van der Loeff MS, Awasana AA, Gooding E, Bailey R, et al. Bacterial vaginosis, vaginal flora patterns and vaginal hygiene practices in patients presenting with vaginal discharge syndrome in The Gambia, West Africa. BMC Infect Dis 2005;5:12. [PubMed: 15757510]

51. Cu-Uvin S, Hogan JW, Warren D, Klein RS, Peipert J, Schuman P, et al. Prevalence of lower genital tract infections among human immunodeficiency virus (HIV)-seropositive and high-risk HIV-seronegative women. HIV Epidemiology Research Study Group. Clin Infect Dis 1999;29:1145–1150. [PubMed: 10524955]

52. Helfgott A, Eriksen N, Bundrick CM, Lorimor R, Van Eckhout B. Vaginal infections in human immunodeficiency virus-infected women. Am J Obstet Gynecol 2000;183:347–355. [PubMed: 10942468]

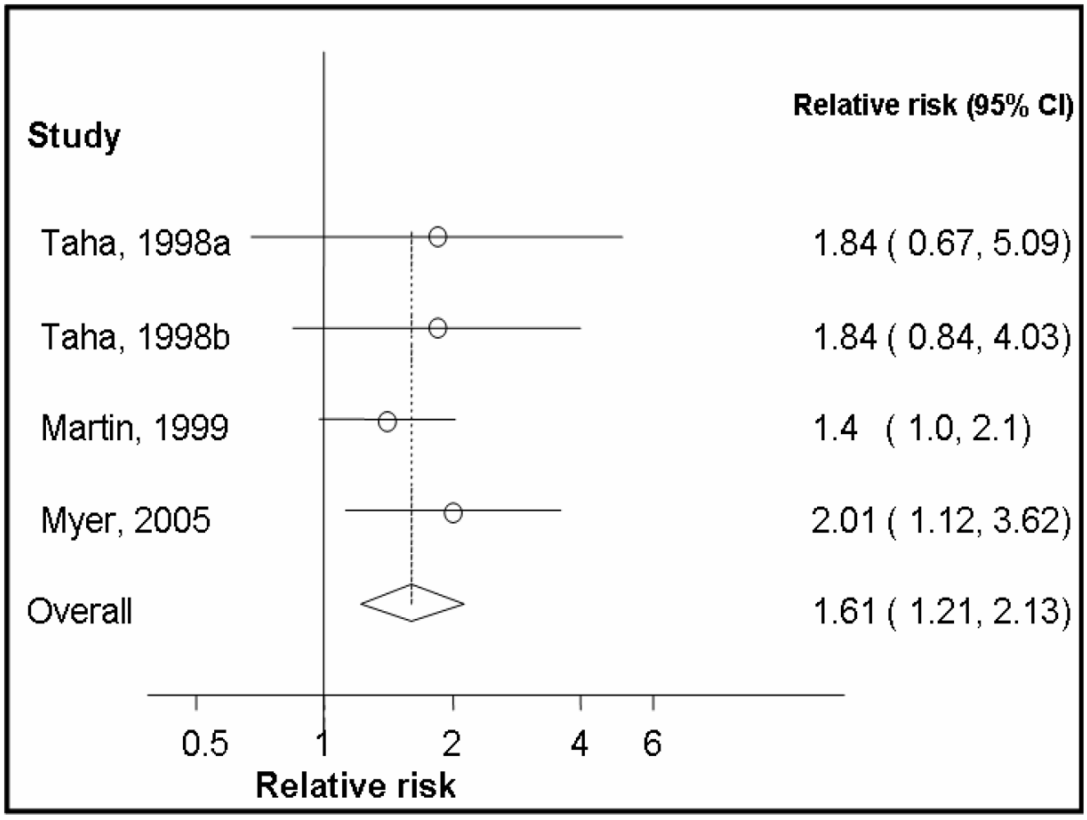

Figure 1. Forest plot of relative risk estimates of incident HIV infection by bacterial vaginosis status, stratified by HIV risk group

