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REVIEW

Sexual dimorphism in HIV-1 infection

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Abstract

Sex-specific differences affecting various aspects of HIV-1 infection have been reported, including differences in susceptibility to infection, course of HIV-1 disease, and establishment of viral reservoirs. Once infected, initial plasma levels of HIV-1 viremia in women are lower compared to men while the rates of progression to AIDS are similar. Factors contributing to these sex differences are poorly understood, and range from anatomical differences and differential expression of sex hormones to differences in immune responses, the microbiome and socio-economic discrepancies, all of which may impact HIV-1 acquisition and disease progression. Ongoing research efforts aiming at controlling HIV-1 disease or reducing viral reservoirs need to take these sex-based differences in HIV-1 pathogenesis into account. In this review, we discuss established knowledge and recent findings on immune pathways leading to sex differences in HIV-1 disease manifestations, with focus on HIV-1 latency and the effect of female sex hormones on HIV-1.

Keywords HIV-1 infection · Sex hormones · Sex differences · HIV-1 reservoirs · HIV-1 cure · HIV-1 immunopathology

Introduction

HIV-1 infection is a worldwide infectious disease and still represents a global public health issue. HIV-1 disease differentially affects women and men. The multi-faceted effects of sex on the susceptibility to infection, course of HIV-1 disease, and establishment of HIV-1 reservoirs are poorly defined. Sex-based differences have been linked to anatomical differences, differential expression of steroid hormones including sex hormones, X- and Y-chromosomally encoded genes, incomplete X-chromosomal inactivation resulting in enhanced gene expression, sex differences in HIV-1 reservoir and latency regulation, epigenetic modifications, and more recently also the microbiota. Large cross-sectional and longitudinal cohort studies have demonstrated that plasma levels of HIV-1 RNA in infected women are lower and $CD4^+$ T cell counts higher compared to men during the early phase of infection [1–3]. Moreover, in HIV-1 controller cohorts, an overproportional fraction of women has been reported [4, 5]. Still, despite the initially lower plasma levels of HIV-1 RNA in women, the rates of progression to AIDS are similar between men and women [6, 7], and women progress faster to AIDS than men after controlling for the levels of viral replication [6, 7]. Beyond socio-economic differences that may impact HIV-1 acquisition and disease progression [3, 8, 9], there is a growing body of research identifying critical biological factors that contribute to the sexual dimorphism observed in HIV-1 disease. In the quest for an HIV-1 cure for both men and women, resting latently HIV-1 infected $CD4^+$ T lymphocytes present the biggest hurdle, as these cells cannot be eliminated by current antiretroviral therapies. Data on sex-specific mechanisms underlying differences in the size of this latent viral reservoir and its stability are however scarce. In this review, we will highlight the latest findings on biological differences accounting for sex-based differences in HIV-1 disease with focus on viral latency and the effect of female sex hormones on HIV-1 pathogenesis.

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Sexual dimorphism in HIV-1 latency, viral replication, and reservoir maintenance

