Antiviral Research 85 (2010) 276–285

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Review

Sexual transmission of HIV-1

Julie Fox[a,*], Sarah Fidler[b,1]

[a] Department of HIV, Faculty of Medicine, Harrison Unit, Lambeth Wing, Guys and St Thomas' NHS Trust/Kings College London, Westminster bridge road, London, UK
[b] Department of Genitourinary Medicine and Infectious Disease, Faculty of Medicine, Imperial College London, Norfolk place, London, UK

ARTICLE INFO

Article history:
Received 21 September 2009
Received in revised form 2 October 2009
Accepted 16 October 2009

Keywords:
HIV-1
Sexual transmission
Risk behaviour
Prevention

ABSTRACT

HIV-1 transmission occurs in a limited number of ways all of which are preventable. Overall, the risk of HIV-1 transmission following a single sexual exposure is low especially in comparison with other sexually transmitted infections (STIs); with estimates of the average probability of male to female HIV-1 transmission only 0.0005–0.0026 per coital act. The risk of acquiring HIV-1 from a single contact varies enormously and is dependant upon the infectiousness of the HIV-1 positive individual and the susceptibility to HIV-1 of their sexual partner. An understanding of the determinants of HIV-1 transmission is important not only to assess the infection risk to an individual when exposed to the virus (e.g. to determine the provision of post exposure prophylaxis), but also to make accurate predictions on the potential spread of HIV-1 infection in a population and to direct appropriate targeted prevention strategies. In this review article we summarise the current literature on the major worldwide source of HIV-1 acquisition, sexual transmission. This article forms part of a special issue of *Antiviral Research* marking the 25th anniversary of antiretroviral drug discovery and development, *Vol 85, issue 1, 2010.*

Contents

* Corresponding author. Tel.: +44 02071882643/7971095949.
E-mail addresses: julie.fox@kcl.ac.uk (J. Fox), s.fidler@imperial.ac.uk (S. Fidler).
[1] Tel: +44 02078866047.

0166-3542/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.antiviral.2009.10.012

1. Introduction

Approximately 2.5 million people worldwide became infected with HIV-1 in 2007 (UNAIDS, 2008). Despite downward trends in some countries, HIV-1 incidence remains high across much of Sub-Saharan Africa. In most communities affected by generalised HIV-1 epidemics, access to antiretroviral therapy (ART) is limited to those with advanced disease (Gilks et al., 2006), leaving large numbers of undiagnosed and untreated individuals at risk of transmitting HIV-1-1 to their sexual partners and offspring. At the current rate of growth of the HIV-1 epidemic, in addition to the increasing human toll, the costs of care of this growing population will become unsustainable (UNAIDS, 2008). Although condom use and behavioural interventions are capable of reducing sexual HIV-1 transmission, acceptance of these measures has been insufficient at a population level to lead to a sustained reduction in HIV-1 incidence (Mayer et al., 2008; Jewkes et al., 2008, 2006). The only proven prevention intervention is male circumcision (Auvert et al., 2005; Mills et al., 2008; Quinn, 2007; Weiss, 2007) although its wide scale implementation will be challenging (Sawires et al., 2007).

Understanding the key factors involved in the mechanisms underlying HIV-1 transmission may provide valuable incite into enhancing transmission prevention strategies. In this article we aim to review the principle factors that determine the sexual transmission of HIV-1 (Figs. 1 and 2).

2. Characteristics of sexually transmitted HIV-1-1 variants

In general a homogeneous (Zhu et al., 1996; Keele et al., 2008), CCR5 using (Roos et al., 1992) non-syncytia forming variant of HIV-1 is preferentially transmitted sexually to a new host. Homogeneity of the transmitted variant is due to either a bottleneck in the transmitting person and/or selective amplification of one specific strain in the recipient (Frater et al., 2006). Although rare, transmission of a CXCR4 coreceptor utilising HIV-1-1 variant can occur (Brumme et al., 2005). Whilst many studies have focused on trying to identify the 'gatekeeping' mechanism restricting transmission of CXCR4-utilizing virus this is not well understood it has been proposed that, the selective transmission of CCR5-using HIV-1 results from the superimposition of multiple imperfect gatekeepers (Margolis and Shattock, 2006) or the selective expansion of CCR5 viruses at the level of interaction between dentritic cells and activated T cells (Yamamoto et al., 2009).

The characterization of full-length genomes from recently transmitted viruses show that transmitted viruses conceal coreceptor binding surfaces of the envelope bridging sheet and variable loop and these mutate rapidly following the successful establishment of infection in a new host (Salazar-Gonzalez et al., 2009; Lee et al., 2009). Whilst most transmissions result from a single infectious unit, multiple HIV-1 variant transmissions are not uncommon, suggesting that there may be important mechanistic differences between these groups (Abrahams et al., 2009). In support of the latter, distinct populations of infected cells have been found at sites of mucosal transmission, and local proliferation of these cells is required for seeding of distal lymphoid tissue to establish systemic infection (Miller et al., 2005).

Whether cell-free or cell-associated virus in genital secretions (measured by HIV-1 RNA and DNA, respectively) is responsible for transmission (Coombs et al., 2006; Patterson et al., 1993; Mostad and Kreiss, 1996) and whether this differs for vaginal, rectal and oral transmission (Baeten and Overbaugh, 2003) is uncertain. Both forms have been found in seminal and vaginal secretions and can transmit onward infection in non-human primate studies (Mostad and Kreiss, 1996; Baeten and Overbaugh, 2003; Coombs et al., 1989).

3. Mucosal transmission events

3.1. The initial cellular targets of infection

It is likely that the initial cellular targets for HIV-1 after mucosal inoculation are either activated $CD4^+$ T cells, dendritic cells (DCs) or macrophages (Gupta et al., 2002; Zaitseva et al., 1997). The intact thick epithelium of vagina (Gupta et al., 2002), ectocervix (Asin et al., 2009), foreskin and rectum (Meng et al., 2002) is interspersed with activated CD4 and CCR5 expressing and immature Langerhans cells (Zaitseva et al., 1997), all susceptible to HIV-1 infection. Genital DCs lie within the subepithelial lining and are potent antigen presenting cells that may express a surface adhesion molecule known as dendritic cell-specific intracellular adhesion molecule-3 grabbing non-integrin (DC-SIGN) (Geijtenbeek et al., 2000; Geijtenbeek and van Kooyk, 2003; Jameson et al., 2002). This adhesion molecule binds and internalizes HIV-1 virions, generally in the absence of productive DC infection, a process that may induce DC activation, maturation and migration to the submucosa and/or regional lymph nodes, where DC-associated antigens are presented to $CD4^+$ T cells and productive infection may occur (Gupta et al., 2002; Asin et al., 2009; Geijtenbeek et al., 2000).

In an *ex vivo* model of the vaginal epithelium, transmission via activated $CD4^+$ T cells appeared to be more efficient than through Langerhans cells or directly to dendritic cells (Sugaya et al., 2004; Hladik et al., 2007). Tissue explant models have identified that the ectocervix is an important site to be considered in heterosexual transmission of HIV-1 (Gupta et al., 2002). It has been observed that it is more conducive to HIV-1 replication than is the endometrium and interleukin-6 (IL-6) enhances HIV-1 transcription at this site. Thus, regardless, it is likely that any natural or external factors that increase the number of genital mucosal DCs or activated $CD4^+$ T cells will increase the probability of HIV-1 acquisition after exposure. Finally, sexual transmission of HIV-1 in men who have sex with men (MSM), viral entry by transcytosis through single columnar epithelial cell layer is a mechanism of virus entry in the intestinal and rectal mucosa but has not yet been proved in the female genital tract (Meng et al., 2002).

3.2. The integrity of the epithelial surface

This determines virus access to the submucosal compartment. This can be disrupted by the presence of STI in particular genital ulcer disease (Hayes et al., 1995; Abu-Raddad et al., 2008a,b) thereby enhancing HIV-1 transmission. However, effective transmission can occur in the absence of breaches in the mucosal epithelial surface. The relative fragility of the rectal mucosal epithelial layer may account for the observed enhanced risk of HIV-1 transmission following receptive anal intercourse (RAI) compared with the female genital tract.

