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Review Series

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The impact of sex on HIV immunopathogenesis and therapeutic interventions

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Globally, the majority of people living with HIV are women or girls, but they have been a minority of participants in clinical trials and observational studies of HIV. Despite this underrepresentation, differences in the pathogenesis of HIV have been observed between men and women, with contributions from both gender- and sex-based factors. These include differences in the risk of HIV acquisition, in viral load set point and immune activation in responses to viremia, and differences in HIV reservoir maintenance. These differences obligate adequate study in both males and females in order to optimize treatments, but also provide a powerful leverage point for delineating the mechanisms of HIV pathogenesis. The shifts in exposure to sex steroid hormones across a lifespan introduce additional complexity, which again can be used to focus on either genetic or hormonal influences as the driver of an outcome. In this Review, we discuss consistent and reproducible differences by sex across the spectrum of HIV, from acquisition through pathogenesis, treatment, and cure, and explore potential mechanisms and gaps in knowledge.

Overview

The HIV pandemic has claimed more than 40 million lives and has been a galvanizing force in research into the prevention, pathogenesis, and treatment of infectious diseases. It has also brought into sharp relief the tremendous variation in the effect of HIV infection when considered across a broad population, ranging from elite control (1, 2) to rapid disease progression (3). Sex and gender are linked to distinct risks of HIV acquisition, pathogenesis, and reservoir maintenance, concordant with the impact of sex on a variety of infectious and inflammatory conditions (4–6). Gender differences in health-associated behavior, access to care and resources, and social stressors have a profound role in health outcomes (7). Although this Review discusses HIV infection and outcomes through the lens of biological sex, particularly genetic and hormonal differences, all studies must be considered within the context of potential gender-based confounders and effects. Approaches to considering risk and research in a gender framework have been expertly discussed elsewhere (8, 9). We focus on differences by sex in the context of HIV, noting where gender factors may intervene, but seeking to leverage sex to identify mechanisms of pathogenesis and potential points for therapeutic intervention. Throughout the Review, we discuss studies of people living with HIV (PLWH) and, when discussing characteristics related to genetic (e.g., XX versus XY) and anatomic features (reproductive organs), specifically use the terms female and male. We have used the terms women and men to refer to cisgender individuals unless otherwise indicated and in describing data from studies in which these terms were used to describe the participants.

Herein, we indicate gaps and opportunities in the data and attempt to highlight comparisons where there are major confounders. A primary consideration is whether studies have adequate inclusion across sex and gender for valid conclusions. The initial description of AIDS as an acquired immune deficiency syndrome among men who have sex with men (10, 11) reflected the epidemic in the US and Europe, which has been dominated by men. This contrasts with the global epidemic, in which women account for 53% of PLWH (12). In sub-Saharan Africa, women constitute more than 61% of PLWH and 62% of new HIV diagnoses in this region (12) (Table 1). Distribution of the infection has important implications for the available data: a high proportion of biomedical research and funding originate in regions with male-dominated epidemics, contributing to an underrepresentation of female study participants (13–15). Elucidating immunologic mechanisms of phenotypic differences by sex across the spectrum from HIV acquisition through efforts towards a cure may facilitate the development of interventions that will serve all PLWH.

Acquisition

Due to the very early integration of HIV into the host cell genome, viral eradication presents a formidable challenge, and a preventive vaccine remains crucial to ending the epidemic. In this section, we explore sex-specific features of HIV acquisition, including through vertical transmission, that inform the development of protective vaccines and deployment of preventive strategies including pre-exposure prophylaxis.

Anatomic risks for HIV acquisition. HIV can be acquired via parenteral exposure to blood products or through sexual activity. Although we lack significant data about sex-differential risk related to parenteral exposures, as discussed below, there is emerging data in the context of vertical transmission.