Studies are identified by the first author and the publication year. The horizontal lines represent the 95% confidence intervals. Overall heterogeneity p=0.7

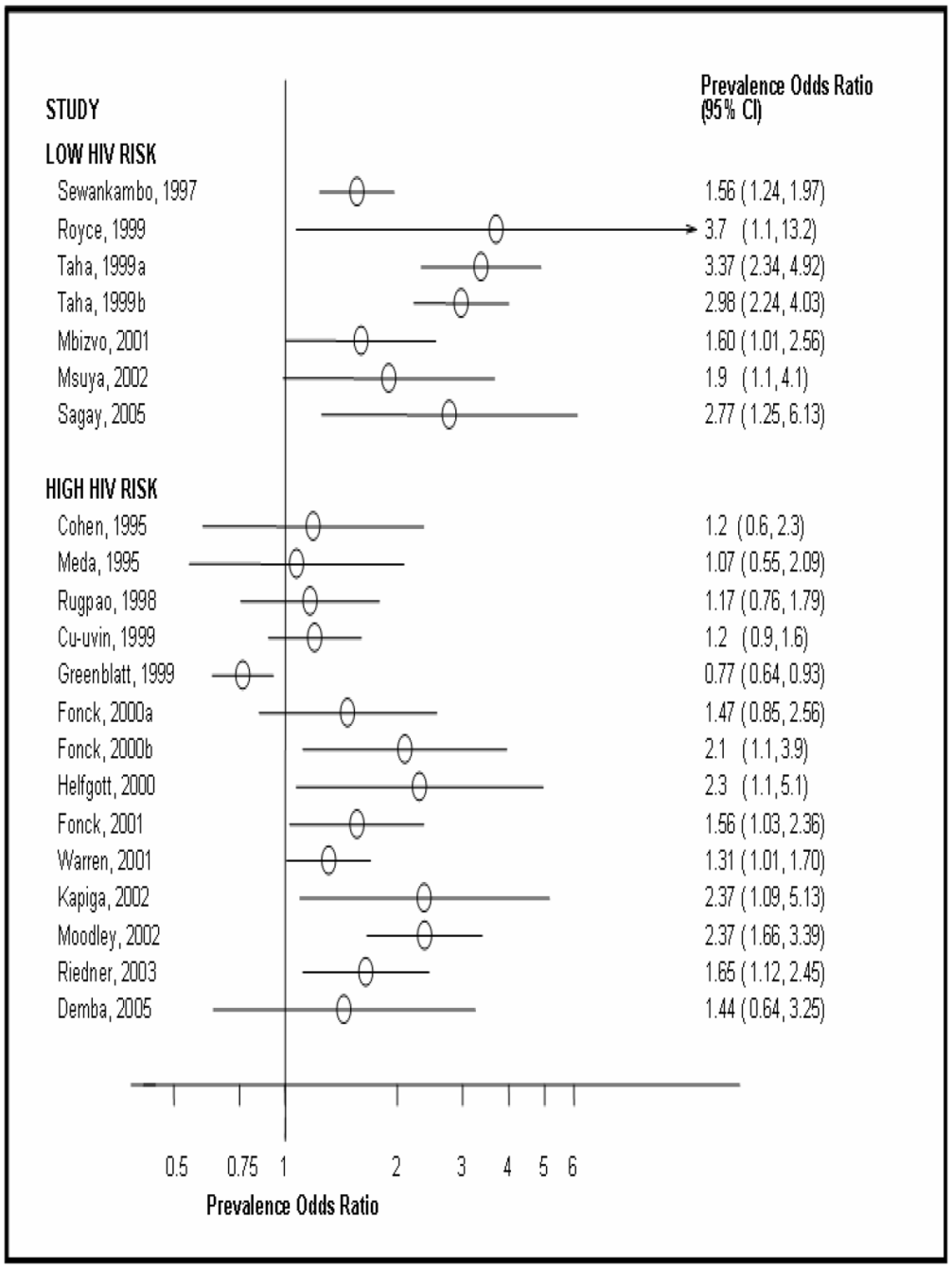

Figure 2. Forest plot of estimates of the association of prevalent HIV infection with bacterial vaginosis, stratified by HIV risk