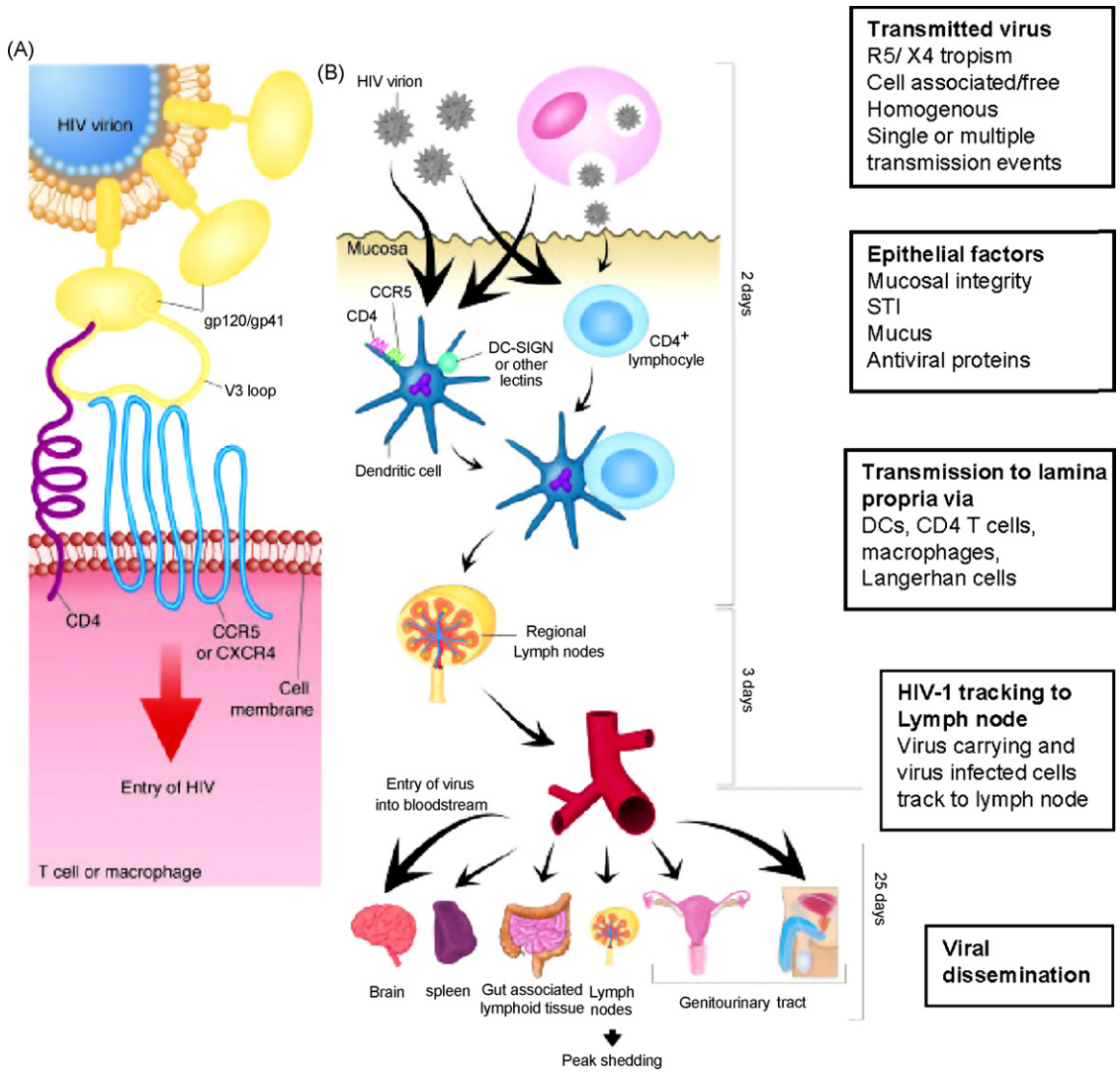

Fig. 1. Viral entry and dissemination during the sexual transmission of HIV-1. (A) Interactions of HIV-1 envelope glycoproteins, CD4, and CCR5 or CXCR4 coreceptors trigger fusion and entry of HIV-1. (B) Outline of the sequence and time course of events involved in viral dissemination.
Adapted from Shattock and Moore (2003)[37].

4. Biological factors influencing sexual transmission of HIV-1-1

4.1. HIV-1 plasma viral load of infected donor

Data from studies of African heterosexual HIV-1-serodiscordant couples identified that HIV-1 plasma viral load (VL) is the single most important determinant in predicting transmission; with minimal risk of onward transmission of HIV-1 when the index case plasma VL remains below 1500 HIV-1 RNA copies/ml (Quinn et al., 2000; Wawer et al., 2005; Gray et al., 2001) and each plasma VL $\log_{10}$ increment associated with a 2.5-fold increase in the risk of transmission (95% CI 1.85–3.26)(Gray et al., 2001). It is not known whether this transmission dynamic is applicable to non-African settings or to MSM. When plasma VL is below 1500 copies, the accuracy of plasma viral load as a proxy for genital shedding or transmission is uncertain (Wawer et al., 2005). For those with an undetectable blood VL (due to ART) up to 20% of men (Krieger et al., 1991; Coombs et al., 2003), and women (Gunthard et al., 2001; Mbopi-Keou et al., 2000) have detectable virus in the genital tract. HIV-1 disease progression does not reliably influence the association between pVL and seminal VL. Research is needed to determine the degree to which plasma VL as well as seminal VL predict HIV-1 transmission. This may explain why even with low viral loads in semen (<5000) transmission can still occur (Lorello et al., 2009; Diem et al., 2008; Kalichman et al., 2008). However, HIV-1 transmission was not observed from HIV-1 discordant couple studies in individuals with plasma VL <400 copies HIV-1 RNA copies/ml (Castilla et al., 2005; Barreiro et al., 2006). Although the risk of onward transmission of HIV-1 in the presence of a plasma VL < 50 copies HIV-1 RNA copies/ml is low it is not necessarily zero (Wilson et al., 2008) as the Swiss statement suggests (Vernazza et al., 2008).

4.2. Stage of infection of the HIV-1 positive index case

4.2.1. Both early and late stage infection have been associated with enhanced HIV transmission

Primary HIV-1 infection (PHI) represents the first 6 months following HIV-1 acquisition, and is characterised by a short lived but very high plasma, oropharyngeal and genital tract VL (Pilcher et al., 2004, 2007). The high level VL confers a marked enhanced risk of onward transmission to sexual partners exposed during this period. Added to this there appear to be specific characteristics of recently transmitted viral variants that make them particularly efficient at

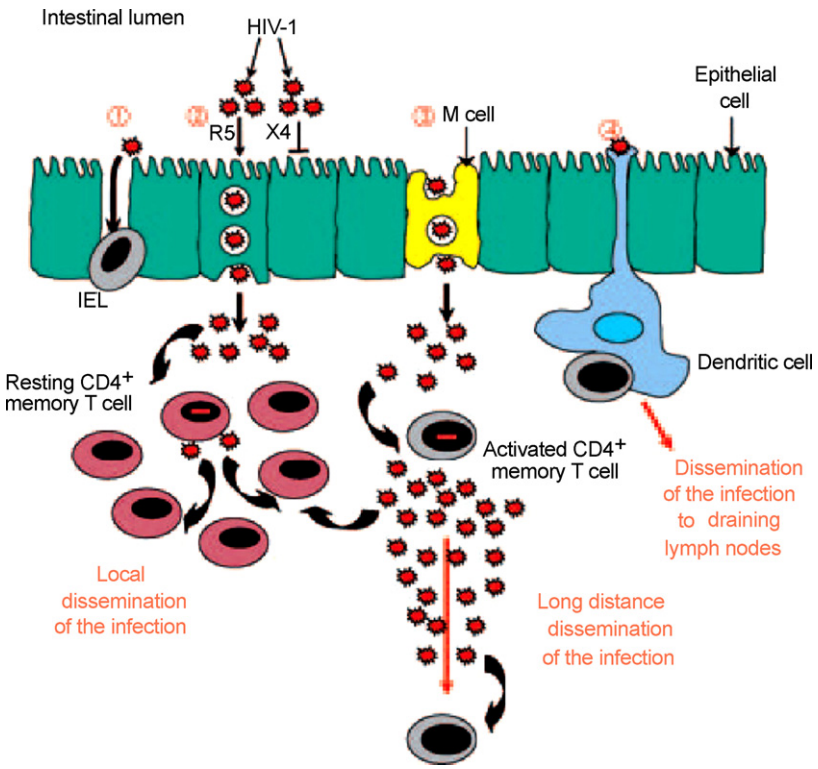

Fig. 2. HIV-1 entry in the GALT and dissemination. Different mechanisms allow the virus to cross the epithelial barrier: (1) breach in the epithelium or direct infection of intra-epithelial lymphocytes (IEL), (2) transcytosis through epithelial cells, (3) transcytosis through M cells, and (4) HIV-1 transport by DC. After the virus crosses the mucosal epithelium, whereas low levels of virus is generated within infected resting CD4 memory T cells relatively high levels of virus replication occurs within fully activated CD4 memory T cells leading to dissemination of the infection to longer distances. DC drain virus to afferent lymph nodes.
From: Centlivre: AIDS, Volume 21(1). January 2, 2007. 1–11.

onward transmission at a time when most individuals continue with high-risk sexual practices unaware of their changed HIV-1 status. For the majority of individuals such unchecked high level viral replication is short lived lasting 3–5 months at most and hence the impact of this stage of disease on overall transmission of HIV-1 at a population level is uncertain. A large study of heterosexual HIV-1 serodiscordant couples in Rakai Uganda showed that the probability of HIV-1 transmission per coital act was 8–10 times more likely in the first 5 months after HIV-1 acquisition of the index case than during the asymptomatic stage of infection (Wawer et al., 2005). Extrapolation of these data to MSM populations maybe inaccurate due to differences in per coital act risks between vaginal and anal sex. A more recent analysis of the Rakai data suggests that PHI maybe up to 26 times more infectious than asymptomatic chronic disease (Hollingsworth et al., 2008).