There are clear distinctions in acquisition risk thresholds based on sexual transmission. Broadly, the risk of sexual acqui-

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Table 1. Regional estimates of the proportion of PLWH who are women

Region	Estimated PLWH who are women
Sub-Saharan Africa	65%
Caribbean	50%
Middle East and North Africa	40%
Eastern Europe and Central Asia	34%
Asia and the Pacific	35%
Latin America	28%
Western/Central Europe and North America	24%

Data source: 2024 Global Aids Report (179).

sition is dictated by the availability of cells that can be infected. This, in turn, is determined by anatomy and the levels of local inflammation (16). Receptive anal intercourse has the highest risk of transmission (17), with studies suggesting that the density of $CD4^+$ T cells and inflammatory environment conditioned by the microbiome may contribute to elevating risk of acquisition, and that this risk may change with age (18). Penile-vaginal intercourse is associated with a higher risk of transmission to the female partner in high-income countries, with a more modest difference in other settings, notably where male circumcision is less common (19). Langerhans cells and $CD4^+$ T cells present in the vaginal mucosa and penile foreskin are the primary targets for early HIV-1 infection (16, 20, 21). Medical male circumcision has been shown to significantly decrease the risk of HIV acquisition, likely both by reducing the local target cell populations and by eliminating inflammatory components of the foreskin microbiome (22). For females, there has been significant debate about the effect of hormone exposure on the vaginal mucosal environment. Two meta-analyses reported an approximately 40% increase in risk of HIV acquisition associated with use of depot medroxyprogesterone acetate (DMPA, a contraceptive injection under the brand name Depo-Provera) (23, 24). Suggested mechanisms include alterations in the epithelial layer, change in frequency of target cells, and inflammation and alterations in the microbiome. However, this is not supported by the results of a prospective randomized trial comparing DMPA with other contraceptive methods, in which there was not a substantial increase in risk (25). Importantly, this study also highlights that hormone exposure must be considered in context of the alternatives, which here would be alternative contraceptive methods or a pregnancy with the associated maternal risks (26). Nevertheless, a greater understanding of the influence of hormones on the local environment may provide information on factors that favor transmission. Further exploration of the effect of exogenous sex steroid hormone exposure in transgender individuals will also be important in order to optimize and target prevention efforts in this population (27).

In parallel with the risk for HIV acquisition that is conferred by the local availability of targets at a mucosal site is the potential protection conferred by vaccine-induced HIV-specific immune responses at these mucosal sites. With respect to humoral immunity, a meta-analysis of mucosal antibody titers across six vaccine platforms of HIV envelope immunogens demonstrated a robust correlation between seminal plasma and rectal mucosal antibody titers in males but poor correlation between cervical and rectal antibody titers in females (28). The authors suggested that sex-specific features in the relationship between serum and genital/rectal mucosal antibody titers may affect the degree of protection (28). Emerging data from phase IIb trials of prophylactic administration of the broadly neutralizing antibody (bNAb) VRC01 provide some further insight into the function of humoral responses at mucosal sites (29). In these trials, one enrolling at-risk cisgender men and transgender individuals in Europe and the Americas and the other enrolling at-risk cisgender women in sub-Saharan Africa, VRC01 was not effective, but both trials showed a signal of preventive efficacy against viruses sensitive to neutralization by VRC01 that was linked to antibody concentration (29). In a separate analysis of the mucosal penetration of VRC01 in healthy volunteers, both rectal and vaginal explants demonstrated resistance to ex vivo challenge with sensitive strains of HIV (30). As strategies of combinations of antibodies for prevention with targeted modifications of the Fc region to enhance mucosal penetration and effector function are pursued, careful evaluation of the sex-specific accumulation and efficacy of these agents will be essential.