Despite suppression of HIV-1 viremia below detection limit with antiretroviral treatment (ART), HIV-1 infection remains incurable. HIV-1 persists throughout the body due to latent but replication-competent integrated proviruses that impede complete virus eradication in patients receiving ART. In the quest for an HIV-1 cure, it is crucial to understand at what sites HIV-1 hides in the body under ART. The rebound viremia from the young infant known as the "Mississippi Baby" who was seemingly cured of HIV-1, but then exhibited HIV-1 viremia 2 years after initial ART and the so called "Boston Patients," in which HIV-1 reemerged after bone marrow stem cell transplantation followed by an experimental antiretroviral therapy protocol, demonstrate that a functional cure for HIV-1 remains a major challenge [10, 11]. Latent HIV-1 infection affects primarily a very small population of memory CD4+ T cells, which, after infection with HIV-1 and subsequent integration of HIV-1 DNA in their genome, return to a resting state [12]. Levels of integrated HIV-1 DNA burden vary throughout the body with much higher levels in lymphocytes in the gut compared to peripheral blood; furthermore, also within the gut, there are variations of HIV-1 DNA levels, which increase from the duodenum to the rectum [13–16]. In lymph nodes, the level of HIV-1 DNA was found to be comparable to or higher than levels found in peripheral blood [17–20], and in particular follicular T helper cells (Tfh cells) harbor integrated HIV-1 DNA. Tfh cells are the major CD4+ T cell compartment in the blood and lymph nodes for HIV-1 infection, replication, and production, even in long-term ART-treated aviremic individuals [21, 22]. Adipose tissues of patients receiving antiretroviral treatment have also been reported to serve as a reservoir for HIV-1, as they contain a high proportion of activated memory CD4+ T cells and HIV-1 DNA [23]. Differences in fat distribution and adipocyte function have been reported for men and women [24, 25], and it has been shown that estrogens, estrogen receptor-α (ERα), and estrogen receptor-β (ERβ) regulate adipose tissue distribution [24, 26]. Despite being less well studied than the effects of gonadal hormones, genes encoded by sex chromosomes have also been shown to have independent and interactive effects on adiposity, lipid metabolism, and inflammation, as reviewed in [27]. Another anatomical sanctuary for the latent HIV-1 reservoir that has gained increasing attention in ongoing HIV-1 cure research efforts is the central nervous system (CNS) [28, 29]. HIV-1 can access the CNS soon after infection and HIV-1 infection has been demonstrated in astrocytes, perivascular macrophages, and microglial cells [28, 30, 31]. Importantly, the CNS is a niche where the virus has been suggested to hide and evolve, as the CNS might be less accessible for antiretroviral drugs due to the blood-brain barrier [32–35]. Steroids, including sex hormones, have been shown to impact characteristics of the blood-brain barrier, such as cellular efflux mechanisms, nutrient uptake, and tight junction integrity, all of which also affect brain homeostasis and delivery of CNS-targeted therapeutics. It is therefore possible that these sex-specific factors also impact the dynamics of the HIV-1 reservoir within the CNS [36]. Taken together, these data suggest sex-specific differences in the organs and tissues involved in the establishment and maintenance of HIV-1 reservoirs.

Current findings on differences in integrated HIV-1 DNA levels between men and women are controversial. A multivariate analysis of a cross-sectional study in HIV-1-positive individuals who were receiving ART for more than 3 years and had HIV-1 RNA < 50 copies/ml for more than 2 years with CD4 cell count > 350 cells/μl, showed that women were more likely to achieve a low level of HIV-1 DNA compared to men [37]. Yet, another study presented by Scully et al. at the Conference on Retroviruses and Opportunistic Infections (CROI) did not show any significant difference in HIV-1 DNA levels in a prospectively enrolled cohort of men and women receiving ART. However, their study showed lower levels of residual viremia and lower levels of multiply-spliced cell-associated HIV-1 RNA in females (Scully et al., Abstract 281, CROI 2017). Using a primary cell model of HIV-1 latency, a recently published study by Macedo et al. investigated whether biological sex influences the intrinsic ability of HIV-1 to replicate and to establish latency in cultured T_{CM} cells. The group showed that HIV-1 replication and levels of latent infection in vitro are comparable in T_{CM} cells derived from males and females, suggesting that biological sex alone is not an intrinsic biological variable in CD4+ T cells with reference to the capacity of HIV-1 to replicate and establish latency [38]. Further studies are clearly needed to clarify the impact of sex-specific factors on the establishment and maintenance of the HIV-1 reservoir, and how these differences may affect future HIV-1 eradication strategies. When interpreting large HIV-1 studies, the underrepresentation of certain groups, including women, older people, and non-Caucasians, needs to be taken into account. According to a systematic review, the representation of the aforementioned groups in relevant HIV-1 studies did not reflect national or international burdens of HIV-1 infection [39].

The factors that might lead to sex differences in integrated HIV-1 DNA burden are diverse. Sex-specific differences in plasma viral loads during the early infection phase may contribute to the establishment of a smaller HIV-1 reservoir in women [37, 40], as plasma viral load levels may serve as predictors of the size of the HIV-1 reservoir [41, 42]. Furthermore, several studies have suggested differences in access to HIV-1 care between women and men, with women starting ART later than men [43–46], what can have a direct impact on the size of HIV-1 reservoirs. Karn et al. demonstrated recently the inhibitory effect of estradiol on HIV-1

transcription after T cell receptor stimulation using well-matched leukapheresis samples of reproductive-age women and men on fully suppressive ART. Females displayed much higher levels of suppression of HIV-1 transcription in response to estradiol and showed higher reactivity following estrogen receptor-1 (ESR-1) modulation, suggesting ESR-1 as a critical regulator of HIV-1 latency [47]. In summary, the sex hormone estrogen was shown to have a direct effect on HIV-1 transcription, which should be taken into consideration in future strategies for latency reversal. Specific studies on regulating factors of viral reactivation in latently HIV-1 infected cells will help to identify the key factors that drive both the formation and maintenance of HIV-1 reservoirs, informing future therapeutic strategies aimed at reducing its size in infected individuals.

