Association of Host and Pathogenic Variation with Sexual Transmission of HIV

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ABSTRACT

Human immunodeficiency virus (HIV) is genetically extremely variable due to the poor proof reading activity of its reverse transcriptase enzyme. Human immunodeficiency virus isolates are highly variable over time, and exhibit changes in biological phenotype during the course of infection. Different HIV variants exist in different tissues, cells and secretions; including genital secretions and cells of human males and females. Virus present in the urogenital cells and secretions determines the risk for sexual transmission of HIV. The precise association of viral variants from genital secretions and cells in the sexual transmission of HIV to the partner is not fully understood. The presence of viral variants may influence affinity to different host cell receptors which may affect the transmission, infectivity, cellular immunity and pathogenesis of HIV. Virus present in the urogenital cells and secretions determines the risk for sexual transmission of HIV. The precise association of viral variants from genital secretions and cells in sexual transmission of HIV to partner is not fully understood. It is not only important to understand the events that occur during sexual transmission of this virus, but also the impact of host and pathogenic variation on HIV transmission. In this review article, we look at a number of factors relevant to the transmission of this infection; with particular emphasis on the challenges posed by host and pathogenic variation on the transmission of HIV. Insights into the process of sexual transmission of HIV will enable the rational design of prevention strategies, such as microbicides and vaccines.

Keywords: HIV, Host factors, Pathogenesis, Sexual transmission, Viral variants.

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INTRODUCTION

Pandemic of acquired immunodeficiency syndrome (AIDS) is increasing globally, and it is estimated that more than 39 million people, including adults and newborns, have died of AIDS. Human immunodeficiency virus (HIV) transmission often occurs at mucosal surfaces and sexual transmission of HIV, though inefficient, is the most prevalent route accounting for about 75 to 80% of infections. Extreme genetic variability is the hallmark of HIV infection due to the poor proof reading activity of its reverse transcriptase enzyme. Human immunodeficiency virus isolates are highly variable over time. They exhibit changes in biological phenotype during the course of infection. Presence of different viral variants in different cells and secretions of the same individual may influence sexual transmission of HIV and viral affinity to different host cells which may affect transmission, infectivity, cellular immunity and pathogenesis of HIV. Virus present in the urogenital cells and secretions determines the risk for sexual transmission of HIV. The precise association of viral variants from genital secretions and cells in sexual transmission of HIV to partner is not fully understood. It is not only important to understand the events that occur during sexual transmission of this virus, but also the impact of host and pathogenic variation on HIV transmission. In this review article, we look at a number of factors relevant to the transmission of this infection; with particular emphasis on the challenges posed by host and pathogenic variation on the transmission of HIV. Insights into the process of sexual transmission of HIV will enable the rational design of prevention strategies, such as microbicides and vaccines.

SEXUAL TRANSMISSION AND THE RISK OF HIV-1 INFECTION

Many aspects of HIV transmission are still unclear and are the focus of extensive research and investigation. An important question which still remains unanswered is whether the transmission of HIV is mediated mainly by the cell-free virus or by infected cells. Both the forms of this virus have been reported to be present in human genital secretions namely semen in the male and vaginal fluids in the female. Moreover, the risk of male to female transmission of HIV is considered to be higher as compared to that of female to male.

Viral load of the infected individual is also known to be a major determinant of the risk of HIV-1 transmission. A 10-fold increase in viral load has been reported to result in a 2.5-fold increase in the transmission of HIV-1 in serodiscordant couples. Although the risk of sexual transmission of HIV has been reported to correlate with the amount of virus present in the blood of the source partner, the correlation between the viral load in the
blood and genital compartments is inconsistent. The viral load in genital fluids is quite variable, and is generally lower in untreated individuals than in the blood.

The clinical stage of infection in the transmitting partner is also known to be a key determinant for the efficiency of transmission, with the risk of infection from individuals with acute infection being higher than that in individuals with an established infection.

The integrity of the epithelial barrier in the vagina of the female also appears to be a crucial determinant for HIV entry via the sexual route. An intact mucosal epithelium is impervious to infection by HIV. However, any micro-aberrations of the vaginal epithelium due to physical insults or inflammation are also known to increase the infectivity of the virus.

Another important factor which impacts viral transmission is the presence of sexually transmitted diseases (STDs), particularly those that result in ulceration and genital inflammation. There is an increased HIV shedding into the genital tract and a concomitant increase in susceptibility to infection in such cases. Sexually transmitted diseases, when accompanied by ulceration, result in breakdown of the mucosal barrier which makes the recipients more susceptible to infection. Additionally, there is also an increase in the number of susceptible cells in the mucosa through inflammation. Bacterial infection of the vagina in the female also results in enhanced infectivity due to an increase in the pH of the vaginal fluid. This is attributed to slower virus inactivation and more efficient env-mediated fusion at a higher pH.