Impact of local inflammation on HIV acquisition. Both the efficacy of local immune responses and available target cells are directly affected by inflammation that may arise from either sexually transmitted infections (STIs) or as a result of the composition of the local microbiome. STIs including HSV-2, syphilis, gonorrhea, and chlamydia cause an increased risk of HIV acquisition during vaginal intercourse (31–35). A systematic review of the effect of herpes found that a relative risk of HIV acquisition was 2.7-fold higher with prevalent HSV-2 in the general population and 4.7-fold higher with incident infection, with no sex difference observed in the estimates (36). Likewise, an analysis of the impact of nonviral STIs demonstrated increased risk of HIV acquisition with coincident STI, although notably the data for males were sparse (37). Some of the enhanced risk may be attributable to behavioral patterns associated with STIs. Biological mechanisms include the influx of target cells to both the male and female genital tracts as a result of an STI (38–43); increased genital shedding of HIV driven by HSV-2 coinfection, which may directly influence HIV-1 acquisition (44); and disruption of the protective epithelial layer by genital ulceration in the setting of syphilis, chancroid, and HSV-2 infection (45, 46).

HIV seroconversion is also more likely when there is more inflammation, as defined by cervicovaginal levels of inflammatory cytokines such as MIP-1α, MIP-1β, and IP-10, which actively recruit target cells for HIV (47). In the absence of an STI, the specific composition of the vaginal microbiota, including when this shifts to a clinical diagnosis of bacterial vaginosis, is linked to increased risk of HIV acquisition (48–51). Inflammation driven by microbiota can activate Langerhans cells and $CD4^+$ T cells, raising the risk of HIV acquisition (52, 53). Specific formulations of oral contraceptives have been linked to more-favorable vaginal microbial communities and to a lower frequency of STIs, suggesting that hormone modulation is a potential risk-modifying strategy (54, 55). The vaginal microbiome is also a critical consideration for topical pre-exposure prophylaxis, as certain species metabolize the antiviral drug tenofovir, lowering its preventive

efficacy for HIV (56). Thus, the vaginal microbiome can confer risk, and understanding variations based on region, ethnicity, and local environment will be important to optimize prevention interventions (51, 57, 58). In parallel, the penile microbiome comprises specific microbial components that promote risk of acquisition, with the notable difference that medical male circumcision can significantly ameliorate, although not eliminate, the risk of seroconversion (22, 59, 60).

Vertical transmission. Intrauterine transmission is an emerging area of sex differential HIV transmission. In a recent single-site cohort study of infants with intrauterine acquisition of HIV, females outnumbered males 1.7:1, consistent with prior studies. This ratio contrasts with the sex ratios of HIV-exposed but uninfected infants and to the overall ratio of sex at birth in the study region (50.6% male) (61). Since the 1990s, multiple studies have assessed the risk of vertical transmission in the context of intrapartum antiretroviral therapy (ART), ART during pregnancy, and various approaches to infant treatment, with very early signals of an increased risk for female infants (62). In a large cohort study in Zimbabwe of 4,495 women living with HIV and their infants between 1997 and 2000, female infants were at greater risk of in utero acquisition (OR 1.53, 95% CI 1.23–1.91), despite 50.4% of all births being male (63, 64). An analysis of more than 2,000 women in Malawi in the 1990s reported higher rates of intrauterine acquisition in female infants (OR 1.4, 95% CI 0.2–2.2) and, notably, in 8 sets of sex-discordant twin pairs, 7 female infants and 1 male infant acquired HIV in utero (65). This finding is important, as it implies a selective pressure from the infant, given that the maternal environment of these twin pregnancies is identical. Separate work from Malawi in the early 2000s again reported a higher risk for female infants (OR 2.06, 95% CI 1.49–2.85), and this estimate was adjusted for maternal viral load, a strong independent predictor of transmission (66). Beyond the African context, the European Collaborative Study of vertical transmission noted that among infants delivered by elective cesarean section (effectively eliminating risk of intrapartum transmission), female infants are at higher risk (2.14, 95% CI 1.14–4.00) after adjustment for antenatal ART use and time period (67). An Italian registry had similar findings of lower risk for male infants (68). While modern ART has substantially reduced vertical transmission, the enhanced risk in female infants appears to persist. A prospective infant treatment trial screened 10,622 infants between 2015 and 2018, identified 42 with HIV within 96 hours of birth, and enrolled 40. Of the 40 infants enrolled in the trial, 78% were female (69). While there are multiple features to consider — including maternal ART, survival of male versus female infants independent of HIV risk, and differences in transmission risk across the timing of delivery — the weight of the collective data indicates that there is a higher risk of intrauterine transmission of HIV to female infants.