Sex differences in IFN-α responses to HIV-1

HIV-1 ssRNA can be recognized intracellularly by Toll-like receptor 7 (TLR 7) on plasmacytoid dendritic cells (pDCs) [48]. pDCs are innate immune cells known to secrete large amounts of type I interferons after stimulation via TLR7 with viral ssRNA, including HIV-1 RNA [49]. Type I interferons display antiviral functions through induction of a wide spectrum of interferon-stimulated genes (ISG) [50], but might also contribute to higher immune activation of CD4+ and CD8+ T cells during persistent HIV-1 infection [51, 52]. Sex-specific differences in the responsiveness of plasmacytoid dendritic cells (pDCs) to TLR7 stimulation [53], including stimulation with HIV-1-derived TLR7 ligands [51], have been well established. Upon HIV-1-mediated TLR7 stimulation, the number of IFN-α-producing pDCs is significantly higher in females than in males [51]. Moreover, upon TLR7 stimulation using HIV-1 derived ssRNA [51] or synthetic ligands [53–56], pDCs from females secrete more IFNα compared to men. This was associated to higher ex vivo levels of ISGs in HIV-1-infected women compared to men for the same level of viral replication [52]. Ziegler et al. recently showed that after TLR7 stimulation of peripheral blood mononuclear cells (PBMCs), all 13 IFNα subtypes and IFNβ are expressed at significantly higher mRNA levels by pDCs from females [54]. The mechanisms underlying the higher production of IFNα following TLR7 stimulation by pDCs from females may be explained by the location of the TLR7 gene on the X chromosome [57] and the phenomenon of escape from X-chromosomal inactivation. In general, X-chromosome inactivation compensates for the differences in the number of X chromosomes between men and women. Escape from inactivation for genes encoded by the X chromosome has been observed near the TLR7 locus [57], potentially leading to an additional TLR7-encoding region on the second X chromosome, resulting in a higher TLR7 mRNA and protein expression. As more than 20% of human X-chromosome-linked genes have been reported to escape from inactivation, these "escaped" genes can significantly add to sex differences in gene expression [58, 59], with potential consequences for antiviral immunity. However, there is currently no published data demonstrating higher TLR7 gene expression in pDCs from women compared to men in humans [56, 60]. Overall, current studies suggest an important role of the TLR7 pathway in the establishment of sex-specific differences in the manifestation of HIV-1 infection, but detailed research on molecular mechanisms underlying TLR7 expression and regulation in pDCs is needed to better understand the role of the TLR7 pathway in type I IFN production in HIV-1-infection. Understanding these sex-specific differences in the TLR7 pathway are of particular importance, as recent studies have suggested using TLR7 agonists as HIV-1 latency reversal agents [61, 62], and sexual discrepancies in TLR7-responsiveness have to be taken into account in the design of these studies.

The effect of female sex hormones in HIV-1 infection

The role of sex hormones has been extensively studied for a number of diseases, in particular in the context of autoimmune disorders and vaccine settings [63, 64]. Sex hormones have furthermore been reported to directly tune host factors that affect HIV-1 acquisition [65]. Generally, estrogens are involved in the modulation of immune cells, including differentiation of T helper cells [66] and expansion of regulatory T cells [67], in particular during the follicular phase [67]. Estrogen has been suggested to protect from HIV-1 acquisition [68, 69]. Progesterone, on the other hand, displays immune-suppressive and anti-inflammatory properties in pregnancy [70] and can increase susceptibility to viral infections [68]. The potential impact of hormonal contraception on HIV-1 acquisition remains a critical public health issue and is still a controversial topic. A detailed meta-analysis from 2013 that reviewed trials on norethisterone enanthate concluded that most of the studies on oral contraceptives did not show an increased risk for HIV-1 acquisition [71]. Yet, a more recent study on progestin-only contraceptives in a prospective cohort study with HIV-1 negative non-pregnant South African women demonstrated that the use of an injectable progestin-only contraceptive and high endogenous progesterone were both associated with increased frequency of activated target cells for HIV-1 infection in the cervix, the site of initial HIV-1 entry in most women, indicating a possible mechanism accounting for increased HIV-1 acquisition in women with high progestin exposure [72]. Several studies furthermore reported an increase in the expression of HIV-1-entry receptors on cervical CD4+ T cells mediated by progesterone [73–75], providing an additional potential mechanism for the observed increase in HIV-1 acquisition. However, one in vitro study reported that