Studies are identified by the first author and the publication year. The horizontal lines represent the 95% confidence intervals. Heterogeneity p-value in low HIV risk group = 0.002. Heterogeneity p-value in high HIV risk group <0.0001. Overall heterogeneity p<0.0001.

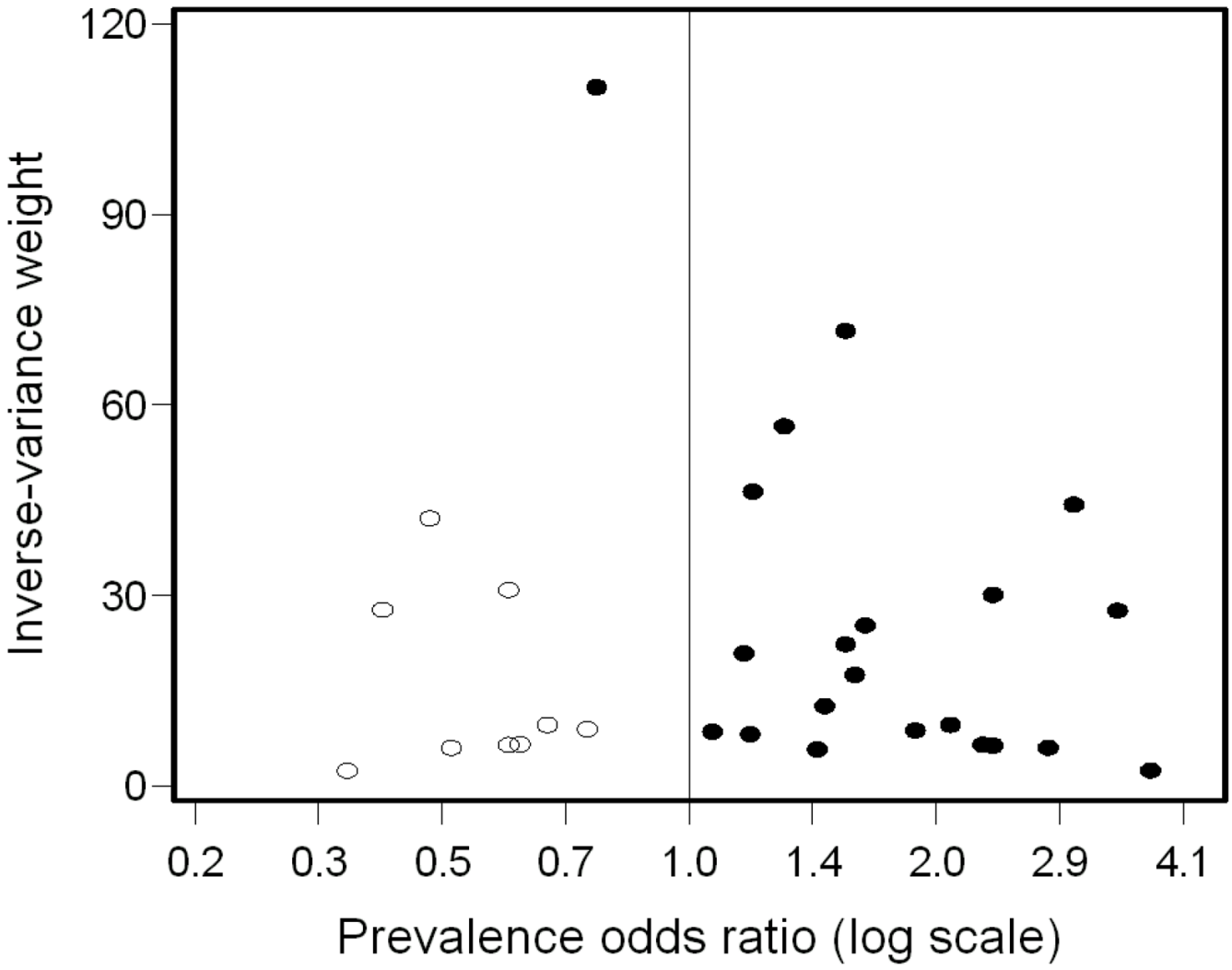

Figure 3. Funnel plot of estimates of the association of prevalent HIV infection with bacterial vaginosis

The full circles represent real study estimates while the blank circles are the imputed estimates from a 'trim and fill' analysis.

Table 1

Summary of studies of the association between Bacterial Vaginosis and HIV (published on or before October 2005)

Study, Publication Year (Country)	Study year	Participants	N	Age* (range)	BV diagnosis	BV (%)†	Factors adjusted for in analysis‡				
							Age	Sex partners	SES	Condom use	STI
HIV incidence studies											
Taha[21], 1998 (Malawi)[A]	1990–1993	HIV-pregnant women	1,196	-	Amsel criteria	30.0	y	y	y	n	y
Taha[21], 1998 (Malawi)[B]	1990–1993	HIV-women in post-partum	1,169	-	Amsel criteria	30.0	y	y	y	n	y
Martin[25], 1999 (Kenya)[§]	1993–1997	FSW	779	(18–48)	Nugent score ≥ 7	40.0	n	y	n	y	n
Myer[24], 2005 (South Africa)	2000–2002	Women screened for cervical cancer	410	(35–65)	I. Amsel criteria	15.7	y	y	y	y	y
					II. Nugent score ≥ 7	62.4					
HIV prevalence studies											
Cohen[15], 1995 (Thailand)[§]	1992	FSW at STI clinic	140	24 (15–49)	I. Amine test, pH>4.5, clue cells	34.0	y	y	n	y	y
					II. Nugent score ≥ 7	39.3					
Meda[41], 1995 (Burkina Faso)[§]	1992	Symptomatic STI patients	220	27	'clue' cells, abundant Gram negative flora	20.0	n	n	n	n	n
Sewankambo[35], 1997 (Uganda)[C]	1994–1995	Population-based sample	4718	(15–59)	Nugent score ≥ 7	50.9	y	y	n	n	y
Rugpao[42], 1998 (Thailand)[§]	1992–1996	Female partners of HIV+ male blood donors	481	27	All 4 elements of Amsel's definition	22.2	n	n	n	n	n