The mechanism of this differential risk is unclear; the twin data suggest that there are features of the infant that drive the difference. Of note, recent work has indicated that viruses recovered from female infants were more likely to be interferon resistant and have differences in replication capacity (61, 70). Production of type I interferon in response to TLR7 stimulation is a prominent feature of sex differential immune responses, as discussed below, and may contribute to this difference in early life.

Pathogenesis

Viral load. Multiple studies have demonstrated that in the absence of HIV treatment, females have lower set point viral loads than males, although this difference attenuates with progression to advanced disease (71–79). In a study of individuals not on ART, females had less plasma virus associated with each HIV RNA$^+$ CD4$^+$ T cell in lymph node biopsies, suggesting that lower plasma viremia is associated with each HIV-infected cell in females (80). The lower systemic viral load is not protective, and males and females exhibit a similar time course of disease progression following seroconversion. This discordance meant that early on in the HIV epidemic, treatment guidelines based on viral load excluded women who were at risk for disease progression (79), highlighting the need for analysis of population variation for health policy–level decisions.

There are also important sex differences in the rates of the rare phenomenon of spontaneous control. In multiple large medical record database studies, rates of viremic and elite control are substantially higher in females, with the OR of female control ranging from 1.9 to 5 (81–84). Female participation in studies of elite controllers has not been representative; for example, an international cohort of 9,705 participants in a study that investigated the genetic determinants of HIV control was 82% male (85), leaving open questions about the effect of sex on this phenotype. Separate from spontaneous control is the phenomenon of posttreatment control, in which individuals who have been viremic are able to maintain viral suppression after a period of ART despite subsequent treatment discontinuation. The determinants of this type of control are under active investigation as a potential model of a functional cure. In one cohort of primary HIV infection, female sex was associated with a higher rate of posttreatment control (86). In other cohorts, there was not a clear signal for enrichment of control among females (87, 88), although the identification of individuals demonstrating posttreatment control was biased by the same factors that have led to the overrepresentation of males in other studies of HIV control described above. In a prospective trial assessing whether short-course ART in primary HIV infection leads to prolonged time to disease progression after ART interruption (89), female sex was a strong predictor of maintaining a viral load of fewer than 400 copies/mL for a longer period of time (90). However, the 40% of participants in the trial who were female were almost exclusively enrolled in African sites, and the contributions of the various geographic locations and HIV-1 virus clades cannot be completely separated from the contributions of the sex of the participants. In an analysis of ART discontinuation in more than 1,000 postpartum women treated during pregnancy as part of the PROMISE trial, 25% of the women remained virally suppressed (<400 copies/mL) at 12 weeks. This is a substantially higher level than the 6.4% of participants who maintained suppression at the same time point after treatment interruption in a comparator group of studies; notably, the comparator group was more than 90% male (91). Again, the effects of location, HIV virus clade, and pregnancy are difficult to disentangle from the effects of sex on the timing of viral rebound. Taken together, the data suggest a higher likelihood of spontaneous control in females, and there are suggestions of a higher likelihood of posttreatment control or significantly prolonged time to viral rebound in females.