progesterone decreased the upregulation of CCR5 on activated peripheral blood-derived CD4+ T cells [76]. Importantly, these effects were dose dependent and only found at higher non-physiological concentrations. A recent study published in early 2018 furthermore evaluated the absolute and relative risk of HIV-1 acquisition during pregnancy and the postpartum period to inform HIV-1 prevention strategies for women. Data from 2751 HIV-serodiscordant couples were collected to compare the probability of HIV-1 acquisition during different stages in pregnancy, the postpartum period, and the non-pregnant period, and showed that the probability for HIV-1 acquisition increased during pregnancy and was highest during the postpartum period. Overall, these findings provide additional support for increased HIV-1 susceptibility among women potentially driven by hormonal changes during pregnancy and the postpartum period [77], and suggest an increased risk of HIV-1 acquisition associated with different levels of female hormones and different methods of contraception.

A potential impact of sex hormones on viral replication has also been suggested by variations of plasma viral load levels during the menstrual cycle. However, results differed between different studies [12, 78–80]. While some studies did not observe any correlation between plasma viral RNA levels and menstrual cycle [78, 79], another study observed a significant shift of HIV-1 RNA plasma levels between different phases of the menstrual cycle after excluding non-ovulating women [80]. Estrogens and estrogen receptor-dependent regulations also play a critical role in dendritic cell development and function [81]. pDCs from postmenopausal women display reduced TLR7 responsiveness and IFNα production in comparison to women of reproductive age. The percentage of IFNα-producing pDCs after TLR7 and TLR9 stimulation can furthermore be enhanced with therapeutic estrogen substitution in postmenopausal women [53]. Moreover, the interferon regulatory factor 5 (IRF5), a central mediator of TLR7 signaling [82, 83], is expressed at higher levels in pDCs from females compared to males [55]. Genetic ablation of the estrogen receptor gene *Esr1* led to the reduction of both IRF5 mRNA expression and IFNα production in pDCs. Taken together, these data implicate a role for estrogen in the regulation of IFN-α production by pDCs through IRF5 modulation, and the subsequent induction of antiviral ISGs. The potential inhibitory effect of estrogen on HIV-1 replication requires careful evaluation. It will be critical to understand the precise mechanisms underlying sex-hormonal regulation of HIV-1 acquisition and replication in order to develop new treatment strategies with optimal efficacy in women.

The female genital tract microbiota and consequences for HIV-1 disease

The female genital tract is one of the first lines of defense against foreign pathogens. The microbiome of the genital tract has been shown to play an important role in the risk of acquisition and transmission of a variety of sexually transmitted infections [84]. Sex-specific differences in the composition of the gut microbiome have been well described [85, 86]. A low-diversity, *Lactobacillus*-rich microbiota is currently considered as healthy [87]. Sex-based differences in the microbiome of the genital tract might also represent possible factors influencing the size and dynamics of the HIV-1 reservoir. A recently published study showed that differences in the vaginal microbial diversity and concentrations of key bacteria