Further support for a role of PHI derives from phylogenetic and epidemiologic analyses of viral sequences taken from recently transmitted HIV-1 variants in MSM populations; studies from the Quebec primary infection cohort (Brenner et al., 2007, 2008) and MSM populations in the UK (Pao et al., 2005) and US (Jacquez et al., 1994; Xiridou et al., 2004; Pinkerton, 2007) have linked between a 24–49% of cases with identified recent infection to other PHI cases.

4.2.2. End stage disease

An independent role for late stage disease in HIV-1 transmission risk has also been found when defined as the 6–35 months period prior to death (Wawer et al., 2005) but not as CD4 < 200 cells/l (Abu-Raddad et al., 2008a,b).

The relative contribution made by disease stage reflects both the maturity of the HIV-1 epidemic within that population as well as the rate of partner change through the different stages of disease. Mathematical models (Hollingsworth et al., 2008; Fraser et al., 2007) show that within populations with high rates of partner change PHI may contribute up to 31% of all new transmissions. However, if such a population have much slower rates of partner change or were serially monogamous then the relative contribution of PHI becomes much less, contributing only 9% of onward transmissions (Fraser et al., 2007). The impact of concurrent relationships has not been fully explored and other models have not identified any one stage of disease as contributing more to the overall transmission (Abu-Raddad et al., 2008a,b).

4.3. Sexually transmitted infections (STIs)-specifically genital ulcer disease (GUD)

STIs facilitate HIV-1-1 transmission by increasing both infectiousness (Gray et al., 2001; Korenromp et al., 2005) and HIV-1 susceptibility (Reynolds et al., 2004; Freeman et al., 2006; Wawer et al., 2005). The largest effect being associated with genital ulcer disease (Wawer et al., 2005; Gray et al., 2001; Sheffield et al., 2007; Moriuchi et al., 2000; Mbopi-Keou et al., 2000; Mbopi-Kéou et al., 2003), gonorrhoea (Macdonald et al., 2008), infectious syphilis (Bichacz et al., 2004) and *Trichomonas vaginalis* (McClelland et al., 2007; Van Der Pol et al., 2008). The mechanisms are multifactorial and are described in Table 1.

Cofactors increasing the risk of HIV-1 acquisition in women include vaginal candidiasis (Hester and Kennedy, 2003), cervical ectopy (Clemetson et al., 1993) and during menses (Brewer et al., 1998). Bacterial vaginosis (BV) (Myer et al., 2005) has been associated in cohort but not discordant couples analysis and Pregnancy vice versa (Gray et al., 2005; Morrison et al., 2007a,b).

Oral hormonal contraception (Morrison et al., 2007a,b; Lazzarin et al., 1991), depot medroxyprogesterone acetate contraception (Morrison et al., 2007b) and copper intrauterine device use

Table 1
Mechanisms in which STI may enhance HIV-1 transmission.

	Sexually transmitted infection	Reference
Breach epithelium	Genital ulcer disease (primary syphilis, HSV-2)	75
Monocytes recruitment increasing levels CCR5 expression	Genital ulcer disease	71
Increased proinflammatory cytokines/immune activation locally	Genital ulcer disease	72
Increased HIV-1 genital shedding	Genital ulcer disease, gonorrhoea	73,74

(Morrison et al., 2007b) have not been associated with HIV-1 transmission, however, there is biological plausibility for hormonal contraception which may increase infectiousness in HIV-1-infected women by increasing HIV-1 shedding in the genital tract (Baeten et al., 2007) and this is supported by studies of female primates treated with progesterone (Marx et al., 1996).

Three randomized, controlled clinical trials in South Africa, Kenya, and Uganda have shown that circumcision of HIV-1-negative adult males reduces their risk of acquiring HIV-1 infection through penile–vaginal sex by 60% Auvert et al., 2005; Bailey et al., 2007; Gray et al., 2007a,b). This may be due to a reduction in penile trauma following sex or a reduction in the number of target cells available. However, circumcision of HIV-1-infected men did not reduce HIV-1 transmission to female partners over 24 months; this is in part thought to be due to exposure prior to circumcision wound healing (Wawer et al., 2009). The effect of circumcision for HIV-1 prevention programs in other countries and anal sex are less clear.

5. Behavioural factors affecting transmission

5.1. Number and nature of sex acts

The frequency, nature and duration of sexual exposure play a critical role in determining transmission of HIV-1 (Nicolosi et al., 1994; Saracco et al., 1993; Siriwasin et al., 1998). Increased duration of a relationship, higher number of sexual partners, and higher frequency of sexual contact have been associated with transmission (Mastro and Kitayaporn, 1998; Grant et al., 1987; Giesecke et al., 1992). However, the relative contribution of each of these factors governing seroconversion remains unclear.

Estimates of per contact risk of transmissions for each sex act vary widely. Discrepancies in estimates may reflect different risks of HIV-1 transmission between populations including biological (STI rates; circumcision, behavioural, random chance or insufficient sample sizes to identify a true difference.

All studies show that unprotected (UP) anal intercourse (AI) is more risky than vaginal sex (VI) and that receptive sex is riskier than active sex (Gray et al., 2001; Macdonald et al., 2008; De Gruttola et al., 1989; Grant et al., 1987).

Several biological mechanisms could explain the higher rates of male to female versus female to male transmission. Among them are the larger anatomical surface area and higher numbers of vulnerable cell types present in the vagina compared to the penis, greater degree of epithelial disruption, hormonal influence, and higher rates of symptomatic STIs in women. Recent observations suggest that components of semen, specifically amyloid fibril derived peptides can substantially enhance HIV infectivity (Münch et al., 2007) which may also help explain the increased risk of HIV acquisition through receptive penetrative sex. Compared to the mucosa of the mature vagina or cervix, rectal mucosa is more susceptible to traumatic abrasions (Levy, 1993) and lacks the protective humoral immune barrier present in cervicovaginal secretions (Belec et al., 1995). However, it is not clear that women are in fact at higher risk than men of acquiring HIV-1-1 from an infected partner in a discordant relationship. This will be one of the critical findings of the HPTN 052 study currently underway (HPTN 052).

6. Behavioural approaches to reduce HIV-1 transmission

Interventions to reduce unprotected sexual contact 'unsafe sex', target both HIV-1-negative (primary prevention) and HIV-1-positive individuals (secondary prevention). These include counselling to encourage behaviour change (increased condom use (Gorbach and Holmes, 2003), decreased numbers of sexual partners and abstinence). Condoms protect against STI and HIV-1 (Royce et al., 1997; Pinkerton et al., 1998; Malamba et al., 2005a,b; Ryder et al., 2000; Hanenberg et al., 1994). Condom use can vary according to type of sex (e.g. receptive AI as opposed to insertive AI), knowledge of partners HIV-1 status, receipt of HIV-1 positive diagnosis (Malamba et al., 2005a,b) or to balance conception desires with HIV-1 prevention (Ryder et al., 2000; Hanenberg et al., 1994). Partnership dynamics such as emotional closeness, communication, relationship problems and domestic violence (Burke et al., 2005; Dunkle et al., 2004) have also been associated with increased risk of HIV-1-1 acquisition. For individuals within long-term relationships, condom use tends to be low irrespective of HIV-1 concordance or discordance (Gorbach and Holmes, 2003; Malamba et al., 2005a,b).

Condom promotion campaigns have had a major impact on reducing HIV-1 incidence in areas where commercial sex work contributed substantially to new HIV-1 infections (Hanenberg et al., 1994; Stall et al., 2000). Unfortunately behaviour-change interventions are costly, and their effects typically transient (Fox et al., 2009).

7. Treatment of STI to prevent transmission

The prompt diagnosis and treatment of sexually transmitted infections (STIs) takes a prominent place in most risk reduction strategies (White et al., 2008), although evidence regarding the population-level effectiveness of STI treatment for HIV-1 prevention (in Africa) is equivocal. A randomized controlled trial (RCT) of improved clinic-based syndromic STI treatment in rural Tanzania was shown to reduce HIV-1 incidence in the general population by 38% and to be highly cost-effective (Wawer et al., 1999). Since then, however, four other RCTs of various STI treatment strategies of mass (irrespective of symptoms) and syndromic/symptomatic treatment using antimicrobials in the general population, have failed to show an impact on HIV-1 incidence (Grosskurth et al., 1995; Gregson et al., 2007; Kaul et al., 2004a,b). These differences have in part been explained by behaviour change and the later stage of the HIV-1 epidemic reducing the role of curable STIs in HIV-1 transmission (Gray and Wawer, 2008; Gray et al., 2007a,b; White et al., 2004; Korenromp et al., 2005).

8. Correlates of HIV-1 protection and transmission

Through studying individuals who are exposed but remain HIV-uninfected (EU), biological mechanisms have been postulated to affect HIV-1 transmission. The different factors that underlie this observed relative resistance to HIV-1 acquisition are summarised here.

8.1. Immune correlates of protection

8.1.1. T-cell responses

Despite a lack of detectable HIV-1 infection, using HIV-1 DNA/RNA PCR and HIV-1-specific serum antibody, 0–70% of EU have measurable HIV-1-specific CD4 and CD8+ T-cell responses (Goh et al., 1999; Clerici et al., 1992; Rowland Jones et al., 1998; Kaul et al., 2004a,b; Pinto et al., 1995; Shalekoff et al., 2009).