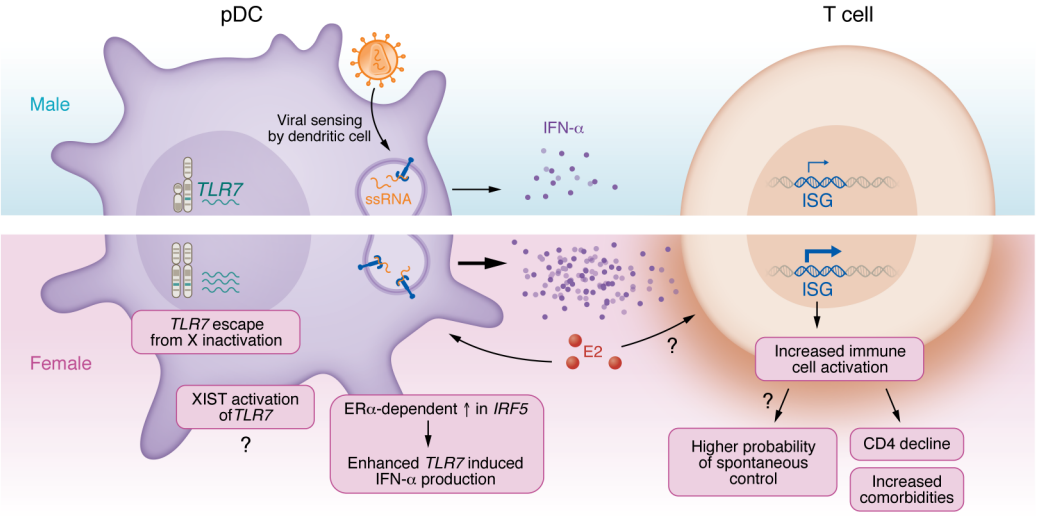

Figure 1. Multilevel effect of sex on HIV pathogenesis. *TLR7* escape from X inactivation in female plasmacytoid DCs (pDC) induces increased IFN-α levels. Increased IFN-α is in part a result of 17β-estradiol– (E2-) and ERα-dependent increases in *IRF5* expression. Expression of the long noncoding RNA XIST, which mediates epigenetic silencing of one X chromosome, also provides a source of TLR7 ligands that may enhance IFN-α. IFN-α promotes expression of interferon-stimulated genes (ISG) linked to increased immune cell activation. This enhanced response may contribute to higher frequency of controller phenotypes in females, but in chronic infection it drives CD4$^+$ T cell decline and comorbidities.

Innate and adaptive immune activation. A key driver of HIV pathogenesis is immune activation, with early studies demonstrating the association of T cell activation with progression to advanced disease (92, 93) (Figure 1). While females tend to have lower viral loads, the level of T cell activation for a given viral load is higher in females than in males (94). In untreated disease, type 1 interferon gene signatures were also higher in females, when controlled for viral load (95). Beyond HIV, females are generally described as having higher antiviral immune responses, a higher proportion of CD4$^+$ T cells, increased production of IFN-α, and enhanced antibody production (4, 96, 97). Thus, one hypothesis is that a more robust response to HIV, as seen in higher production of IFN-α from plasmacytoid DCs (pDCs) after stimulation by HIV or other TLR7 ligands (94, 98, 99), may have two possible consequences: The first is a higher likelihood of virologic control as observed in the higher frequency of female spontaneous controllers discussed above. The second is a higher level of ongoing inflammation despite failure to control or eliminate the virus; this outcome would be linked to greater immune activation and risk of disease progression at a lower level of virus exposure. In studies assessing the rates of disease progression in males and females, lower viral load is not protective, with women progressing at similar rates despite lower median viral load levels (79); at least one study suggests that women progress at a faster rate (100). Higher levels of interferon-induced gene signatures in females may also be linked to the cell-intrinsic restriction of HIV replication and potentially lower per-cell production of HIV observed in lymph node CD4$^+$ T cells in females (80). This has been described in macrophages, where female-derived cells had lower levels of HIV replication and higher levels of SAMHD1-based restriction (101). In recent work from murine model systems, isolated immune cells (macrophages, T and B cells) showed distinct patterns of interferon-stimulated gene transcription, notably with cells from female animals responding faster across all conditions (102). Taken together, the data suggest that a robust early antiviral response by females may be linked to lower viral loads, but at the cost of higher immune activation in chronic untreated HIV.

