# THE ROLE OF SEXUALLY TRANSMITTED DISEASES IN HIV TRANSMISSION

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More than 42 million people worldwide are now infected with HIV, in spite of sustained prevention activities. Although the spread of HIV has been primarily sexual, epidemiological studies have indicated that the efficiency of the spread of HIV is poor, perhaps as infrequently as 1 in every 1,000 episodes of sexual intercourse. However, sexually transmitted diseases (STDs) that cause ulcers or inflammation greatly increase the efficiency of HIV transmission — by increasing both the infectiousness of, and the susceptibility to HIV infection. STDs might be particularly important in the early stages of a localized HIV epidemic, when people with risky sexual behaviour are most likely to become infected. In China, eastern Europe and Russia, there has been a remarkable increase in the incidence of STDs in recent years, and this is reflected in the rapid increase in the spread of HIV in these areas. Targeted STD detection and treatment should have a central role in HIV prevention in these emerging epidemics.

Effective control of the HIV pandemic will require a complete understanding of the transmission of this virus. The potential routes of HIV transmission are known (TABLE 1), and the efficiency of transmission has been derived from epidemiological and, more recently, clinical studies. The main route of HIV transmission continues to be sexual transmission.

In 1987, May and Anderson[1] developed a powerful mathematical tool to predict the spread of infectious diseases see equation 1:

$$R_0 = \beta Dc \qquad (1)$$

where $R_0$ is the secondary spread of an agent, $\beta$ is the efficiency of transmission, $D$ is the duration of infectiousness and $c$ is the number of individuals that are exposed to the infection. For HIV transmission, the $c$ value does not simply reflect the number of individuals that are exposed (that is, the number of sexual partners). It reflects the mean number of partners plus the ratio of the variance of the distribution of the number of new sexual partners over time to the mean, and therefore reflects the enhanced role of individuals with many new partners in the spread of HIV.

In this review we will focus on $\beta$, the efficiency of transmission, although the duration of infectiousness of HIV is also important, given that in infected individuals there can be a prolonged asymptomatic state. In their recent review[2], Shattock and Moore described our current understanding of the molecular basis of HIV transmission. Inherent in this description is the idea that the efficiency of HIV transmission is defined by the infectiousness of the HIV-infected individual and the susceptibility of those exposed to the virus.

Given the magnitude of the HIV pandemic, it is perhaps difficult to understand how a microorganism that seems to require 500–1,000 episodes of intercourse for transmission (TABLE 1) could be so far reaching. It is precisely this concern that has led political columnists to blame the HIV pandemic in Africa on promiscuous sexual behaviour[3], and other theorists to propose that it is primarily dirty needles rather than sexual intercourse

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Table 1 | **Routes of exposure to HIV**

| Infection route | Risk of infection |
|---|---|
| ***Sexual transmission*** | |
| Female-to-male transmission | 1 in 700–1 in 3,000 |
| Male-to-female transmission | 1 in 200–1 in 2,000 |
| Male-to-male transmission | 1 in 10–1 in 1,600 |
| Fellatio | 0–1 in 16 |
| ***Parenteral transmission*** | |
| Transfusion of infected blood | 95 in 100 |
| Needle sharing | 1 in 150 |
| Needle stick | 1 in 200 |
| Needle stick/AZT PEP | 1 in 10,000 |
| ***Transmission from mother to infant*** | |
| Without AZT treatment | 1 in 4 |
| With AZT treatment | <1 in 10 |

AZT, azidothymidine (now called Retrovir/zidovudine; PEP, post-exposure prophylaxis. Modified with permission from REF. 5 © (1997) Massachusetts Medical Society.

that are crucial for transmission[4]. These ideas focus on increasing the magnitude of *c* (the number of people that are exposed to the virus) to account for the large numbers of people that are infected in highly endemic areas. However, it is equally likely that factor(s) that amplify the infectiousness of the virus and enhance the susceptibility of individuals to infection are crucial for the spread of HIV[5–7]. Indeed, recent studies comparing heterosexual couples living in different countries where the prevalence of HIV varies markedly show few differences in sexual behaviour[8]. Likewise, there is limited evidence to support the 'dirty-needle' hypothesis.

In this article, we will divide the sexual transmission of HIV into two aspects — infectiousness and susceptibility. The factors that are known to affect infectiousness and susceptibility will be discussed, and then the role that sexually transmitted diseases (STDs) in particular have in transmission through their effects on both infectiousness and susceptibility will be elucidated. Finally, clinical trials that provide information on the role of STDs in HIV transmission will be reviewed.

HIV DISCORDANT COUPLE
Two sexual partners in, usually, a stable monogamous relationship, in which one person is infected with HIV and the other is not.

SEROCONVERSION
The appearance of antibodies in the serum after exposure to an antigen.

CLADE
A group of species derived from a single ancestor that includes all the descendants of that ancestor.

