Bacterial vaginosis and HIV infection

It has been over 10 years since reports were published that sexually transmitted infections (STIs) facilitate the transmission of HIV infection, and 8 years since the first review of the subject. None of these early reports mentioned bacterial vaginosis (BV). Following initial in vitro work by Klebanoff and Coombs in 1991, which suggested that BV may facilitate HIV transmission,[1] it was not until the clinical observations of Cohen *et al* in 1995[2] that the association between BV and HIV transmission has become a focus of attention (although other work was probably ongoing). There may be two broad reasons for the delay in recognition of the association.

Firstly, there is conflicting opinion as to whether BV is an STI. For this reason, researchers concentrating on the link between STIs and HIV infection may have simply "overlooked" the disease. Secondly, limited knowledge of the microenvironment and pathological response of the vagina affected by BV probably led researchers away from considering whether BV might affect HIV transmission. The enhancing effect of STIs on HIV transmission has generally focused on broken mucosal/skin defences, inflammatory exudates, or bleeding as reasons why STIs increase transmission of HIV. BV is not characterised by these vaginal changes.

An understanding is emerging of how BV might enhance the susceptibility to HIV infection.[3] The vagina is normally colonised by *Lactobacillus* species. Lactobacilli produce lactic acid, which maintains a low vaginal pH and inhibits the growth of many micro-organisms, including those associated with BV. Additionally, some lactobacilli—particularly those that "protect" against development of BV—produce hydrogen peroxide, which is toxic to a number of micro-organisms, including HIV.[1] BV is characterised by an absence of lactobacilli and, thus, an elevated pH. A low vaginal pH may inhibit CD4 lymphocyte activation and therefore decrease HIV target cells in the vagina[4]; conversely, an elevated pH may make the vagina more conducive to HIV survival and adherence (summarised by Taha *et al* [5]). BV has also been shown to increase intravaginal levels of interleukin-10, which increases susceptibility of macrophages to HIV.[6]

Although most clinical and epidemiological research has focused on the susceptibility of women with BV to HIV infection, some of the same factors that enhance susceptibility to HIV could also enhance transmission from HIV infected women with BV. Additionally, the findings that a heat stable protein elaborated by *Gardnerella vaginalis* increases production of HIV by HIV infected cells by as much as 77-fold[7] or that *Mycoplasma hominis* is the most potent inducer of HIV-1 expression among several vaginal bacterial or fungal species studied,[8] may have considerable clinical relevance. Were women with HIV and BV found to be efficient transmitters of HIV, they might be especially selected for HIV prevention efforts.

Most epidemiological studies that have looked for an association between BV and HIV have found one. Further, these studies have found a "dose-response" relation in which increasingly abnormal flora or severe BV is associated with increasing risk of HIV. Understanding this "dose-response" relation will help clarify why BV enhances HIV transmission.

Initial studies were cross sectional. A study of 144 commercial sex workers in Thailand found 24% of HIV uninfected women had clinical BV compared with 47% of those HIV infected (adjusted OR = 4.0, 95% CI = 1.7–9.4)[2]; although BV by Gram stain (Nugent score, 7–10) was not statistically associated with HIV, abnormal vaginal flora (score 4–10) was. Similar findings were reported from the community trial of STI control for HIV prevention in the Rakai district of Uganda. There, initial cross sectional data showed HIV infection, compared with women with normal flora (HIV seroprevalence, 14.2%), was more frequent among women with moderate (20.5%) or severe BV (26.7%) on Gram stain (RR 1.45, 95% CI = 1.20–1.75; RR 1.89, 95% CI = 1.46–2.43, respectively).[9] A third study, from Malawi, found increasing HIV seroprevalence among two cohorts of pregnant women with increasingly abnormal flora (judged by equating increasingly abnormal flora with increasing number of Amsel criteria met); HIV seroprevalence (combining cohorts) increased from 13% in those with normal vaginal flora to 34% in those with severe BV (χ^2 trend, $p<0.01$).[10] Lastly, a study from the United States of 724 pregnant women found a trend ($p=0.03$) of increased HIV prevalence with increasingly abnormal flora by Gram stain; 0.8% of women with normal flora to 3.3% with the most abnormal flora.[11]

A causal relation between BV and HIV is further supported by prospective studies. In Kenya, commercial sex workers without lactobacilli were more likely to acquire HIV (adjusted hazard ratio = 2.0, 95% CI = 1.2–3.5).[12] In Malawi, among 1196 pregnant women with a prevalence of BV of 24%, women with BV had an increased risk of HIV seroconversion in both antenatal (adjusted OR = 3.7) and postnatal periods (adjusted OR = 2.3).[5] These authors found, again equating degree of abnormality of flora with number of Amsel criteria present, that patients with increasingly abnormal flora had a higher risk of HIV acquisition (linear trend, $p<0.05$).