Royce[43], 1999 (USA)[D]	1995–1997	Pregnant women	616	-	Nugent score ≥ 7	20.9	n	n	n	n	n
Taha[16], 1999 (Malawi)	1990	HIV-pregnant women	6677	-	Amsel criteria	31.1	y	y	y	n	y
Taha[16], 1999 (Malawi)	1993	HIV-pregnant women	2449	-	Amsel criteria	27.0	y	y	y	n	y
Fonck[44], 2000 (Kenya)[§]	1998	FSW	256	32 (18–57)	Nugent score ≥ 7	47.3	n	n	n	n	n
Fonck[34], 2000 (Kenya)[§]	1996–1997	STI clinic attendees	324	26 (14–49)	pH>4.5, Amine test, clue cells	19.0	n	n	n	n	y
Fonck[45], 2001 (Kenya)[§]	1998–1999	FSW	532	30 (22–38)	Nugent score ≥ 7	39.7	n	n	n	n	n
Mbizvo[36], 2001 (Zimbabwe)[§]	1999	Clinic attendees	386	27 (16–49)	Amsel criteria	36.4	n	n	n	n	y
Warren[22], 2001 (USA)[§]	1993–1995	Matched HIV+/− women	1288	35 (16–55)	I. Amsel criteria	34.9	n	y	n	n	y
					II. Nugent score ≥ 7	46.2					
Kapiga[46], 2002 (Tanzania)[A§]	2000	Bar/hotel workers	268	28 (16–55)	Amsel criteria	26.1	y	y	n	n	n
Moodley[47], 2002 (South Africa)[§]	1999–2000	STI-Symptomatic women in a clinic	598	24 (17–70)	Nugent score ≥ 7	70.0	n	n	n	n	n
Msuya[48], 2002 (Tanzania)	1999	Clinic attendees	382	27 (16–46)	Amsel criteria	34.0	n	n	n	n	y
Riedner[37], 2003 (Tanzania)[§]	2000	Bar/hotel workers	600	25	Nugent score ≥ 7	40.2	y	n	n	n	n
Sagay[49], 2005 (Nigeria)	2002–2003	Pregnant women	2931	28 (<19-> 40)	Amsel criteria	17.8	y	n	n	n	y
Demba[50], 2005 (Gambia)[§]	2000	STI clinic attendees	210	28 (18–50)	Nugent score ≥ 7	47.6	n	n	n	n	n
Cu-uvin[51], 1999 (USA)[E,F§]	1993–1995	Matched HIV+/− women	1285	35 (16–55)	Amsel criteria	33.0	n	y	n	y	n
Greenblatt[23], 1999 (USA)[A,F§]	1994–1995	Matched HIV+/− women	2521	36 (16–73)	I. Amsel criteria	18.5	n	n	n	n	n
					II. Nugent score ≥ 7	42.3					
Helfgott[52], 2000 (USA)[F§]	1995–1997	HIV +/− women from STI and FP clinics	303	27 (20–35)	Amsel criteria	11.1	n	n	n	n	n