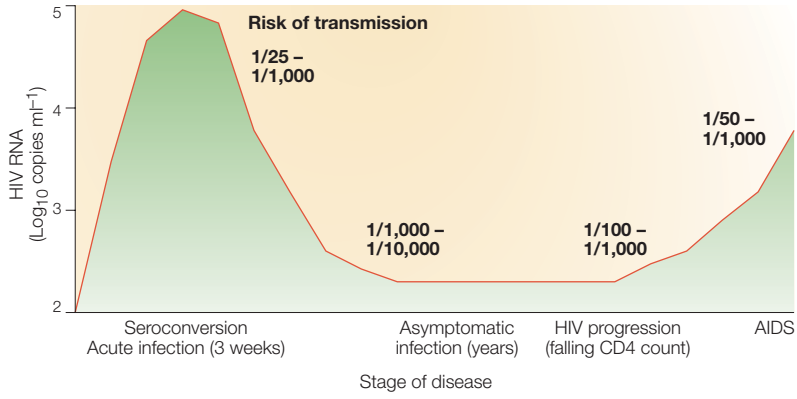


Figure 1 | **The changing viral load during the different stages of disease and the effects of viral load on the probability of sexual transmission of HIV.**

## Factors that increase HIV transmission

*Infectiousness.* Biological factors that increase the concentrations of HIV in the blood and in genital secretions, or that promote the evolution of a more infectious HIV variant would be expected to increase the infectiousness of the virus. Blood viral levels in HIV-positive individuals are important in determining infectiousness. This is exemplified by the fact that the concentration of HIV in the mother's blood at the time of delivery determines the risk of neonatal infection[9,10], and antiretroviral therapy (ART) provided to the mother to reduce replication of HIV reduces vertical transmission[10,11]. Additionally, the concentration of HIV in the blood of the infected index case can be correlated directly with the sexual transmission of HIV. In a landmark study of HIV DISCORDANT COUPLES in Uganda, Quinn *et al.*[12] noted that HIV transmission was not observed when the concentration of HIV was <1,500 copies $ml^{-1}$, and that the risk of transmission increased directly with increasing blood viral burden. Each log increment in viral load of the infected partner resulted in a rate ratio of 2.45 for SEROCONVERSION of the uninfected partner.

Therefore, factors that increase blood viral loads would be expected to increase infectiousness. High concentrations of HIV can be recovered from the blood in acute HIV infection (C.D. Pilcher *et al.*, unpublished observations), in late HIV disease[13,14] and in some patients who develop systemic or other infections[15], such as tuberculosis[16], malaria[17], herpes outbreaks[18] and intestinal worms[19].

The particular stage of HIV disease could also be of importance in transmission — modelling experiments indicate that people with acute HIV infection (which we define as the first three weeks of infection) or early infection (the first six months) represent the greatest risk for transmission (C.D. Pilcher *et al.* unpublished observations)[20]. In individuals with acute HIV infection, viral replication is unrestrained by host defences[21]. The effects of the presence of high concentrations of HIV RNA on sexual transmission are shown in FIG. 1. Using empirical data from a Ugandan study, Wawer and co-workers[22] calculated that HIV transmission during early HIV infection (the first five months) was 0.0081 per coital act, compared with 0.0010 and 0.0043 per coital act in individuals with more established or late HIV infection, respectively. In a separate study in Malawi, 24 people with acute HIV infection were identified[23]. These subjects had median blood viral burdens of >1,000,000 copies $ml^{-1}$. Using a probabilistic model[24], the probability of heterosexual transmission during acute HIV infection was calculated to be 20-fold greater than in control subjects with established infection.

Even among people who are at the same stage of disease there can be important variations in the levels of HIV in the blood. In some studies, it has been shown that HIV-infected individuals in Africa have a higher viral burden in blood and semen than HIV-infected individuals in the United States, even though they have the same CD4 counts[25]. Such an increase in viral burden might reflect differences in the replication capacity of different HIV CLADES, co-infections that increase viral burden, host genetics or other as-yet-undefined factor(s)[6].

The viral load in genital fluid is another determinant of infectiousness[26]. Most patients with detectable plasma viral loads shed HIV in genital secretions[26]. In general, viral levels in the female genital tract[27] and in semen[28,29] correlate with systemic viral loads. This relationship remains true even during acute infection (C.D. Pilcher *et al.*, unpublished observations). The concept that viral shedding in genital fluids reflects the plasma viral load is furthered by findings that successful ART decreases the viral load in both cervicovaginal fluids[30] and semen[31]. However, some men with undetectable plasma viral loads shed HIV in their semen[29,31].

Plasma viral loads are not the only determinant of genital viral loads. Low CD4 counts are also associated with higher genital viral loads, and therefore, infectiousness[32,33]. As will be discussed further below, one of the most important determinants of genital viral load is the presence of STDs[34–36]. In women, bacterial vaginosis (BV), herpes simplex virus (HSV), human papillomavirus, *Chlamydia trachomatis, Neisseria gonorrhoeae, Candida*, genital ulceration and vaginal discharge have been associated with increased HIV shedding. In men, *N. gonorrhoeae, Trichomonas vaginalis*, cytomegalovirus (CMV), urethritis and genital ulcer disease (GUD) have been linked to HIV shedding in semen[36].

Other, more controversial, determinants of genital viral load include nutritional deficiencies and the use of contraceptives. Observational studies found that deficiencies in selenium and vitamin A were linked to higher rates of female genital viral shedding[37,38]. Nutritional deficiencies might increase genital viral loads through decreased antioxidant activities[38], and, in the case of a study on vitamin A, the authors suggested that increased vaginal shedding of HIV was related to the role of adequate levels of vitamin A in maintaining epithelial integrity[37]. However, clinical trials of vitamin A supplementation did not decrease vaginal shedding[39] or maternal-to-child transmission[40], and instead might increase transmission through breastfeeding[41]. Nutritional deficiencies, then, might be a marker of more advanced HIV disease rather than a cause of increased viral shedding. The same studies documented a relationship between the use of oral contraceptives and the recovery of cervical HIV-1 DNA[37], possibly by creating a thicker, more cellular, cervical mucous, which leads to greater shedding of HIV-infected cells[37]. However, the role of sexual hormones in HIV infectiousness remains unclear.