The relative risks found in these studies are similar to those used in HIV transmission models for non-ulcerative STIs, about 2 to 5. And BV is pervasively common.[13] In every society, BV is the most common abnormal vaginal infection. In many countries in the developing world, and in particular some of those hardest hit by the HIV epidemic, BV is considerably more common than other STIs which have been used in models to estimate an effect on HIV. These observations suggest that the attributable risks for BV are high (and that models of HIV transmission may need to be re-evaluated).

The population attributable risk percentage is the proportion of a particular disease occurring in a given population that occurs as a result of presence of an enhancing factor. The population attributable risk percentage is important because it indicates the proportion of disease (HIV) that could be prevented by eliminating the enhancing factor (BV). In one study in Malawi, the population attributable risk percentage of HIV seroconversion for BV was 23% among antenatal pregnant women and was 14% among women in the postnatal period.[5]

Given that there is considerable evidence that BV enhances acquisition of HIV infection, and that a high enough population attributable risk percentage exists to make intervention desirable, the question becomes "what intervention?" Therapy for BV is not highly effective, particularly when judged by cure rates a month or more following therapy; thus, relapse, even after initially effective therapy, is common. The most commonly used therapy for BV is a single 2 g dose of metronidazole. The effectiveness of this therapy is only 84% at 1 week following therapy and 62% when cure is judged at 3–4 weeks.[14] Alternative therapies exist, both oral and topical, but involve longer courses of treatment. While these longer courses (including metronidazole) are more effective than the single 2 g dose of

metronidazole, with initial cure rates often >90%,[15] the limited worldwide availability of these therapies, added expense, lessened patient acceptability, and uncertainty of patient compliance with these therapies and regimens mitigate against their widespread use. In addition, a programme introducing widespread therapy for BV in populations with high BV prevalence, as found in Africa, would need to monitor antimicrobial resistance not only of the organisms characteristic of BV (to ensure continuing efficacy) but ideally also of other micro-organisms.

The one study which evaluated an intervention for BV (a single 2 g dose of metronidazole at two 10 month intervals) did not show a significant decline in BV prevalence in the intervention compared with the control group at either the first or second post-treatment measurements, compared with one another or with pretherapy prevalences.[16] Although a modest decline occurred in the intervention group at the second post-treatment visit (46.6% *v* 53.8% in the control group), these prevalences were not statistically different and quite close to the pretreatment values of 50.4% and 51.2%, respectively. There was no difference in HIV acquisition between the treatment and control groups. A substudy of pregnant women did show a difference in BV prevalence post partum (39.1% *v* 52.8%), and it may be because these women were studied an average of only 4 months following therapy. Again, no difference in HIV acquisition between the two groups was demonstrated.

Given the therapeutic inadequacies for BV, and that the single study which evaluated a therapeutic intervention for BV to prevent HIV infection showed no significant effect, approaches to prevention of BV would be attractive; however, prevention options are also limited. Why women acquire or reacquire BV is not well known and the recognised risk factors for BV—for example, multiple or new sex partners, are generally not easy to modify. Replacement of the altered flora of BV with hydrogen peroxide producing lactobacilli appears promising but requires further investigation. Intravaginal microbicides containing nonoxynol-9, which might be prophylactically used against STIs and HIV, are also active against some of the organisms that characterise BV, although data on the clinical use of nonoxynol-9 for prevention of BV are conflicting. Importantly, lactobacilli concentrations may decrease transiently after use of nonoxynol-9 and the effects of chronic use of such agents need to be further evaluated.[17]

Data on the association between BV and HIV have shed light on an important risk factor for HIV infection. The challenge now is to determine how to reduce BV related HIV transmission. More research is needed on BV, its aetiology, and how to better treat and prevent it.