Where blood derived CD8+ T-cell activity exists in EU, they occur at lower frequencies (Goonetilleke et al., 2006) and at different epitopes (Kaul et al., 2001) than HIV-1 infected donors. Indeed EU CD8+ responses are restricted by only those HLA class I alleles that are associated with a reduced risk of HIV-1 infection (Goonetilleke et al., 2006). This suggests that particular CD8 epitopes and HLA types may facilitate transmission more than others.

HIV-1 specific CD8+ T-cell responses have also been detected at sites of viral exposure (e.g. cervical mucosa) at higher levels than in blood cells of the same individuals (Kaul et al., 2000). In the absence of on-going exposure, the longevity of these 'protective' CTL responses is uncertain. Generally, responses have not been demonstrated by all groups (Dorrell et al., 2000) and where they have been reported to fall below the limit of assay detection within 2–8 months of exposure and this has been associated with a loss of resistance to infection (Shalekoff et al., 2009).

HIV-1-specific CD4+ T-helper responses have also been identified in 38–100% of EU (Dorrell et al., 2000; Suy et al., 2007). Controversially, HIV-1 specific CD4+ T-cell responses targeting the same epitopes as those seen in EU have also been detected in low risk, HIV-1 negative subjects (Suy et al., 2007) and have been attributed to irrelevant antigens, which are cross-reactive to some HIV-1 proteins. As such, the detection of HIV-1-1-specific CD4+ and CD8+ T-cell responses in EU must be approached with caution. In conclusion, there is no consensus that virus-specific immunity can explain protection from or acquisition of HIV-1; however, the role they do play may prove invaluable to the development of a preventative HIV-1 vaccine.

8.1.2. B-cell responses to HIV-1

HIV-1-reactive IgA in mucosal secretions, urine or sera in the absence of apparent IgG or IgM has been reported in EU (Nguyen et al., 2006; Devito et al., 2000, 2002; Mestecky et al., 2004; Clerici et al., 2002; Read et al., 1996), and some with *in vitro* neutralising properties (Mestecky et al., 2004; Read et al., 1996). The HIV-1-specific IgA responses are sporadic and of low frequency or low titre with different epitope specificity to that of HIV-1-infected individuals and maybe dependent on the frequency of HIV-1-exposure (Mestecky et al., 2004). Their presence in mucosal fluids is controversial partly due to the low frequency as is the variety of assays used.

A further role in protection is supported by the ability of neutralizing monoclonal antibody infusions to provide sterilising immunity in macaque challenge models (Foresman et al., 1998; Shibata et al., 1999). However, the failure of placentally transferred IgG and IgA antibodies directed at env to prevent infection in 30% of cases does not support this (Read et al., 1996).

8.1.3. Innate immunity

Little is known about the role of the innate immune system in protection from HIV-1. NK cells play an important role in the innate immune system by providing the first line of defence against viral infections and tumours (Ravet et al., 2007) and various patterns of NK-cell activation have been demonstrated in HIV-1-EU (Montoya et al., 2006). It is possible that NK cells may allow EU to generate a more rapid and effective immune response to HIV-1, thereby contributing to prevention toward infection.

8.1.3.1. Human leukocyte antigen (HLA). HLA determines epitope recognition of antigen (class I is associated with CD8 and Class II with CD4 cells). Reduced susceptibility to HIV-1 infection has been associated with the presence of specific class I HLA molecules, in particular with HLA-A2, -B*1801 and A*2402 in a Kenyan cohort (MacDonald et al., 2001). The mechanisms underlying this observation assumes that these class I alleles might restrict particularly efficient HIV-1-specific CTL or present specific "protective" epitopes (Wang et al., 1999). For Class II HLA molecules certain alleles have been associated with a reduced risk of HIV-1-1 infection but findings are not consistent or reproducible (Liu et al., 2004; Tang et al., 2004; Bejrachandra et al., 2004). HLA concordance has been associated with increased risk of perinatal HIV-1-1 transmission in mother–child cohort studies (MacDonald et al., 1998), which may be due to reduced allo-immunity or less effective cellular immune responses. The contribution of HLA concordance in sexual transmission maybe similar but remains unknown.

8.2. Host genetic correlates of protection

Certain genetic polymorphisms have been found that correlate with protection against HIV-1 acquisition *in vitro*, but are rare and almost absent in African populations (Kaslow et al., 2005; O'Brien and Nelson, 2004; Detels et al., 1996). Genetic polymorphisms found to date affect viral entry, the immune response to HIV-1 and HIV-1 processing.

The most significant polymorphism associated with HIV-1 infection is a 32-bp deletion in the coding region of the CCR5 gene (Dean et al., 1996; Huang et al., 1996), where homozygotes (CCR5-D32/D32) show resistance (Trecarichi et al., 2006; Samson et al., 1996) and heterozygotes partial resistance (Kostrikis et al., 1999) to infection with CCR5 using strains of HIV-1. The frequency of CCR5-D32/D32 is approximately 1% in Caucasians almost zero in Africans (Louisirirotchanakul et al., 2002; McDermott et al., 2000).

Other genetic polymorphisms contributing to resistance to infection by entry inhibition, have been found in the promotor region of CCR5 (An et al., 2002; Duggal et al., 2003; Modi et al., 2003; Detels et al., 1996) e.g. CCR2-64I (Louisirirotchanakul et al., 2002) and RANTES (An et al., 2002) and in the following genes: CXCR6 (Duggal et al., 2003), CC chemokines (MCP1 MCP3 and exotoxin) (Modi et al., 2003), TAP 1.4 (Transporter protein associated with antigen processing) (Detels et al., 1996) and α (1,2) fucosyltransferase *FUT2* gene (which regulates the expression of a carbohydrate on the gastrointestinal epithelium) (Ali et al., 2000).

8.2.1. Early restriction genes/innate protection

Factors interfering with the early steps of HIV-1-1 infection have been identified as potential contributors to 'resistance to HIV-1 acquisition' and include TRIM-5alpha (Sawyer et al., 2006; Stremlau et al., 2004; Yap et al., 2005) and APOBEC3G (Peng et al., 2006). Specific polymorphisms in exon 6 of the TRIM5 alpha genes play a role in protection in rhesus macaques against HIV-1-1 infection but have not shown protection in humans. Higher basal and IFN-alpha induced APOBEC3G mRNA and protein expression levels have been detected in EU PBMCs compared to HIV-1 infected individuals and health controls (Biasin et al., 2007). In addition, *in vitro* HIV infection of PBMC of EU results in p24 production and a much more rapid up-regulation of APOBEC3G than HIV negative controls (Biasin et al., 2007).

8.2.2. Late restriction gene

The tumour suppressor gene 101 protein is essential for budding of the virus from infected cells (Demirov et al., 2002; Garrus et al., 2001). One study has suggested a role of two single-nucleotide polymorphism (SNP) variants, located at positions −183 and +181 relative to the translation start site in EU (Garrus et al., 2001).

9. Interventions to prevent transmission

The safest, cheapest and most readily available technique to prevent sexual transmission of HIV-1 is the condom (Hira et al., 1997). The impact of condom promotion on the spread of HIV has been particularly successful in areas where sex workers contributed substantially to new HIV infections. For example, Thailand's promotion of "100% condom" use in brothels led to condom use among sex workers of more than 90%. HIV infection rates among military recruits decreased by about half, and the cases of five other STI decreased by nearly 80% among brothel workers (Hanenberg et al., 1994). Unfortunately, behaviour change interventions are costly and their effects typically transient (Stall et al., 2000; Truong et al., 2006).

The lack of acceptability and availability of condoms particularly in resource poor settings where the highest risk of sexual transmission occurs makes alternative options more attractive. Male circumcision is to date the only proven effective alternative method, conferring >50% protection from HIV-1 acquisition, although its widespread implementation is challenging and will compromise its impact globally.

9.1. ART to prevent transmission

Given that HIV-1 plasma VL is the most significant factor in determining onward HIV-1 transmission, the use of ART to limit viral replication in both plasma and genital tract secretions, is a logical method to reliably and durably limit transmission as well as treat the HIV-1 infected individual. ART is already used in specific settings to reduce HIV-1 transmission; including perinatal, postnatal exposure, and pre-exposure prophylaxis (Cooper et al., 2002; Gay and Cohen, 2008; Cohen et al., 2007; Buckheit et al., 2009). There is intense interest using it to reduce onward sexual transmission especially in high-risk populations.

Mathematical models simulating HIV-1 transmission have explored the effect that ART may have on HIV-1 transmission at a population level (Granich et al., 2009; Law et al., 2001; Velasco-Hernandez et al., 2002; Baggaley et al., 2006). In addition to being potentially cost-effective, depending on uptake of intervention at a population level, such an approach could potentially eliminate the HIV-1 epidemic in certain populations and certainly significantly limit HIV-1 incidence if universal uptake could not be achieved. The consequences of ART use in this setting are far from intuitive. Successful ART decreases HIV-1 infectiousness, yet its main function, increasing the life expectancy of infected individuals (Baggaley et al., 2006), will over time increase the pool of potential transmitters. These two factors, decreased infectivity but increased duration of infectiousness, have opposing effects on transmission and may be further confounded by increases in risk behaviour resulting from enhanced optimism concerning HIV-1 prognosis.