Increases in the genital viral load have great impact on the rates of sexual transmission. Using a probabilistic empirical model that accounts for semen viral load and the number of cervical CCR5 receptors, the probability of transmission was 3 per 10,000 episodes of intercourse when the semen viral load was 1,000 copies per ejaculate, but 1 in 100 when the semen contained 100,000 viral copies per ejaculate[26].

Variations in infectiousness could occur even at equivalent viral loads if some HIV variants are more infectious than others. Most transmitted viruses use the CCR5 chemokine receptor as an entry co-receptor; these virus types are also called non-synctium-inducing variants (NSI) or macrophage-trophic variants[42] (FIG. 2). In clade B infection, variants emerge during the course of infection that use another chemokine receptor, the CXCR4 receptor. These variants are referred to as synctium-inducing (SI) or T-cell trophic. Clade B is the predominant HIV clade in North America and Europe. The predominant clade in many parts of southern Africa, and also the clade that accounts for the most HIV cases worldwide, is clade C. It has been found that clade C rarely progresses to CXCR4 trophism[43]. This could lead to enhanced infectiousness for persons with clade C infections if they have the more commonly transmitted CCR5 variant throughout the entire course of their illness[43].

HUMAN LEUKOCYTE ANTIGEN
Also known as major histocompatibility complex (MHC), it is a glycoprotein that is found on the surface of cells that present antigen for recognition by T cells.

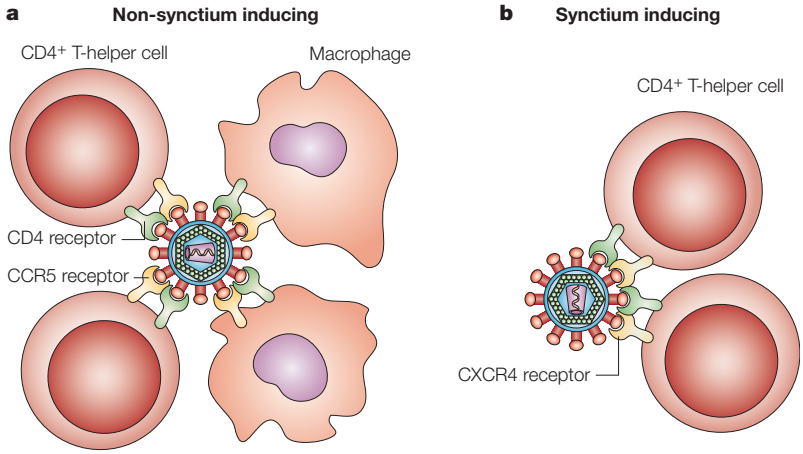


Figure 2 | **The HIV co-receptors. a** | The CCR5 chemokine receptor is used as an entry co-receptor by most transmitted viruses early in infection. These virus types are referred to as non-synctium-inducing variants (NSI), macrophage-trophic variants or 'R5 viruses'. **b** | In infection with HIV from clade B — the predominant clade in North America and Europe — variants emerge during the course of infection that use CXCR4, a different chemokine receptor. These virus types are referred to as synctium-inducing (SI), T-cell trophic or 'X4 viruses'. For cell entry, each HIV particle binds to both co-receptors (yellow) and CD4 receptors (green).

***Susceptibility.*** Factors that affect the body's innate and specific immune responses can increase susceptibility to HIV. Interruption of the genital mucosal barrier alters the body's main defence against sexually transmitted infections. Practices that increase genital trauma, such as dry sex[44], can increase susceptibility in this manner. Mucosal irritation might explain the increased susceptibility to HIV that is observed with the use of some spermicides, such as nonoxynol-9 (REF. 45).

Different HUMAN LEUKOCYTE ANTIGEN (HLA) types and HIV co-receptors are also associated with susceptibility to developing AIDS[46]. The HLAs B35, A1, A2 and DR5 have all been associated with an increased risk of progression to AIDS in HIV-infected individuals, whereas the HLAs A3, B27, B57 and B44 have been associated with delayed progression. Co-receptors are important in susceptibility to infection. HIV uses chemokine receptors that are found on macrophages, lymphocytes and some other cell types as entry co-receptors[47]. As already described, the predominant co-receptor is the CCR5 receptor. Individuals who are homozygous for the CCR5 Δ32 mutation have decreased expression of

Table 2 | **Types of sexually transmitted infections**

| Characteristics | Aetiological agents |
|---|---|
| Systemic infections without mucosal disease | HIV, hepatitis B, cytomegalovirus |
| Genital ulcers | *Haemophilus ducreyi*, herpes simplex virus 1 and 2, *Treponema pallidum* |
| Mucosal inflammation | *Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis* |
| Changes in epithelial cells | Human papillomavirus |

the CCR5 receptor and are highly resistant to HIV infection[48]; conversely, higher expression of CCR5 co-receptors might be associated with an increase in susceptibility to HIV infection[49].

Some differences in susceptibility could be related to gender. There is evidence that women might become infected with more HIV variants than men or infants[50]. Different viral variants were found in 20 of 32 recently HIV-infected women compared with 0 of 10 recently infected men. These viral variants were found before seroconversion, indicating that they did not develop after immune selective pressure, and were not co-infections from multiple partners[51]. It is still unknown what causes this tendency towards infection with multiple viral variants in women[51].