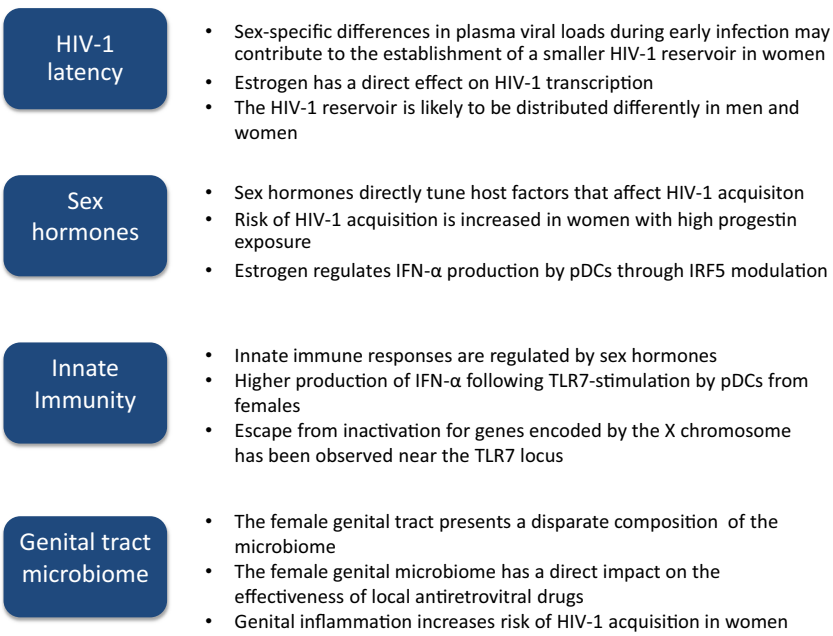

Fig. 1 Summary of current state of key insights on sex-specific differences in HIV-1 infection

were associated with a greater risk of HIV-1 acquisition in women [88]. Another study on the impact of the vaginal microbiome on HIV-1 acquisition in women from sub-Saharan African countries came to the same conclusion, showing that specific bacterial vaginosis-associated taxa increased the risk of HIV-1 infection and transmission to partners [89]. Parvimonas species type I and *Gemella asaccharolytica*, common constituents of vaginal microbial dysbiosis, strongest predicted HIV-1 infection. Furthermore, Arnold et al. showed that a signature of inflammatory cytokines in the cervicovaginal lavage was associated with altered expression of mucosal barrier proteins and an influx of HIV-1 susceptible target cells, potentially increasing the risk of HIV-1 infection [90]. Finally, a recent post hoc analysis of the CAPRISA 004 trial that studied the effectiveness and safety of a 1% tenofovir vaginal gel for the prevention of HIV-1 acquisition in women showed that inflammation of the female genital tract reduced the effectiveness of the antiretroviral gel in preventing HIV-1 acquisition [91]. For the same trial, Klatt et al. reported that tenofovir reduced the incidence of HIV-1 infection in *Lactobacillus*-dominant women three times more than in women with non-*Lactobacillus* vaginal bacterial type [92]. Overall, these studies show that genital inflammation associated with vaginal dysbiosis facilitates HIV-1 infection. Studies focusing on key factors that affect the vaginal microbiome and contribute to increased HIV-1 susceptibility are needed in order to design a targeted prophylactic strategy. In particular, strategies aiming at minimizing genital inflammation in women have to be considered in conjunction with HIV-1 prevention efforts. Both the mere existence but also the absolute quantity of certain bacteria may account for genital inflammation and subsequent increased risk for HIV-1 infection. Filling these knowledge gaps will provide important targets for future prevention research and risk-mitigation strategies for HIV-1-infected women.

Conclusion

The underlying mechanisms leading to sexual dimorphism in HIV-1 disease manifestations are multifactorial, many of which are incompletely understood. Important factors contributing to gender-specific differences in HIV-1 go beyond socio-economic and behavioral influences, and include biological sex-specific factors. In the ongoing efforts aimed at not only controlling HIV-1 disease but eventually accomplishing a functional or sterilizing cure of HIV-1, X-chromosomal factors, sex-hormonal factors, sex-specific differences in immune responses, and sex differences in the microbiome need to be considered. Ultimate strategies for HIV-1 cure may eventually differ between men and women, as certain treatment protocols may be more or less effective in women, due to regulatory effects of female sex hormones. The enrollment of more women in clinical studies will be critical to further elucidate the impact of sex on antiviral immunity, HIV-1 acquisition, and disease progression. The current state of key insights on sex-specific differences in HIV-1 infection is summarized in Fig. 1. Overall, sex differences in the establishment and maintenance of HIV-1 reservoirs represent a largely underexplored research territory. Knowledge gaps in the dynamics of HIV-1 latency, including the size and sex-specific distribution of HIV-1 reservoirs, need to be adressed to take these into account for strategies aimed at reducing or eliminating the latent HIV-1 reservoir, which represents one of the main obstacles to HIV-1 cure approaches.

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