Studies to investigate the feasibility and acceptability of such an approach are currently planned. Whilst models predict that a test and treat approach could have a huge impact at a population level (Granich et al., 2009), such a strategy maybe limited by ethical, feasibility, capacity and financial constraints. The clinical study (HPTN 052) is following 1750 discordant couples for 5 years and monitoring transmission to the negative partner and its relationship to viral load addresses this question; couples are randomized into either receiving ART at enrolment or when the HIV-1 infected partners CD4 count falls within or below the range of 200–250 cell/ml or an AIDS-defining illness develops. In addition, pre-exposure prophylaxis (PrEP) trials predominantly using Tenofovir are underway, however unless the cost is substantially reduced and/or the efficacy of PrEP increased, impactful implementation of PrEP would be costly (Paltiel et al., 2009).

9.2. Vaginal and rectal microbicide agents for transmission prevention

To prevent mucosal transmission of HIV-1, a microbicide either alone or in combination with ART should ideally act locally at and near the virus portal of entry[181]. Investigation of acceptability feasibility and efficacy of single microbicide agents have been studied (Buckheit et al., 2009). A large scale RCT where HIV-1 seroconversion is the end point is due to report by the end of 2009 (MDP, 2009). Methods that employ microbicidal agents in combination with tenofovir have been trialled and proven to confer protection from establishment of infection in primate models (García-Lerma et al., 2008).

In conclusion, the sexual transmission of HIV is a multifactorial process dependent on interplay of biological and behavioural factors between host and recipient. An understanding of the determinants of HIV transmission is essential, not only to assess the infection risk to an individuals when exposed to the virus e.g. in the provision of post exposure prophylaxis, but also to predict the spread of HIV infection in a population and the implementation of prevention strategies. This continues to be of the utmost importance with HIV incidence stable and no preventative vaccine available.

References

Abrahams, M.R., et al., 2009. Quantitating the multiplicity of infection with human immunodeficiency virus type 1 subtype C reveals a non-poisson distribution of transmitted variants. J. Virol. 83 (April (8)), 3556–3567.

Abu-Raddad, L.J., et al., 2008a. Genital herpes has played a more important role than any other sexually transmitted infection in driving HIV-1 prevalence in Africa. PLoS One 3 (May (5)), e2230.

Abu-Raddad, L.J., et al., 2008b. No HIV-1 stage is dominant in driving the HIV-1 epidemic in sub-Saharan Africa. AIDS 22 (May (9)), 1055–1061.

Ali, S., et al., 2000. Secretor polymorphism and human immunodeficiency virus infection in Senegalese women. J Infect Dis. 181, 737–739.

An, P., et al., 2002. Modulating influence on HIV-1/AIDS by interacting RANTES gene variants. Proc. Natl. Acad. Sci. U.S.A. 99 (15), 10002–10007.

Asin, S.N., et al., 2009. HIV type 1 infection in women: increased transcription of HIV type 1 in ectocervical tissue explants. J. Infect. Dis. 200 (Sep (6)), 965–972.

Auvert, B., et al., 2005. Randomized, controlled intervention trial of male circumcision for reduction of HIV-1 infection risk: the ANRS 1265. Trial. PLoS Med. 2, e298.

Baeten, J.M., Overbaugh, J., 2003. Measuring the infectiousness of persons with HIV-1: opportunities for preventing sexual HIV-1 transmission. Curr. HIV Res. (January (1)), 69–86.

Baeten, J.M., et al., 2007. The influence of hormonal contraceptive use on HIV-1-1 transmission and disease progression. Clin. Infect. Dis. 45 (August (3)), 360–369 (Epub 2007 June 18. Review).

Baggaley, R.F., Garnett, G.P., Ferguson, N.M., 2006. Modelling the impact of antiretroviral use in resource-poor settings. PLoS Med. 3, e124.

Bailey, R., et al., 2007. Male circumcision for HIV-1 prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet 369 (February (9562)), 643–656.

Barreiro, P., del Romero, J., Leal, M., Spanish HIV-Discordant Study Group, 2006. Natural pregnancies in HIV-serodiscordant couples receiving successful antiretroviral therapy. J. Acquir. Immune Defic. Syndr. 43 (3), 324–326.

Bejrachandra, S., Kitayaporn, D., Kaewkungwal, J., 2004. HLA class II (DRB1, DQA1 and DQB1) allele and haplotype frequencies among HIV-1-infection discordant Thai couples. Asian Pac J Allergy Immunol. 22 (2–3), 143–151.

Belec, et al., 1995. Cervicovaginal overproduction of specific IgG to human immunodeficiency virus (HIV-1) contrasts with normal or impaired IgA local response in HIV-1 infection. J. Infect. Dis. 172, 691–697.

Biasin, M., et al., 2007.Apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3G: a possible role in the resistance to HIV of HIV-exposed seronegative individuals. J. Infect. Dis. 195 (7), 960–964.

Bichacz, K., et al., 2004. Syphilis increases HIV-1 viral load and decreases CD4 cell counts in HIV-1-infected patients wit new syphilis infections. AIDS 15, 2075–2079.

Brenner, B.G., et al., 2007. High rates of forward transmission events after acute/early HIV-1-1 infection. J. Infect. Dis. 195 (April (7)), 951–959.

Brenner, B.G., et al., 2008. Transmission networks of drug resistance acquired in primary/early stage HIV-1 infection. AIDS 18, 2509–2515.

Brewer, T., et al., 1998. Migration, ethnicity and environment: HIV-1 risk factors for women on the sugar cane plantations of the Dominican Republic. AIDS 12 (14), 1879–1887.

Brumme, Z.L., et al., 2005. Molecular and clinical epidemiology of CXCR4-using HIV-1 in a large population of antiretroviral-naive individuals. J. Infect. Dis. 192 (August (3)), 466–474.