The proposed role that female sexual hormones might have in infectiousness has already been discussed. Other studies have documented the role of female sexual hormones in susceptibility to HIV infection. Progesterone therapy increases susceptibility to simian immunodeficiency virus (SIV) in macaques — possibly owing to a thinning of the vaginal epithelium[52]. Treatment of ovariectomized macaques with subcutaneous oestrogen protected the animals from vaginal SIV challenge[52], leading the authors to conclude that topical vaginal oestrogen might be useful in reducing HIV susceptibility in post-menopausal women or women receiving only progesterone.

## STDs and HIV transmission

STDs can be divided into four categories: those that produce no mucosal signs or symptoms; those that produce varying degrees of mucosal inflammation; those that produce genital ulcers; and those that cause epithelial-cell changes and/or MUCOSAL NEOPLASM (TABLE 2). The interaction between these 'traditional' STD pathogens and HIV has attracted a great deal of attention, and has been referred to as 'epidemiological synergy'[34]. HIV can influence the prevalence or manifestations of other STDs, and other STDs can have an impact on HIV transmission. There is compelling evidence for the effects of STDs on the transmission of HIV[34–36]. However, it has been difficult to determine whether an individual STD increases the infectiousness of HIV, the susceptibility of individuals to HIV or (more than likely) to both HIV and an STD, or to determine which STD has the greatest effect on HIV transmission.

A remarkable number of epidemiological studies have been undertaken to link STDs and HIV[5,34–36]. In their review, Fleming and Wasserheit[34] examined STDs and HIV transmission in the context of studies of biological plausibility, COHORT STUDIES and clinical trials. The greatest attention has been directed towards cohort studies that focus on HIV acquisition and 'attributable risk'[34]. In such studies, the HIV status of a study subject is determined together with the history or record of detection of an STD. By comparing STDs in subjects with and without HIV infection, the contribution of STDs can be estimated. The problems with this approach include the limitations of the use of historical data as a proxy for an STD; the limitations of the STD assays that are available; and an inability to detect co-transmission of HIV and STD pathogens[34–36].

To examine the role of STDs further, we will attempt to 'deconstruct' the effects of STDs on the infectiousness and susceptibility of HIV.

## STDs and infectiousness

The effects of an STD on the infectiousness of HIV could be measured prospectively, but such work has not been undertaken so far. Rather, several indirect approaches have been used.

***Effects on HIV shedding.*** It is possible to examine the influence of STD pathogens on the excretion of HIV in genital secretions. On the basis that the concentration of HIV in genital secretions determines the probability of transmission, the direct measurement of HIV seems to be a reasonable proxy, both in men and women. However, there are technical limitations to this approach[5,36], including difficulty sampling the female genital tract, contamination of genital secretions with blood and variability between different assays[27]. Additionally, it remains unclear whether HIV is transmitted by infected cells or by cell-free virus.

STDs that cause ulcers generally increase shedding (detection) of HIV in the genital tract[34–36,53]. This can occur by direct shedding of HIV from the ulcerative lesion. HIV has been detected by culture and PCR from the exudate of CHANCROID LESIONS[54]. Studies in female sex workers showed a 3.9 ADJUSTED-ODDS RATIO for shedding HIV in the presence of a vaginal or cervical ulcer[33]. The lesions need not be purely infectious in nature to have an effect — ulcerations of the cervix that are associated with treatment of intraepithelial lesions were found to increase HIV levels[55]. GUD can also affect HIV levels in semen by affecting systemic viral loads or increasing local inflammation. In a study in Malawi, men with genital ulcers and non-gonococcal urethritis were found to shed higher amounts of HIV in semen compared with men with urethritis alone[56].

MUCOSAL NEOPLASM
Usually carcinomas, such as cervical carcinomas, that are associated with certain types of HIV.

COHORT STUDIES
Studies in which subsets of a defined population are identified.

CHANCROID LESIONS
Single or multiple painful, necrotizing ulcers at the site of infection, which are frequently accompanied by painful swelling and suppuration of regional lymph nodes.

ADJUSTED-ODDS RATIO
The estimated odds ratio after any confounding factors have been taken into account.

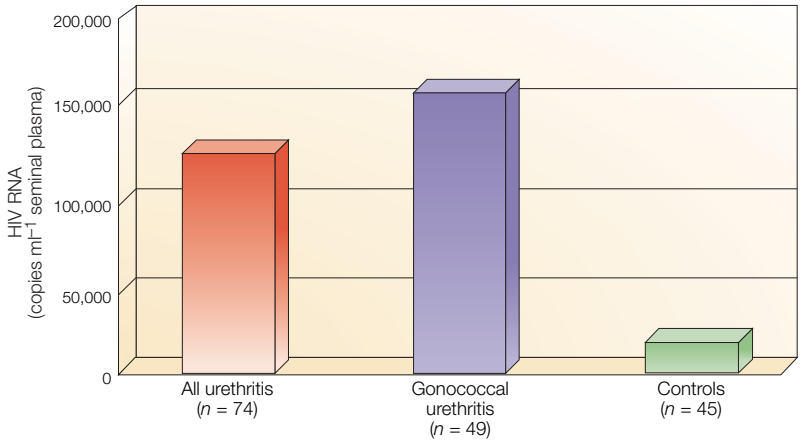


Figure 3 | **The effects of urethritis on the viral load of HIV in semen.** *n* denotes the number of patients in each sample. Modified with permission from REF. 66 © (1997) Elsevier Science

As the most common causative agent of GUD worldwide, HSV has an important role in HIV infections[57,58]. HIV-1 RNA was detected in ulcer swabs in 25 of 26 men with symptomatic HSV-2 infection, and the levels exceeded 10,000 copies $ml^{-1}$ of swab sample in most cases[59]. The levels of HSV shedding correlate with HIV plasma viral levels[60]. Even asymptomatic HSV shedding was found to be associated with increased HIV shedding[61].