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1 Klebanoff SJ, Coombs RW. Virucidal effects of Lactobacillus acidophilus on human immunodeficiency virus type-1: possible role in heterosexual transmission. *J Exp Med* 1991;**174**:289–92.
2 Cohen CR, Duerr A, Pruithithada N, *et al.* Bacterial vaginosis and HIV seroprevalence among female commercial sex workers in Chaing Mai, Thailand. *AIDS* 1995;**9**:1093–7.
3 Hillier SL. The vaginal microbial ecosystem and resistance to HIV. *AIDS Res Hum Retroviruses* 1998;**14(S17)**:S17–21.
4 Hill JA, Anderson DJ. Human vaginal leukocytes and the effects of vaginal fluid on lymphocytes and macrophage defense function. *Am J Obstet Gynecol* 1992;**166**:720–6.
5 Taha TE, Hoover DR, Dellabetta GA, *et al.* Bacterial vaginosis and disturbances of vagina flora: association with increased acquisition of HIV. *AIDS* 1998;**12**:1699–706.
6 Cohen CR, Plummer FA, Mugo N, *et al.* Increased interleukin-10 in the endocervical secretions of women with non-ulcerative sexually transmitted diseases: a mechanism for enhanced HIV-1 transmission? *AIDS* 1999;**13**: 827–32.
7 Hashemi F, Ghassemi M, Roebuck KA, *et al.* Activation of human immunodeficiency virus type 1 expression by Gardnerella vaginalis. *J Infect Dis* 1999;**179**:924–30.
8 Al-Harthi L, Roebuck KA, Olinger GG, *et al.* Bacterial vaginosis-associated microflora isolated from the female genital tract activates HIV-1 expression. *J Acquir Immunol Def Synd* 1999;**21**:194–202.
9 Sewankambo N, Gray RH, Wawer MJ, *et al.* HIV-1 infection associated with abnormal vaginal flora morphology and bacterial vaginosis. *Lancet* 1997;**350**:546–50.
10 Taha TE, Gray RH, Kumwenda NI, *et al.* HIV infection and disturbances of vaginal flora during pregnancy. *J Acquir Immunol Def Synd Hum Retrovirol* 1999;**20**:52–9.
11 Royce RA, Thorp J, Granados JL, *et al.* Bacterial vaginosis associated with HIV infection in pregnant women from North Carolina. *J Acquir Immunol Def Synd Hum Retrovirol* 1999;**20**:382–6.
12 Martin Jr HL, Richardson BA, Nyange PM, *et al.* Vaginal lactobacilli, microbial flora, and risk of human immunodeficiency virus type I and sexually transmitted disease acquisition. *J Infect Dis* 1999;**180**:1863–8.
13 Hillier S, Holmes KK. Bacterial vaginosis. In: Holmes KK, Sparling PF, Mardh P-A, Lemon SM, Stamm WE, Piot P, Wasserheit JN, eds. *Sexually transmitted diseases.* 3rd ed. Chapter 42. New York: McGraw Hill, 1999.
14 Joesoef MR, Schmid GP, Hillier SL. Bacterial vaginosis: review of treatment options and potential clinical indications for therapy. *Clin Infect Dis* 1999; **28(Suppl 1)**:S57–65.
15 Joesoef MR, Schmid GP. Bacterial vaginosis: review of treatment options and potential indications for therapy. *Clin Infect Dis* 1995;**20 (Suppl 1)**:S72–9.
16 Wawer MJ, Sewankambo NK, Senwadda D, *et al.* Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. *Lancet* 1999;**353**:525–35.
17 Watts DH, Rabe L, Krohn MA, *et al.* The effects of three nonoxynol-9 preparations on vaginal flora and epithelium. *J Infect Dis* 1999;**180**:426–37.

The British Co-operative Clinical Group (BCCG)

Tempus fugit. The British Co-operative Clinical Group (BCCG) was established in 1951 for the immediate purpose of collecting information concerning the venereal diseases from case records available in the United Kingdom. It was due to the perspicacity of one distinguished consultant venereologist (for that is what he called himself), the late Dr R R (Dick) Willcox, who died in 1985, that this group, still flourishing, exists, is independent, finds information on behalf of the specialty of genitourinary medicine in the United Kingdom, and is producing more publications from its numerous projects than ever before. I chaired the BCCG for some years between 1990 and 1995, before handing on to my successor, Dr George Kinghorn ably assisted by Dr Chris Carne, who have kept me informed about recent developments. I suppose I am seen as a link between the events of over 25 years ago and the present. Hence tempus fugit. Among other achievements, Dr Willcox travelled and wrote more than any other British contemporary venereologist of his time, and was on the council (and was president 1965–7) of the Medical Society for the Study of Venereal Diseases (MSSVD) for 31 years from 1953 to 1984, reporting about the BCCG annually to council and the society. He was an advocate of cross fertilisation from other disciplines, especially epidemiology. At the present time, epidemiologists from the Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre (CDSC) belong to the BCCG and bring their expertise to the design and analysis of various studies.