ASSOCIATION OF HOST CELLS WITH HIV TRANSMISSION AND PATHOGENESIS

Association of Genital Secretions with the Sexual Transmission of HIV

Human immunodeficiency virus-1 present in the seminal plasma, seminal leukocytes and sperm is known to be the primary source of infection. Seminal plasma and leukocytes were considered to be the sole source of infection, but subsequent reports demonstrated that HIV binds and enters into the spermatozoa and further transmits the virus into distal cells. Moreover, due to the acidic pH of the vagina and the temporal sequel of seminal leukocytes in the vaginal tract, infection of female through cell-free virus or by seminal leukocytes from the male seems less risky. Furthermore, the viral load required for transmission of HIV through the vaginal route has been demonstrated to be very high as compared to that of the systemic route. This suggests that the spermatozoa is a risk factor in sexual transmission of HIV. However, due to lack of conventional CD4 receptors on spermatozoa, the precise mechanism of sexual transmission of HIV has not been fully understood. Presence of human mannose receptor (hMR) on spermatozoa has been shown to be responsible for sexual transmission of HIV. Human immunodeficiency virus binds specifically to hMR and enters into the sperm which further transmits the virus into urogenital cells. Therefore, the sperm-bound virus may determine the risk of sexual transmission of HIV.

Human Immunodeficiency Virus Binding Receptors Present on Different Host Cells

Human immunodeficiency virus binds to CD4 receptor, CXCR4 and CCR5 co-receptors as well as to other receptors on host cells which include hMR, dendritic-cell-specific ICAM-3-grabbing–non-integrin (DC SIGN) receptor, galactosyl ceramide (GalCer) receptor, heparan sulfate (HS) and syndecan-3. Sexual transmission of HIV has been shown to be associated with hMR as human sperm and vaginal epithelial cells are devoid of conventional CD4 receptors. Human immunodeficiency virus specifically binds to hMR and further transmits the virus into distal cells. Furthermore, it has also been reported that less than 10% vaginal epithelial cells in seronegative female partners of serodiscordant couples showed the presence of hMR, while 90 to 95% vaginal epithelial cells of the normal females from general population showed the presence of hMR. The study suggested the role of hMR in the sexual transmission of HIV.

Dendritic cells (DCs) are also known to play a major role in HIV pathogenesis. Peripheral or surveillance mucosal DCs are distributed in the vaginal, ectocervical and anal mucosa, allowing contact with HIV during mucosal exposure. Following vaginal entry of the virus, DCs have been shown to be responsible for further transmission, and subsequently stimulated T-cells may also play a key role in establishing infection. Different types of DCs from skin, mucosa and blood of humans and macaques can participate in highly productive CD4-dependant and CD4-independent HIV and simian immunodeficiency virus infection. These host cell responses are also affected by viral variation and presence of distinct variants in different cells and secretions of the same individual.

Astrocytes are also found on CD4 negative cells in the brain and it has been postulated that HIV neuropathogenesis occurs via hMR. In human astrocytes, HIV binds to hMR and activates matrix metalloproteinases, which in turn are reported to degrade the extracellular matrix proteins.
Association of Viral Variation in HIV Transmission and Pathogenesis

Poor proofreading activity of HIV-1 reverse transcriptase enzyme results in extensive diversification during the natural course of infection. Peripheral blood mononuclear cell (PBMC)-derived isolates exhibit increased variability over time. They exhibit changes in the biological phenotype during the course of infection. Human immunodeficiency virus-1 isolates from PBMCs during early infection show slow/low titer, non-syncytium inducing phenotype and preferentially infect monocyte-derived macrophages (MDM) and PBMCs. With the onset of AIDS, most but not all patients harbor rapid/high titer viruses, often with syncytium-inducing phenotype, which infect T-cell lines efficiently but may have reduced ability to infect MDM. The genetic diversity of HIV-1 in an infected person, typically investigated in blood plasma, manifests itself as a collection of closely related but genetically distinct viral variants termed 'quasispecies'. Distinct HIV variants have been shown to exist in different tissues and secretions including lymph nodes, spleen, brain, lungs and semen. These variants also show changes in the biological phenotype during the course of infection. Furthermore, viral variants present in sperm and seminal secretions may also determine the risk of sexual transmission of HIV. The infectivity of HIV-1 is known to vary because of the differences in virus subtypes, and the set of virus quasispecies present in an infected individual.