Burke, J.G., et al., 2005. Intimate partner violence, substance use, and HIV-1 among low-income women: taking a closer look. Violence Women 11 (September (9)), 1140–1161.
Buckheit, R.W., Watson, K.M., Morrow, K.M., Ham, A.S., 2010. Development of topical microbicides to prevent the sexual transmission of HIV. Antivir. Res. 85, 142–158.
Castilla, J., et al., 2005. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. J. Acquir. Immune Defic. Syndr. 40 (1), 96–101.
Clemetson, D., et al., 1993. Detection of HIV-1 DNA in cervical and vaginal secretions. Prevalence and correlates among women in Nairobi, Kenya. JAMA 269 (22), 2860–2864.
Clerici, M., et al., 2002. Serum IgA of HIV-1-exposed uninfected individuals inhibit HIV-1 through recognition of a region within the alpha-helix of gp41. AIDS 16 (September (13)), 1731–1741.
Clerici, M., et al., 1992. Cell mediated immune responses to human immunodeficiency virus (HIV-1) type 1 in seronegative homosexual men with recent sexual exposure to HIV-1-1. J. Infect. Dis. 165, 1012–1019.
Cohen, M.S., Gay, C., Kashuba, A.D., Blower, S., Paxton, L., 2007. Narrative review: antiretroviral therapy to prevent the sexual transmission of HIV-1-1. Ann. Intern. Med. 146, 591.
Coombs, R.W., et al., 2006. Lower genitourinary tract sources of seminal HIV-1. J. Acquir. Immune Defic. Syndr. 41 (April (4)), 430–438.
Coombs, R.W., et al., 2003. Recent observations on HIV-1 type-1 infection in the genital tract of men and women. AIDS 17 (March (4)), 455–480 (Review).
Coombs, R.W., et al., 1989. Plasma viraemia in human immunodeficiency virus infection. NEJM 321 (24), 1626–1631.
Cooper, E.R., et al., 2002. Women and Infants' Transmission Study Group. Combination antiretroviral strategies for the treatment of pregnant HIV-1-1-infected women and prevention of perinatal HIV-1-1 transmission. J. Acquir. Immune Defic. Syndr. 29 (April (5)), 484–494.
Dean, M., et al., 1996. Genetic restriction of HIV-1-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE. Science 273, 1856–1862.
De Gruttola, et al., 1989. Infectiousness of HIV-1 between male homosexual partners. J. Clin. Epidemiol. 42, 849–856.
Demirov, D., Ono, J., Orenstein, J., et al., 2002. Overexpression of the N-terminal domain of TSG101 inhibits HIV-1-1 budding by blocking late domain function. PNAS 99, 955–960.
Detels, R., et al., 1996. Resistance to HIV-1-1 may be genetically mediated. AIDS 10, 102–104.
Devito, C., et al., 2000. Mucosal and plasma IgA from HIV-1-exposed seronegative individuals neutralize a primary HIV-1-1 isolate. AIDS 14 (September (13)), 1917–1920.
Devito, C., et al., 2002. Cross-clade HIV-1-specific neutralizing IgA in mucosal and systemic compartments of HIV-1-exposed, persistently seronegative subjects. J. Acquir. Immune Defic. Syndr. 30 (4), 413–420.
Diem, K., et al., 2008. Male genital tract compartmentalization of human immunodeficiency virus type 1 (HIV-1). AIDS Res. Hum. Retroviruses 24 (April (4)), 561–571.
Dorrell, L., et al., 2000. Absence of specific mucosal antibody responses in HIV-1 exposed uninfected sex workers from the Gambia. AIDS 4 (9), 1117–1122.
Duggal, P., et al., 2003. Genetic influence of CXCR6 chemokine receptor alleles on PCP-mediated AIDS progression among African Americans. Genes Immun. 4 (4), 245–250.
Dunkle, K.L., Jewkes, R.K., Brown, H.C., et al., 2004. Gender-based violence, relationship power, and risk of HIV-1 infection in women attending antenatal clinics in South Africa. Lancet 363 (9419), 1415–1421.
Foresman, L., et al., 1998. Neutralizing antibodies administered before, but not after, virulent SHIV-1 prevent infection in macaques. AIDS Res. Hum. Retroviruses 14 (August (12)), 1035–1043.
Fox, J., et al., 2009. Reductions in HIV-1 transmission risk behaviour following diagnosis of primary HIV-1 infection: a cohort of high-risk men who have sex with men. HIV-1 Med. 10 (August (7)), 432–438.
Fraser, C., et al., 2007. Variation in HIV-1-1 set point viral load: epidemiological analysis and an evolutionary hypothesis. PNAS 104, 17441–17446.
Frater, A.J., et al., 2006. Passive sexual transmission of human immunodeficiency virus type 1 variants and adaptation in new hosts. J. Virol. 80 (14), 7226–7234.
Freeman, E.E., et al., 2006. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. AIDS 20 (1), 73–83, Review.
García-Lerma, J.G., et al., 2008. Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. PLoS Med. 5 (February (2)), e28.
Garrus, J.E., et al., 2001. Tsg101 and the vacuolar protein sorting pathway are essential for HIV-1 budding. Cell 107, 55–65.
Gay, C.L., Cohen, M.S., 2008. Antiretrovirals to prevent HIV-1 infection: pre- and postexposure prophylaxis. Curr. Infect. Dis. Rep. 10 (July (4)), 323–331.
Geijtenbeek, T.B., et al., 2000. Identification of DC-SIGN a novel dendritic cell specific ICAM-3 receptor that supports primary immune responses. Cell 100 (5), 575–585.
Geijtenbeek, T.B., van Kooyk, Y., 2003. DC-SIGN: a novel HIV-1 receptor on DCs that mediates HIV-1-1 transmission. Curr. Top. Microbiol. Immunol. 276, 31–54 (Review).
Giesecke, J., et al., 1992. Partner notification as a tool for research in HIV-1 epidemiology: behaviour change, transmission risk and incidence trends. AIDS 6 (1), 101–107, 27; 4(3).
Gilks, C.F., et al., 2006. The WHO public-health approach to antiretroviral treatment against HIV-1 in resource-limited settings. Lancet 368, 505–510.
Goh, W.C., et al., 1999. Protection against human immunodeficiency virus type 1 infection in persons with repeated exposure: evidence for T cell immunity in the absence of inherited CCR5 coreceptor defects. J. Infect. Dis. 179 (3), 548–557.
Goonetilleke, N., et al., 2006. Induction of multifunctional human immunodeficiency virus type 1 (HIV-1-1)-specific T cells capable of proliferation in healthy subjects by using a prime-boost regimen of DNA- and modified vaccinia virus Ankara-vectored vaccines expressing HIV-1-1 Gag coupled to CD8+ T-cell epitopes. J. Virol. 80 (May (10)), 4717–4728.
Gorbach, P.M., Holmes, K.K., 2003. Transmission of STIs/HIV-1 at the partnership level: beyond individual-level analyses. J. Urban Health 80 (4 (Suppl. 3)), 15–25.
Granich, R.M., et al., 2009. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet 373 (January (9657)), 48–57.
Gray, R.H., et al., 2007 Jan. Empirical observations underestimate the proportion of HIV-1 infections attributable to sexually transmitted diseases in Mwanza and Rakai STD treatment trials: simulation results. Sex Transm. Dis. 34 (1), 61.
Gray, et al., 2001. Probability of HIV-1 transmission per coital act in monogamous, heterosexual. HIV-1-1 discordant couples in Rakai, Uganda. Lancet 357 (9263), 1149–1153.
Gray, R.H., et al., 2007b. Male circumcision for HIV-1 prevention in men in Rakai, Uganda a randomised trial. Lancet 369 (February (9562)), 657–666.
Gray, R.H., et al., 2005. Increased risk of incident HIV-1 during pregnancy in Rakai, Uganda: a prospective study. Lancet 366 (9492), 1182–1188.
Gray, R.H., Wawer, M.J., 2008. Reassessing the hypothesis on STI control for HIV-1 prevention. Lancet. 371 (June (9630)), 2064–2065.
Gregson, S., et al., 2007. Impact and process evaluation of integrated community and clinic-based HIV-1-1 control: a cluster-randomised trial in eastern Zimbabwe. PLoS Med. (March).
Grant, R.M., et al., 1987. Infectivity of the human immunodeficiency virus: estimates from a prospective study of homosexual men. J. Infect. Dis. 156 (1), 189–193.
Grosskurth, H., et al., 1995. Impact of improved treatment of sexually transmitted diseases on HIV-1 infection in rural Tanzania: randomised controlled trial. Lancet 346 (8974), 530–536.
Gunthard, H.F., et al., 2001. Residual human immunodeficiency virus Type 1 RNA and DNA in lymph nodes and HIV RNA in genital secretions and in cerebrospinal fluid after suppression of viremia for 2 years. J. Infect. Dis. 183, 1318–1327.
Gupta, P., et al., 2002. Memory CD4(+) T cells are the earliest detectable human immunodeficiency virus type 1 (HIV-1)-infected cells in the female genital mucosal tissue during HIV-1 transmission in an organ culture system. J. Virol. 76 (October (19)), 9868–9876.
Hanenberg, R.S., et al., 1994. Impact of Thailand's HIV-1 control programme as indicated by the decline of sexually transmitted diseases. Lancet 344 (8917), 243–245.
HIV-1 prevention trials network. HPTN 052: a randomized placebo-controlled trial to evaluate the effectiveness of antiretroviral therapy to prevent the sexual transmission of HIV-1 in serodiscordant couples. http://www.hptn.org/research_studies/hptn052.asp.
Hira, S.K., et al., 1997. Condom and nonoxynol-9 use and the incidence of HIV infection in serodiscordant couples in Zambia. Int. J. STD AIDS 8 (4), 243–250.
Huang, Y., et al., 1996. The role of a mutant CCR5 allele in HIV-1-1 transmission and disease progression. Nat. Med. 2, 1240–1243.
Hayes, et al., 1995. The cofactor effect of genital ulcers in the per-exposure risk of HIV-1 transmission in sub-Saharan Africa. J. Trop. Hyg. 98, 108.
Hester, R., Kennedy, S., 2003. Candida infection as a risk factor for HIV-1 transmission. J. Womens Health (Larchmt) 12 (5), 487–494.
Hladik, F., et al., 2007. Initial events in establishing vaginal entry and infection by human immunodeficiency virus type-1. Immunity 26, 257–270.
Hollingsworth, T.D., et al., 2008. HIV-1-1 transmission, by stage of infection. J. Infect. Dis. 198, 687–693.
Jameson, B., et al., 2002. Expression of DC-SIGN by dendritic cells of intestinal and genital mucosae in humans and rhesus macaques. J. Virol. 76 (February (4)), 1866–1875.
Jacquez, J.A., et al., 1994. Role of the primary infection in epidemics of HIV-1 infection in gay cohorts. J. Acquir. Immune Defic. Syndr. 7 (November (11)), 1169–1184.
Jewkes, R., et al., 2008. Impact of stepping stones on incidence of HIV-1 and HSV-2 and sexual behaviour in rural South Africa: cluster randomised controlled trial. BMJ 337, a506.
Jewkes, R., et al., 2006. A cluster randomized-controlled trial to determine the effectiveness of Stepping Stones in preventing HIV-1 infections and promoting safer sexual behaviour amongst youth in the rural Eastern Cape, South Africa: trial design, methods and baseline findings. Trop. Med. Int. Health 11, 3–16.
Kalichman, S.C., et al., 2008. Human immunodeficiency virus viral load in blood plasma and semen: review and implications of empirical findings. Sex Transm. Dis. 35 (January (1)), 55–60 (Review).
Kaslow, R.A., et al., 2005. Influence of host genetic variation on susceptibility to HIV type 1 infection. J. Infect. Dis. 191 (February (Suppl. 1)), S68–S77 (Review).
Kaul, R., et al., 2004a. Monthly antibiotic chemoprophylaxis and incidence of sexually transmitted infections and HIV-1-1 infection in Kenyan sex workers: a randomized controlled trial. JAMA 291, 2555–2562.