STDs that cause inflammation increase the concentration of HIV in the urethra, semen[62–66] and cervical fluid[32,33]. In patients with urethritis, gonorrhoea seems to have a greater effect on the viral load in the genital tract than chlamydia[67], as might be predicted by the higher degree of inflammation that is usually caused by gonorrhoea. However, less purulent STDs, such as *Trichomonas*-associated urethritis in men, have been shown to increase semen viral load[62,63], and this is also correlated with the degree of urethral inflammation.

UNIVARIATE ANALYSIS
Examines the effect of one variable.

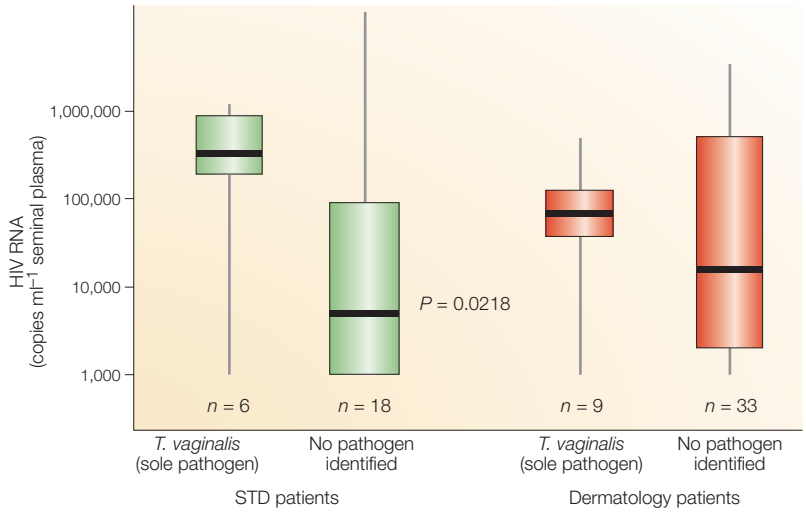


Figure 4 | **The effects of *Trichomonas vaginalis* infection on the viral load of HIV in semen.** *n* denotes the number of patients in each sample. The mean viral load for each patient group is shown by the thick black bar.

Even asymptomatic urethritis has been associated with HIV shedding in semen[64]. As shown in FIGS 3 and 4, gonococcal and *Trichomonas* urethritis cause a substantial increase in the concentration of HIV in the semen. A study that examined women from Cote d'Ivoire[33], found that GUD, gonorrhoea and chlamydia have effects in UNIVARIATE ANALYSIS, whereas trichomonas, syphilis and vaginitis do not.

Treatment of STDs reduces the concentration of HIV in genital secretions[33,66–68]. In HIV-infected women with an STD that was successfully treated, the proportion who had detectable cervicovaginal HIV fell from 42% to 21% at a seven-day follow-up visit; whereas in women whose STD was not cured and women without STDs, there was no change in the proportion who were shedding HIV (36% and 17%, respectively)[33]. In men who were treated for urethritis, the concentrations of HIV RNA in the semen fell from an average of $1.24 \times 10^5$ copies $ml^{-1}$ to $4.12 \times 10^4$ copies $ml^{-1}$ at two weeks[66]. In most cases, treatment of the STD does not reduce the concentrations of HIV RNA to those seen in HIV-infected persons without STDs[67].

Analyses of the blood viral burden in subjects with genital-tract infections show somewhat conflicting results. In men, the HIV concentration in the blood remained unchanged before and after treatment of urethritis[66]. However, Anzala *et al.* reported that HIV blood levels rose during gonococcal cervicitis and pelvic-inflammatory disease, and returned to baseline levels after treatment[69]. In one study, GUD was associated with a higher plasma viral load[56]. The effect of HSV infection on the viral burden of HIV in blood has been the subject of unresolved but important debate about the adjunctive potential of HSV antiviral therapy on the management of HIV. HIV viral load has been found to increase in subjects having a HSV outbreak[18]. In a trial of individuals who are co-infected with HIV and HSV-2, Schacker *et al.* found that treatment with acyclovir reduced HIV plasma viral loads[60].

***Effects on HIV replication.*** A modest number of experiments have been conducted *in vitro* to examine the direct effect of various STD pathogens on HIV replication. Ho *et al.* found that replication of HIV in mononuclear cells is increased in the presence of polymorphonuclear cells (PMNs) and that this effect is even greater with the addition of *C. trachomatis*[70]. Another study showed that human herpesvirus-8 induces HIV replication[71]. *Treponema pallidum* (the aetiological agent of syphilis) induces HIV gene expression and this increased expression correlates with increased binding of nuclear factor (NF)-κB to the promoter region of the HIV provirus long-terminal repeat[72]. Clinical evidence comes from work that showed that HSV shedding without clinical ulcers still increases cervical HIV levels[61]. Speck *et al.* have reported that the presence of CMV in the genital tract can also increase HIV replication, perhaps through direct viral transactivation[65]. CMV shedding from the cervix is significantly associated with HIV shedding in women with both CMV and HIV infections[73].