FP: Family planning; FSW: Female sex workers; N: number of participants; SES: Socio-economic status; STI: Sexually transmitted infections.

[A]Relative risk (RR) or Odds Ratio (OR) comparing BV to no BV estimated from data presented in article;

[B] Only OR comparing BV to absence of any Amsel criterion presented in article.;

[C] Moderate BV (score 7–8, and severe BV (score 9–10) were combined;

[D] HIV status self-reported on a standardized telephone interview;

[E] HIV status determined from participants medical records;

[F] studies that used a case-control design.

* ean or median age in years;

† BV prevalence;

‡ y= adjusted for, n=not adjusted for;

§ Study populations categorized as “High HIV-risk” in this analysis.

Table 2

Summary of analysis stratified by study characteristics

Characteristic		N	Summary		Within-stratum Heterogeneity p-value*	Funnel plot p-values†	Meta-regression ratio of odds ratios (heterogeneity p-values)‡
			OR	95% CI			
Study design	**HIV Prevalence**	21	1.69	1.36, 2.10	0.00	0.29; 0.06	1§
	HIV Incidence	4	1.61	1.21, 2.13	0.74	1.00; 0.24	1.02 (0.95)
BV diagnosis#	**Clinical**	11	1.93	1.45, 2.57	0.00	0.44; 0.95	1§
	Nugent	10	1.47	1.11, 1.94	0.00	0.86; 0.12	0.75 (0.12)
HIV risk group#	**Low**	7	2.30	1.68, 3.15	0.00	0.44; 0.02	1§
	High	14	1.44	1.15, 1.80	0.00	0.54; 0.52	0.62 (0.01)
Adjustment#	**Unadjusted**	7	1.33	0.90, 1.97	0.00	0.06; 0.28	1§
	Adjusted	14	1.90	1.53, 2.35	0.00	0.76; 0.16	1.44 (0.05)

*heterogeneity p-values for all studies within each level of study characteristics.

†Begg's test p-value (continuity corrected); Egger's test p value

‡Ratio of odds ratios (between-stratum heterogeneity p-values) from meta-regression;

§Referent category

#Only for HIV prevalence studies N: Number of estimates