Free as well as cell-associated virus has been detected in genital cells and secretions which are the major source of sexual transmission of HIV. Male and female genital tract cells and secretions serve as sites of viral replication and are likely to differ from peripheral tissues in immunological surveillance, target cell characteristics and efficiencies of drug penetration. Recent studies in sub-Saharan Africa with subtype B and subtype C transmission pairs have suggested that a single variant from the chronically infected partner can establish infection in their newly infected partner. However, in subtype A, infected individuals from a sex worker cohort and subtype B individuals from STD clinics demonstrated that the infection was frequently established by multiple variants too.

Human immunodeficiency virus-related mortality and morbidity has been significantly reduced by highly active antiretroviral therapy (HAART). However, lack of proofreading activity of HIV reverse transcriptase results into continuous mutations during the course of infection, which leads to drug resistant mutations, and may therefore accelerate the viral load in circulation. Human immunodeficiency virus present in genital tract secretions has been reported to be responsible for sexual transmission of HIV. Presence of drug resistant viral mutant has been reported in genital tract secretions due to poor accessibility to different antiretroviral drugs and may also influence HIV transmission to the partner.

Subtype C has been reported in nearly every region affected by HIV and predominates in India and Africa. However, little is known about sequence variation of HIV-IC in India. Lole et al. studied the complete genome of HIV-1 isolates of six seroconverters from Pune, India. HIV-IC isolates from these individuals were amplified, cloned and sequenced. Five out of six were reported to be subtype C, while one was a mosaic of subtype A and C with multiple break points in env, negative factor and long terminal repeats (LTR). A total of 38% well defined cytotoxic T-lymphocyte (CTL) epitopes were identical and showed substantial differences with CTL epitopes of subtype B.

Genotypic characterization of C2-V3 region of HIV-IC from PBMCs, spermatozoa and vaginal epithelial and cervical cells of the same individual demonstrated the presence of distinct viral variants in PBMCs and sperm. Translated amino acid sequences of C2-V3 region of these isolates present in PBMCs and sperm or vaginal epithelial and cervical cells of the same individuals showed different numbers of N-linked glycosylation (NLG) sites; suggesting the differential affinity of these variants to host cells. Moreover, these variants showed differential infectivity in PBMCs and sperm, or vaginal epithelial and cervical cells of HIV-infected individuals.

The biological determinants that influence the transmissibility of different viral variants within the genital tract of the HIV-infected source are still incompletely understood. Since transmitted virus represents the initial virus that the immune system encounters, the understanding of its composition will be critical in development of modalities in prevention of sexual transmission of HIV. The HIV variants in urogenital cells may also influence the response to anti-retroviral therapy (ARV) drugs. Therefore, the drug resistant mutations of the HIV variants, PBMCs, as well as urogenital cells and secretions will be useful for administration of appropriate combination of ARV drugs to control the disease.

DISCUSSION

Spermatozoa are known to be a risk factor for sexual transmission of HIV. Sperm-associated virus has also been shown to be efficiently transmitted to DCs, macrophages and T-cells even at lower vaginal pH. Furthermore, HIV transmission also results in the phenotypic maturation of DCs and the production of interleukin-10 (IL-10) but not interleukin-12 (IL-12), suggesting the role of sperm associated virus in mucosal transmission.
Cell-free virus as well as proviral DNA has been detected in the sperm and HIV replicates in the sperm mitochondria. Presence of distinct viral variants has not only been detected in PBMCs, but also in genital secretions and tissues during the course of infection. Human immunodeficiency virus-1 infected men receiving highly active antiretroviral therapy have been reported to have undetectable levels of viral ribonucleic acid (RNA) in blood plasma, but showed the presence of virus in seminal plasma. The present study also demonstrated that one of the studied participants on ART had undetectable viral load in the blood plasma, but seminal plasma showed the presence of 457 copies of viral RNA. In addition, five out of the seven sperm samples from infected males were found to be infectious as detected by estimation of p24 antigen levels in the culture supernatant following co-culture with PBMCs from normal individuals. The viral load in seminal plasma of one of the individuals was undetectable, but showed the presence of proviral DNA in the spermatozoa. Therefore, sperm washing procedure used for assisted-reproductive technology may not always prevent HIV transmission to fetus and/or female partner. This also confirms the earlier findings that sperm-associated HIV is the risk factor for sexual transmission of HIV, and although the seminal viral load is undetectable the sperm may still carry the virus.