***Clinical trials and HIV excretion.*** Clinical trials can be designed to dissect the effect(s) of an STD on transmission of HIV. For example, Celum and co-workers have focused on HSV[57]. The development of specific and sensitive HSV diagnostic serological tests has led to the realization that many HIV-infected people also have an HSV-2 infection[53,57,58]. HSV-2 infection is associated with intermittent asymptomatic excretion of HSV in the genital tract[74]. HSV lesions are associated with HIV shedding[59]. Celum and co-workers plan to conduct a trial in HIV discordant couples in which HSV-2–HIV dually infected 'index' partners (who do not require ART directed at HIV) are randomized to receive acyclovir to suppress HSV reactivation, with the hypothesis that HIV acquisition will be reduced[57]. It should be noted that, in a recent study, valacyclovir effectively suppressed the transmission of HSV from an infected subject to his/her sexual partner[75].

***Co-transmission of STDs and HIV.*** Compelling evidence for the co-transmission of STDs and HIV has been provided by recent work in Malawi[23]. 1,361 men presenting to two outpatient clinics were studied. About half the men had an established HIV infection, as determined by HIV enzyme-linked immunosorbent assays (ELISA). However, nearly 2.5% of clients presenting with an STD had an acute HIV infection (antibody-negative, HIV-RNA-positive). MULTIVARIATE ANALYSIS showed that the factors that were most associated with acute HIV infection were the presence of an STD, INGUINAL ADENOPATHY and, for men, an age of >23 years. There was also a trend towards increased acute HIV infection with the presence of GUD. HIV and the STD might have been acquired at the same time. Investigators in Pune, India, looked at how acquiring a HSV infection affects the acquisition of a HIV infection. Individuals were defined as having a recent HSV infection if there was documentation of HSV seroconversion in the past six months. Of 224 people who acquired HIV during the study, 28 also acquired HSV during the same time period, indicating some co-transmission. Recent HSV infection conferred a 3.81-fold increased adjusted hazard of HIV acquisition[76].

***STDs, inflammation and viral diversity.*** Ping and colleagues[77] conducted a detailed study of viral diversity in variants that were harvested from the semen of HIV-infected men before and after antibacterial therapy for an STD. The results showed that three-quarters of both STD and control subjects had multiple HIV variants in their blood, with even more variability in semen. Subjects with STDs who received treatment had more changes in semen variants than blood variants at follow-up — showing that local genital conditions were affecting viral diversity in the semen in a way that was not reflected in the blood.

***ART and STDs.*** Triple-drug antiviral therapy that is directed against HIV inhibits replication of the virus in the genital tract of men and women[27,30,31]. Indeed, it is difficult to detect HIV in the seminal plasma in men who are receiving ART with viral loads of <400 copies $ml^{-1}$ (REF. 31). However, the HIV provirus can still be harvested from seminal cells[78], and cell-associated HIV DNA can still be detected — although at a much lower frequency than in untreated patients[31]. In addition, viral variants in the semen of men receiving ART are often resistant to the antiviral therapy that is used[79]. The viral sequences in the blood and plasma are often discordant, emphasizing the fact that resistance begins in sequestered compartments. Also, different antiretroviral agents are present at different concentrations in the genital tract[80], creating different selective pressures. In a study of men receiving ART who acquired an STD, effective ART limited the effect of urethritis on the seminal viral load, thereby implying that controlling the plasma viral load is more important in seminal viral shedding than the presence of urethritis. However, of 18 patients with undetectable plasma viral loads who had urethritis, two had detectable semen viral loads that resolved with treatment; although of 13 subjects without urethritis and controlled viral loads, two also had detectable semen viral loads[81].

## STDs and susceptibility to HIV

The effects of STDs on susceptibility to HIV are supported by many studies that link a history of an STD to HIV acquisition[34–36]. Trials have shown that persons with STDs have an increased risk of acquiring HIV[82–86]. The ADJUSTED-RISK RATIO for HIV acquisition for a person with GUD ranges from 2.2 to 11.3, whereas non-ulcerative STDs show adjusted-risk ratios of 3–4 (REF. 34). These associations persist in most cases, even when adjusted for sexual behaviour and other confounding factors[87]. Recurrent GUD was independently associated with a sevenfold increased risk, and cervicitis/urethritis was associated with a threefold increased risk of acquiring a HIV infection over a two-year period in a group of patients attending an STD clinic in India[88]. In another study, the acquisition of HIV was found to be highly associated with GUD, as well as with being uncircumcised and having frequent contact with sex workers. The men who reported a single contact with sex workers and who seroconverted all had genital ulcers[82]. Male military conscripts in Thailand who seroconverted for HSV-2 and *Haemophilus ducreyi* were more likely to develop HIV infection[83]. In Kenyan female sex workers, seroconversion to HIV was also associated with genital ulcers and *C. trachomatis*, even when adjusted for other associations[84]. In a case-control study in an STD clinic in Baltimore, USA, a multivariate analysis showed HIV seroconversion to be associated with a diagnosis of gonorrhoea[85]. In another case-control study in Kinshasa, Congo, the adjusted-odds ratios for seroconversion were 4.8 for gonorrhoea, 3.6 for chlamydia and 1.9 for trichomonas[86].

There are several possible mechanisms for the increased susceptibility to HIV that is seen in individuals with STDs.

***Mucosal disruption.*** To model the transmission of HIV and STDs in the genital tract, an *in vitro* organ-culture model was developed by Collins *et al.*[89], which includes a

MULTIVARIATE ANALYSIS
Analysis that considers several dependent variables simultaneously.

INGUINAL ADENOPATHY
Swelling of the lymph nodes that are located in the groin.