Kaul, R., et al., 2004b. HIV-1 Env-specific cytotoxic T-lymphocyte responses in exposed, uninfected Kenyan sex workers: a prospective analysis. AIDS 18 (October (15)), 2087–2089.
Kaul, R., et al., 2001. CD8(+) lymphocytes respond to different HIV-1 epitopes in seronegative and infected subjects. J. Clin. Invest. 107 (May (10)), 1303–1310.
Kaul, R., et al., 2000. HIV-1 specific mucosal CD8+ lymphocyte responses in the cervix of HIV-1-resistant prostitutes in Nairobi. J. Immunol. 164 (February (3)), 1602–1611.
Keele, et al., 2008. Identification and characterisation of transmitted and early founder virus envelopes in primary HIV-1-1 infection. PNAS 105 (21), 7552–7557.
Korenromp, E.L., et al., 2005. Determinants of the impact of sexually transmitted infection treatment on prevention of HIV-1 infection: a synthesis of evidence from the Mwanza, Rakai, and Masaka intervention trials. J. Infect. Dis. 191 (February (Suppl. 1)), S168–S178.
Kostrikis, L.G., et al., 1999. A polymorphism in the regulatory region of the CC-chemokine receptor 5 gene influences perinatal transmission of human immunodeficiency virus type 1 to African-American infants. J. Virol. 73 (12), 10264–10271.
Krieger, et al., 1991. Recovery of human immunodeficiency virus type 1 from semen: minimal impact of stage of infection and current antiviral chemotherapy. JID 163 (2), 386–388.
Law, M.G., et al., 2001. Modelling the effect of combination antiretroviral treatments on HIV-1 incidence. AIDS 15, 1287–1294.
Lazzarin, A., et al., 1991. Man-to-woman sexual transmission of the human immunodeficiency virus. Risk factors related to sexual behavior, man's infectiousness, and woman's susceptibility. Arch. Intern. Med. 151 (12), 2411–2416.
Lee, H.Y., et al., 2009. Modeling sequence evolution in acute HIV-1 infection. J. Theor. Biol. 261 (Nov (2)), 341–360.
Levy, J.A., 1993. The transmission of HIV-1 and factors influencing progression to AIDS. Am. J. Med. 95 (1), 86–100 (Review).
Lorello, G., et al., 2009. Discordance in HIV-1-1 viral loads and antiretroviral drug concentrations comparing semen and blood plasma. HIV-1 Med. (June (8)).
Liu, C., et al., 2004. Lack of associations between HLA class II alleles and resistance to HIV-1 infection among white, non-Hispanic homosexual men. J. Acquir. Immune Defic. Syndr. 37 (October (2)), 1313–1317.
Louisirirotchanakul, S., et al., 2002. Genetic analysis of HIV-1 discordant couples in Thailand: association of CCR2 64I homozygosity with HIV-1-negative status. J. Acquir. Immune Defic. Syndr. 29 (3), 314–315.
Margolis, L., Shattock, R., 2006. Selective transmission of CCR5-utilizing HIV-1: the 'gatekeeper' problem resolved? Nat. Rev. Microbiol. 4 (April (4)), 312–317.
Mayer, K., et al., 2008. The social ecology of HIV-1/AIDS. Med. Clin. North Am. 92, 1363–1375.
Macdonald, N., et al., 2008. Factors associated with HIV-1 seroconversion in gay men in England at the start of the 21st century. Sex Transm. Infect. 84 (1), 8–13.
MacDonald, K.S., et al., 1998. Mother-child class I HLA concordance increases perinatal human immunodeficiency virus type 1 transmission. J. Infect. Dis. 177 (March (3)), 551–556.
Malamba, S.S., et al., 2005a. Couples at risk: HIV-1-1 concordance and discordance among sexual partners receiving voluntary counseling and testing in Uganda. J. Acquir. Immune Defic. Syndr. 39 (5), 576–580.
Mastro, T.D., Kitayaporn, D., 1998. HIV-1 type 1 transmission probabilities: estimates from epidemiologic studies. AIDS Res. Hum. Retrovirol. 14 (Suppl 3), 223–227.
Marx, P.A., et al., 1996. Progesterone implants enhance SIV vaginal transmission and early virus load. Nat. Med. 2 (October (10)), 1084–1089.
Malamba, S.S., et al., 2005b. Couples at risk: HIV-1-1 concordance and discordance among sexual partners receiving voluntary counseling and testing in Uganda. J. Acquir. Immune Defic. Syndr. 39 (August (5)), 576–580.
Mbopi-Keou, F., et al., 2000. Interactions between herpes simplex virus type 2 and human immunodeficiency virus type 1 infection in African women: opportunities for intervention. J. Infect. Dis. 182, 1090–1096.
Mbopi-Kéou, F.X., et al., 2003. Genital shedding of herpes simplex virus-2 DNA and HIV-1-1 RNA and proviral DNA in HIV-1-1- and herpes simplex virus-2-coinfected African women. J. Acquir. Immune Defic. Syndr. 33 (June (2)), 121–124, 24.
McClelland, R.S., et al., 2007. Infection with *Trichomonas vaginalis* increases the risk of HIV-1-1 acquisition. J. Infect. Dis. 195 (5), 698–702.
McDermott, D.H., Colla, J.S., Kleeberger, C.A., et al., 2000. Genetic polymorphism in CX3CR1 and risk of HIV-1 disease. Science 290 (December (5499)), 2031.
MacDonald, K.S., et al., 2001. The HLA A2/6802 supertype is associated with reduced risk of perinatal human immunodeficiency virus type 1 transmission. J. Infect. Dis. 183 (3), 503–506.
Medical Development Programme. http://www.mdp.mrc.ac.uk/downloads/MoreMDPinfo_18Feb08_v0%202_final.pdf (accessed August 2009).
Meng, G., et al., 2002. Primary intestinal epithelial cells selectively transfer R5 HIV-1-1 to CCR5+ cells. Nat. Med. 8 (February (2)), 150–156.
Mestecky, J., et al., 2004. Paucity of antigen-specific IgA responses in sera and external secretions of HIV-1-type 1-infected individuals. AIDS Res. Hum. Retroviruses 20 (9), 972–988.
Miller, C.J., et al., 2005. Propagation and dissemination of infection after vaginal transmission of simian immunodeficiency virus. J. Virol. 9 (14), 9217–9227.
Mills, E., et al., 2008. Male circumcision for the prevention of heterosexually acquired HIV-1 infection: a meta-analysis of randomized trials involving 11,050 men. HIV-1 Med. 9, 332–335.
Modi, W.S., et al., 2003. MCP-1-MCP-3-Eotaxin gene cluster influences HIV-1-1 transmission. AIDS 17 (16), 2357–2365.
Montoya, C.J., Rugeles, M.T., et al., 2006. Increased IFN-gamma production by NK and CD3+/CD56+ cells in sexually HIV-1-exposed but uninfected individuals. Clin. Immunol. 120 (August (2)), 138–146.
Moriuchi, M., et al., 2000. Herpes simplex virus infection induces replication of human immunodeficiency virus type 1. Virology 278 (2), 534–540.
Morrison, C.S., et al., 2007a. Pregnancy and the risk of HIV-1-1 acquisition among women in Uganda and Zimbabwe. AIDS 21 (May (8)), 1027–1034.
Morrison, C.S., et al., Hormonal Contraception and the Risk of HIV Acquisition (HC-HIV) Study Group, 2007b. Hormonal contraception and the risk of HIV acquisition. AIDS 21 (1), 85–95.
Mostad, S.B., Kreiss, J.K., 1996. Shedding of HIV-1 in the genital tract. AIDS 19, 1305–1315.
Myer, L., et al., 2005. Bacterial vaginosis and susceptibility to HIV-1 infection in South African women: a nested case-control study. J. Infect. Dis. 192 (8), 1372–1380.
Münch, J., et al., 2007. Semen-derived amyloid fibrils drastically enhance HIV infection. Cell 131 (December (6)), 1059–1071.
Nguyen, M., et al., 2006. HIV-1-specific antibodies but not T-cell responses are associated with protection in seronegative partners of HIV-1-infected individuals in Cambodia. J. Acquir. Immune Defic. Syndr. 42 (August (4)), 412–419.
Nicolosi, A., et al., 1994. The efficiency of male-to-female and female-to-male sexual transmission of the human immunodeficiency virus: a study of 730 stable couples. Epidemiology 5, 570–575.
O'Brien, S.J., Nelson, G.W., 2004. Human genes that limit AIDS. Nat. Genet. 36 (6), 565–574 (Review).
Paltiel, A.D., et al., 2009. HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. Clin. Infect. Dis. 48 (Mar (6)), 806–815.
Patterson, et al., 1993. Detection of HIV-1 DNA and messenger RNA in individual cells by PCR-driven in situ hybridisation and flow cytometry. Science 260 (5110), 976–979.
Pao, D., et al., 2005. Transmission of HIV-1-1 during primary infection: relationship to sexual risk and sexually transmitted infections. AIDS 19 (January (1)), 85–90.
Peng, G., Lei, K.J., Jin, W., Greenwell-Wild, T., Wahl, S.M., 2006. Induction of APOBEC3 family proteins, a defensive maneuver underlying interferon-induced anti-HIV-1-1 activity. J. Exp. Med. 203 (January (1)), 41–46.
Pilcher, C., et al., 2004. Brief but efficient: acute HIV-1 infection and the sexual transmission of HIV-1. JID 189, 1785–1792.
Pilcher, C.D., et al., 2007. Amplified transmission of HIV-1-1: comparison of HIV-1-1 concentrations in semen and blood during acute and chronic infection. AIDS 21 (August (13)), 1723–2358.
Pinkerton, S.D., 2007. How many sexually-acquired HIV-1 infections in the USA are due to acute-phase HIV-1 transmission? AIDS 21 (July (12)), 1625–1629.
Pinkerton, S.D., et al., 1998. Model-based evaluation of HIV-1 prevention interventions. Eval. Rev. 22, 155–157.
Pinto, L., et al, A., et al., 1995. ENV-specific cytotoxic T lymphocyte responses in HIV-1 seronegative health care workers occupationally exposed to HIV-1-contaminated body fluids. J. Clin. Invest. 96 (2), 867–876.
Quinn, T.C., 2007. Circumcision and HIV-1 transmission. Curr. Opin. Infect. Dis. 20, 33–38.
Quinn, T., et al., Rakai Project Study Group, 2000. Viral load and heterosexual transmission of human immunodeficiency virus type 1. N. Engl. J. Med. 342 (13), 921–929.
Read, S.E., et al., 1996. Transplacental and autologous HIV-1-IgA antibodies in babies born to seropositive women. American Pediatric Association and Society for Pediatric Research annual meeting, 1996, vol. 7 (No. August (4)), Washington, DC, May 6–10. Pediatr. AIDS HIV-1 Infect., 284.
Roos, M.T., et al., 1992. Viral phenotype and immune response in primary human immunodeficiency virus infection. J. Infect. Dis. 165 (March (3)), 427–432.
Ravet, S., et al., 2007. Distinctive NK-cell receptor repertoires sustain high-level constitutive NK-cell activation in HIV-1-exposed uninfected individuals. Blood 109 (10), 4296–4305.
Reynolds, S.J., et al., 2004. Recent herpes simplex virus type 2 and the risk of HSV-1 in India. JID 187, 1513–1521.
Rowland Jones, S., et al., 1998. The role of cytotoxic T-cells in HIV-1 infection. Dev. Biol. Standards 92, 209–214.
Royce, R.A., et al., 1997. Sexual transmission of HIV-1. NEJM 336, 1072–1078.
Ryder, R.W., et al., 2000. Pregnancy and HIV-1 incidence in 178 married couples with discordant HIV-1-1 serostatus: additional experience at an HIV-1-1 counselling centre in the Democratic Republic of the Congo. Trop. Med. Int. Health 5 (7), 482–487.
Salazar-Gonzalez, J.F., et al., 2009 Jun. Genetic identity, biological phenotype, and evolutionary pathways of transmitted/founder viruses in acute and early HIV-1 infection. J. Exp. Med. 206 (6), 1273–1289.
Samson, M., et al., 1996. Resistance to HIV-1-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature 382, 722–725.
Saracco, A., et al., 1993. Man-to-woman sexual transmission of HIV-1: longitudinal study of 343 steady partners of infected men. J. Acquir. Immune Defic. Syndr. 6 (5), 497–502.
Sawires, S.R., et al., 2007. Male circumcision and HIV-1/AIDS: challenges and opportunities. Lancet 369, 708–713.
Sawyer, S.L., Wu, L.I., Akey, J.M., Emerman, M., Malik, H.S., 2006. High-frequency persistence of an impaired allele of the retroviral defense gene TRIM5alpha in humans. Curr. Biol. 16 (January (1)), 95–100.