The characterization of viral variants by sequence analysis of C2-V3 region of HIV-1C env gene demonstrated the presence of distinct variants in the spermatozoa and PBMCs of the same individuals (Fig. 1). Figure 2 shows the comparative translated amino acid sequences of C2-V3 region of HIV-1C isolated from PBMCs of 12 infected males, which demonstrated variation in the sequence of all the participants studied. Figure 3 shows the comparative translated amino acid sequences of C2-V3 region of env gene from sperm samples. The constant regions have been highlighted in green color. The region from 241 to 263 predominantly showed the conserved region in all individuals and corresponds to the C2 region of env gene. This may possibly be an important region for consideration of a potential candidate for development of peptide-based vaccine. Additionally, smaller constant regions were also found to be conserved in C2 as well as the V3 regions. Association of these constant and variable regions needs to be investigated in a larger population to determine their role in transmission and response to neutralizing antibody.

The viral variants in sperm and PBMCs also show a variable number of NLG sites. Alterations in NLG patterns have been reported to successfully mask effective antibody neutralization responses. Furthermore, an N-glycan within the HIV type 1 gp120 V3 loop has been reported to affect virus neutralization. Numbers of NLG sites also showed variability. Moreover, variable numbers of NLG sites have also been observed in the sperm and PBMCs of the same individuals.

The sperm as well as PBMCs of two individuals showed absence of NLG sites in the V3 loop. The absence of NLG sites in the V3 loop was also observed in PBMCs of additional six individuals suggesting possible association of these variants with CXCR4 co-receptor usage in these males. Remaining nine individuals showed the presence of NLG sites in the V3 loop of HIV-1C env gene, which indicates CCR5 co-receptor usage. The numbers of NLG sites in the sperm-associated virus were found to be less in four out of six individuals as compared to those from PBMCs of the same individuals. Different individuals showed different number of NLG sites in C2-V3 region, suggesting the variable affinity of HIV for binding to

Fig. 1: Translated amino acid sequence of C2-V3 region of env gene of HIV-1C present in spermatozoa and PBMCs of the same individual. The letters highlighted with green color show the conserved regions of the variants in sperm (SP) and PBMCs (PB) of the same individual. Letters marked with red color are the NLG sites. C2 region 221 to 295; V3 region 296 to 340.
different host cells of the infected individuals.\textsuperscript{28} Four NLG sites were found to be conserved in all the sperm as well as PBMC samples. The number of NLG sites of viral envelope proteins, through the formation of a ‘glycan shield’, is one of the major mechanisms for blocking or minimizing virus-neutralizing-antibody response.\textsuperscript{54} The density of gp120 NLG sites has been considered to be a significant obstacle to the design of an effective vaccine and the elicitation of a humoral immune response. Human immunodeficiency virus is now known
to bind to hMR on spermatozoa\textsuperscript{18} which are devoid of conventional CD4 receptors. Therefore, the alterations in the number of NLG sites of HIV env gene and its association with transmission to distal cells, needs to be further investigated.

These studies suggest the sperm-associated virus is the risk factor for sexual transmission of HIV, and possibly also for the transmission from parent to child. They also suggest that assisted reproductive technology is not a completely safe procedure for maternal or fetal transmission of HIV. Human immunodeficiency virus-IC env sequence diversity appears to influence affinity to receptor/co-receptor and effective immune responses against the virus, thereby implying a link between strong immune selection and slower disease progression. Moreover, the diversity of sperm-associated virus may influence its binding to hMR which is a CD4-independent receptor, it’s further transmission into distal cells and therefore, also the sexual transmission of HIV. However, the precise involvement of viral variants and alteration in the number of NLG sites, their association with sexual transmission of HIV and disease progression needs to be investigated in a larger population. This will be useful in designing strategies for prevention of HIV infection and also the development of therapeutics for HIV/AIDS.

CONCLUSION

Human immunodeficiency virus is primarily transmitted through the sexual route. Efforts are being made to understand the mechanism of HIV transmission, pathogenesis and control of HIV/AIDS. Recently, the presence of hMR has been demonstrated to be responsible for sexual transmission of HIV. Human immunodeficiency virus binds specifically to hMR on sperm and vaginal epithelial cells, and further transmits the virus into distal cells. Additionally, other receptors, such as DC-SIGN, GalCer, heparan sulfate and syndecan-3 have also been identified on different cells; and viral affinity to these receptors may influence HIV pathogenicity. However, the poor proofreading activity of HIV reverse transcriptase enzyme results into the presence of distinct variants in different cells and secretions of the same individual. These viral variants may influence HIV affinity to different host cell receptors, and therefore influence the pathogenicity and progression to disease, which remains the major challenge in management and control of HIV/AIDS. Therefore, the characterization of HIV variants and their affinity to different host cell receptors may provide the information to design the strategies for ART, prevention of sexual transmission of HIV and development of effective therapeutic and/or preventive vaccine.

REFERENCES

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