ADJUSTED-RISK RATIO
The estimated risk ratio after any confounding factors have been taken into account.

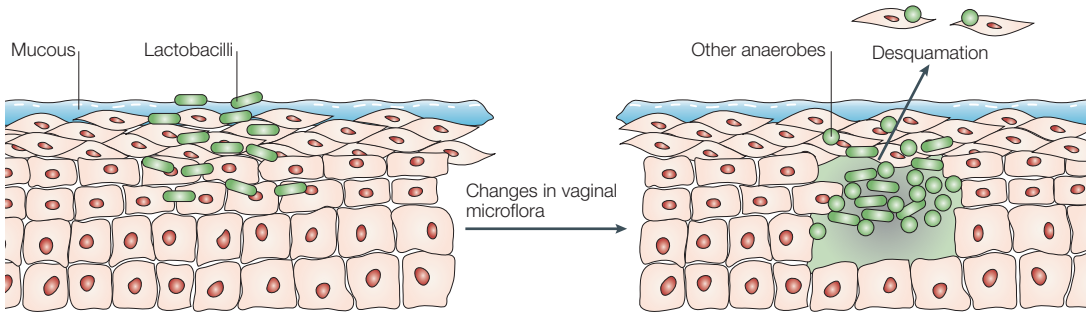


Figure 5 | **Bacterial vaginosis.** The vaginal microenvironment can affect transmission of HIV. In most healthy women, the vaginal microflora comprises large quantities of a limited number of lactobacilli species. For reasons that are as-yet-unknown, dynamic changes in the vaginal microflora can reduce the number of lactobacilli and stimulate the growth of several species of anaerobic bacteria. As these organisms grow, the pH of the vagina increases, and a watery malodorous discharge develops. These changes, together with detection of anaerobic bacteria that are attached to desquamated vaginal epithelial cells (known as clue cells), characterize bacterial vaginosis.

multi-layer mucosal-epithelial layer, memory T cells, dendritic cells and macrophages. The cells that were most often infected were $CD4^+$ T cells immediately below the epithelial layer[90]. The main targets for HIV transmission might be mucosal lymphocytes that are rendered accessible by breakdown in the mucosal integrity, or transepithelial migration of LANGERHANS CELLS, which are present on the surface[91]. STD pathogens target either the SQUAMOUS EPITHELIUM (for example, HSV) or the COLUMNAR EPITHELIUM (for example, *C. trachomatis* and *N. gonorrhoeae*). The agents that cause ulcers usually do so by necrosis of epithelial cells, which would expose subepithelial cell types to HIV-infected genital fluids. Both ulcerative and non-ulcerative diseases lead to cellular infiltration to the site of infection, also increasing the potential target cells for HIV infection[36,74].

***Immune changes.*** Even in a healthy genital tract, a higher proportion of T cells from the genital tract express the HIV co-receptor CCR5 than do T cells in the blood, which could facilitate transmission[92]. Patterson *et al.* found that cervical CCR5 expression was increased in women with STDs[93]. Syphilis was found to increase expression of CCR5 in macrophages[94]. *H. ducreyi* infection increases T-cell activation, which can lead to enhanced infection[95,96]. CD4 lymphocytes are also increased in endocervical specimens from women with STDs compared with control subjects[97].

***Effects on the genital tract microenvironment.*** The vaginal and penile microenvironment can affect the transmission of HIV. The vaginal microflora of women living in the United States and western Europe has been extensively studied. Most women harbour large quantities of a limited number of lactobacilli species. *In vitro*, these lactobacilli can produce hydrogen peroxide[74]. For reasons that are poorly understood, dynamic changes in the vaginal microflora lead to a reduction of lactobacilli with intense growth of several species of anaerobic bacteria. As these organisms grow, the pH of the vagina increases, and a watery malodorous discharge develops. These changes, together with detection of anaerobic bacteria that are attached to desquamated vaginal epithelial cells (known as clue cells), characterize BV[74] (FIG. 5). BV is relevant to HIV transmission for two reasons. First, several studies indicate that the risk of HIV acquisition is increased in women with BV[98,99]. Second, hydrogen peroxide that is produced by lactobacilli can interfere with the growth of HIV, at least *in vitro*[100]. Unfortunately, BV is difficult to treat, especially in developing countries[101]. Indeed, many studies from Africa have shown that BV microflora is often recovered from otherwise healthy study subjects[101], and that such microflora cannot be readily eradicated with antibiotic agents.

Circumcision has a dramatic effect on the biology of the penis. In the uncircumcised man, the foreskin that covers the glans meets the penile shaft at the frenum. Genital ulcers that are caused by STDs develop on the glans and especially in the area of the frenum, and inflammation would be expected to increase the number of receptive cells. The mucosal side of the foreskin is rich in $CD4^+$ T cells, macrophages and Langerhans cells[102], and is more susceptible to HIV infection than the external penile skin. Circumcision has been found to be associated with reduced rates of HIV acquisition[103,104].

## STDs, HIV and community-based studies

Given the importance of STDs in HIV transmission, several community-based studies have attempted to shed light on this relationship, and to develop valuable and productive interventions.

***The four cities study.*** This detailed study by European investigators compared STDs, sexual behaviour and many other variables in four cities in Africa — two with a high prevalence of HIV (Kisumu in Kenya and Ndola in Zambia) and two where HIV represents a more modest problem (Cotonou in Benin and Yaounde in Cameroon)[105]. Although this was an observational study, the results indicated that differences in biological risk were more likely to account for different rates of HIV prevalence than were differences in sexual

LANGERHANS CELLS
Dendritic, antigen-presenting cells that contain characteristic racquet-shaped granules, known as Birbeck granules, and which express the CD1a antigen. Principally found in the stratified squamous epithelium.