Shalekoff, S., et al., 2009. Identification of human immunodeficiency virus-1 specific CD8+ and CD4+ T cell responses in perinatally-infected infants and their mothers. AIDS 27 (April (7)), 789–798.
Shattock, R.J., Moore, J.P., 2003. Inhibiting sexual transmission of HIV-1-1 infection. Nat. Rev. Microbiol. 1 (October (1)), 25–34 (Review).
Sheffield, J.S., et al., 2007. Effect of genital ulcer disease on HIV-1-1 coreceptor expression in the female genital tract. J. Infect. Dis. 196 (November (10)), 1509–1516.
Shibata, R., et al., 1999. Neutralizing antibody directed against the HIV-1 envelope glycoprotein can completely block HIV-1/SIV chimeric virus infections of macaque monkeys. Nat. Med. 5 (February (2)), 204–210.
Siriwasin, W., et al., Bangkok Collaborative Perinatal HIV-1 Transmission Study Group, 1998. HIV-1 prevalence, risk, and partner serodiscordance among pregnant women in Bangkok. JAMA 280 (July (1)), 49–54.
Stall, R.D., et al., 2000. The gay'90s: a review of research in the, 1990s on sexual behaviour and HIV-1 risk among men who have sex with men. AIDS 14 (Suppl. 3), S101–S114.
Stremlau, M., et al., 2004. The cytoplasmic body component TRIM5alpha restricts HIV-1-1 infection in Old World monkeys. Nature 427 (February (6977)), 848–853.
Sugaya, M, et al., 2004. HIV-1-infected Langerhans cells preferentially transmit virus to proliferating autologous CD4+ memory T cells located within Langerhans cell-T cell clusters. J. Immunol. 172 (February (4)), 2219–2224.
Suy, A., et al., 2007. Immunological profile of heterosexual highly HIV-1-exposed uninfected individuals: predominant role of CD4 and CD8 T-cell activation. J. Infect. Dis. 196 (October (8)), 1191–1201.
Tang, J., et al., 2004. HLA-DRB1 and -DQB1 alleles and haplotypes in Zambian couples and their associations with heterosexual transmission of HIV-1 type 1. J. Infect. Dis. 189 (May (9)), 1696–1704.
Trecarichi, E.M., et al., 2006. Partial protective effect of CCR5-Delta 32 heterozygosity in a cohort of heterosexual Italian HIV-1-1 exposed uninfected individuals. AIDS Res. Ther. 3, 22.
Truong, H.M., et al., 2006. Increases in sexually transmitted infections and sexual risk behaviour without a concurrent increase in HIV incidence among men who have sex with men in San Francisco: a suggestion of HIV serosorting? Sex. Transm. Infect. 82 (6), 461–466.
UNAIDS, 2008. Report on the global HIV-1/AIDS epidemic. In: UNAIDS, 2008.
Van Der Pol, B., et al., 2008. Trichomonas vaginalis infection and human immunodeficiency virus acquisition in African women. J. Infect. Dis. 197 (4), 548–554.
Velasco-Hernandez, J.X., Gershengorn, H.B., Blower, S.M., 2002. Could widespread use of combination antiretroviral therapy eradicate HIV-1 epidemics? Lancet Infect. Dis. 2, 487–493.
Vernazza, et al., 2008. Les personnes seropositives ne souffrant d'aucune autre MST et suivant un traitment antiretroviral efficace transmettent pas le VIH par voie sexuelle. Bulletin des medecins suisses 89 (5), 18–21.
Wang, C., et al., 1999. Risk of HIV-1 infection in oral contraceptive pill users: a meta-analysis. J. Acquir. Immune Defic. Syndr. 21 (1), 51–58.
Wawer, M.J., et al., 2009. Circumcision in HIV-1-infected men and its effect on HIV-1 transmission to female partners in Rakai, Uganda: a randomised controlled trial. Lancet 374 (July (9685)), 229–237.
Wawer, M.J., et al., 2005. Rates of HIV-1 transmission per coital act, by stage of HIV-1-1 infection, in Rakai, Uganda. J. Infect. Dis. 191 (May (9)), 1403–1409.
Wawer, M.J., et al., 1999. Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. Lancet 353, 525–535.
Weiss, H.A., 2007. Male circumcision as a preventive measure against HIV-1 and other sexually transmitted diseases. Curr. Opin. Infect. Dis. 20, 66–72, -10.
White, R.G., et al., 2008. Treating curable sexually transmitted infections to prevent HIV-1 in Africa: still an effective control strategy? J. Acquir. Immune Defic. Syndr. 47 (March (3)), 346–353.
White, R.G., et al., 2004. Can population differences explain the contrasting results of the Mwanza, Rakai, and Masaka HIV-1/sexually transmitted disease intervention trials? A modeling study. J. Acquir. Immune Defic. Syndr. 37 (4), 1500–1513.
Wilson, D.P., et al., 2008. Relation between HIV-1 viral load and infectiousness: a model-based analysis. Lancet 372 (July (9635)), 314–320.
Xiridou, M., et al., 2004. Primary HIV-1 infection as source of HIV-1 transmission within steady and casual partnerships among homosexual men. AIDS 18 (June (9)), 1311–1320.
Yap, M.W., Nisole, S., Stoye, J.P., 2005. A single amino acid change in the SPRY domain of human Trim5alpha leads to HIV-1-1 restriction. Curr. Biol. 15 (January (1)), 73–78.
Yamamoto, T., et al., 2009. Selective transmission of R5 HIV-1 over X4 HIV-1 at the dendritic cell-T cell infectious synapse is determined by the T cell activation state. PLoS Pathog. 5 (January (1)), e1000279.
Zaitseva, et al., 1997. Expression and function of CCR5 and CXCR4 on human Langerhans cells and macrophages: implications for primary infection. Nat. Med. 3 (12), 1369–1375.
Zhu, et al., 1996. Genetic and phenotypic characterisation of human immunodeficiency virus type 1 in blood and genital secretions: evidence for viral compartmentalisation and selection during sexual transmission. J. Virol. 70, 3098–3107.