SQUAMOUS EPITHELIUM
An epithelium consisting of flattened cells. Can be simple (for example, endothelium) or stratified (for example, epidermis).

COLUMNAR EPITHELIUM
An epithelium that is formed of a single layer of cells, which are taller than they are wide.

behaviour. A higher prevalence of HSV infection, trichomoniasis in women and a lower prevalence of male circumcision were the main factors that correlated significantly with areas of high HIV prevalence, whereas factors such as condom use, sexual partnerships and behaviour, and *N. gonorroheae*, *C. trachomatis* and *T. pallidum* infections were less correlated with HIV prevalence[8]. HSV infection was a strong HIV-risk factor, and was documented in up to 86% of women in the high-prevalence areas of Kisumu and Ndola. Although the overall rates of HSV infection in Cotonou and Yaounde were also significant at 29.5% and 50.9%, respectively, the difference in HSV prevalence between the high- and low-HIV-infected areas was most pronounced among women under 25 years of age. This is important as women under 25 have a very high prevalence of HIV infection in Kisumu and Ndola[105], and differences in sexual behaviour could not account for this.

***The Mwanza (Tanzania) STD intervention trial.*** In this trial, investigators undertook a prevention study that was focused on health education, risk reduction and STD recognition and detection in a region of Tanzania[106]. In communities that were receiving STD intervention, an STD reference clinic, enhanced training and supervision of medical staff, a regular supply of drugs and community health education were all available. Six pair-matched comparison communities received standard care. The incidence of HIV was reduced by 40% in the communities receiving enhanced STD care[106].

***The Rakai (Uganda) mass therapy trial.*** In this study, three rounds of mass antibiotic therapy were given every 10 months over a 20 month period to experimental communities. HIV-prevention activities and improved general healthcare were available in both experimental and control communities . Mass therapy reduced the prevalence of syphilis and trichomonas, reduced the incidence of trichomonas and also caused transitory changes in BV. However, the incidence of HIV infection was not affected[101].

***Further studies.*** In a more recent study in Uganda, rural communities were randomized to receive behavioural interventions, behavioural and enhanced STD treatment, or routine care. Across all groups, there was an overall increase in condom use and a decrease in high-risk sexual behaviour; in the groups receiving behavioural intervention and enhanced STD treatment, condom use was higher than the group receiving routine care . The incidence of HSV decreased in the behavioural group and gonorrhoea and syphilis decreased in the STD treatment group. However, no difference was seen in the incidence of HIV infection between either intervention group[107]. Another study randomized HIV-negative Kenyan female sex workers to receive monthly azithromycin or placebo. The incidence of gonorrhoea, chlamydia and trichomonas decreased in the treatment group, but there was no effect on the incidence of HIV infection[108].

***Interpreting community-based interventions.*** A remarkable number of articles comparing and interpreting the results of these large intervention trials have been published[34–36,109], focusing particularly on the differences in the effects that were seen in the Mwanza and Rakai trials. The arguments that have been used to account for the positive effect seen in Mwanza compared with the lack of effect seen in Rakai include: mebendazole — the placebo that was used in the Rakai trial — treats worm infections, which affected the viral burden in the index case; improved STD treatment was a more powerful intervention than intermittent mass therapy; symptomatic STDs in HIV-infected individuals are of the greatest importance, and such subjects would be expected to be overrepresented in the Mwanza trial; STDs might be more important in early epidemics (for example, in Mwanza) than in late epidemics; and the STDs that were studied have different importances. Also, HSV-2 infection, which would not have been treated by the antibiotic therapy that was used in the Rakai trial, and the genital ulcers documented in Rakai could have been influential factors in the HIV epidemic. Additionally, it has been hypothesized that in the Rakai trial, the end of the Ugandan civil war resulted in less 'risky' behaviours at the time the trial was conducted, and therefore might have reduced the overall incidence of STDs and HIV — thereby masking any effects of STD treatment[109]; although the more recent study by Kamali *et al.* also showed no reduction in the incidence of HIV infection. Overall, improving the control of STDs has had disappointing effects on the incidence of HIV infection. Possibly, reducing STDs might have a greater effect in the early stages of an epidemic, where HIV is still found mainly in high-risk groups such as in India or eastern Europe. Finally, trials that attempt to treat HSV aggressively might show improved outcomes.

## Summary and conclusions

Preventing the spread of HIV is one of the greatest challenges of the twenty-first century. An overwhelming body of evidence indicates that STDs that cause mucosal inflammation and ulcers contribute to the spread of HIV, by increasing infectiousness, susceptibility or both. However, the benefits of detection and treatment of STDs in combating the spread of HIV have been more difficult to prove. It has been difficult to identify and treat the STDs of greatest potential importance, and to treat STDs in the populations that are likely to experience the greatest benefit from such an intervention. India, eastern European countries, Russia and China are now experiencing rapid increases in the prevalence of HIV and STDs[47,110]. In China, for example, the economic reforms of the 1980s have led to an STD epidemic[111] and a high risk of the heterosexual spread of HIV, especially through commercial sex workers[112]. A focus on STDs is therefore an important part of HIV prevention, especially in countries with emerging HIV epidemics. Further research must define the STDs that deserve the greatest attention, and the most effective STD intervention strategy.

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## Competing interests statement

The authors declare that they have no competing financial interests.

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