Emerging data about sex differences in intrauterine transmission again show links to interferon-based restriction, with viruses transmitted to females more likely to be interferon resistant (61, 70). Separate studies have confirmed that TLR7/TLR8 responses are lower in male infants (~2 months of age), confirming that differences in this axis are present even in early life (103). This immediately raises the question of which features of sex — genetic composition, sex steroid hormone exposure, epigenetic regulation — are underlying drivers of differences in immune response phenotype and viral restriction given the changes in these factors over a lifetime.

Sex steroid hormones. Sex steroid hormones and the expression and function of their receptors affect immune responses. In females, 17β-estradiol (E2), and progesterone concentrations fluctuate during the menstrual cycle and throughout life, while male androgen levels remain relatively consistent after puberty (104). In vitro studies showed that lower sex hormone concentrations, modeling the mid-proliferation hormone phase, are associated with higher levels of HIV transcription compared with the higher-concentration, midsecretory phase, suggesting that HIV replication is linked to hormone level (105).

Much of the literature on sex differences in HIV replication has focused on E2 and estrogen receptor α (ERα). ERα is activated upon E2 binding and is expressed in immune cells, and most studies have not demonstrated differences in expression at the transcriptional (106) or protein level (107) between males and females. ERα activation can induce nuclear localization and direct DNA binding at estrogen response elements (EREs) or indirect transcription effects via tethering transcription factors such as RUNX1, AP-1, and Sp1 (108–111). EREs have been found in the promoter region of many immune-related genes that affect activation (112), but it is unclear how the effect of E2 exposure intersects

with direct immune-activating signals. Beyond the indirect effects E2 may have on host transcriptional machinery, in vitro studies demonstrated suppression of HIV replication by E2/ERα signaling (113). However, viral load levels in prepubertal females are lower than those in males even when E2 concentrations are similar between the sexes (114). The role of E2 in HIV transcriptional control in the context of ART is further discussed below in *Cure*.

Beyond these direct effects on viral dynamics, sex steroid hormones can also modulate immune pathways. Notably, the level of interferon regulatory factor 5 (IRF5), a downstream signaling component in the TLR7 response, is higher in pDCs from females and correlates with IFN-α production and with expression of ERα (115). TLR7 is also a canonical example of sex-specific genetic features, as discussed below.

Genetics. At the most basic level, sex differences in gene expression can arise from the chromosomal complement. Females have two copies of the X chromosome (XX), while males only have one (XY). One X chromosome in females undergoes X inactivation to normalize gene dosage between males and females, but X inactivation escape has emerged as a key contributor to sex differences (96, 116, 117). There are multiple immune active genes on the X chromosome, including TLR7, which has been shown to have dual expression in XX females and in XXY males (Klinefelter syndrome) in the immune system, with consequences for diseases including systemic lupus erythematosus (SLE) (118–121). Thus, females have higher TLR7 expression, and estrogen enhances the downstream signaling through IRF5. Further complicating this system is the recent identification that XIST, the long noncoding RNA that mediates X chromosome inactivation, acts as an endogenous TLR7 ligand, contributing to SLE pathogenesis (122, 123). Notably, a hypomorphic variant of *TLR7* has been described to have an effect on acute HIV viremia specifically in females, highlighting the sex-specific relationship between interferon and viral load (124). Taken together, the data indicate that gene dosage, hormone exposure, and epigenetic regulation all contribute to differences between males and females in the TLR7/interferon pathway.

Notwithstanding the importance of the sex chromosomes, the majority of sex-based gene expression variation in immune cells is derived from autosomal genes (106). There has been limited exploration of how sex-specific autosomal gene expression contributes to HIV outcomes. A recent study tested for sex chromosome and sex-stratified genomic markers in the largest GWAS of HIV set point viral load and spontaneous control (125). The analysis was limited by the relatively low representation of females in the cohort (<20%) but identified a gene-based association with set point viral load on chromosome 19 in males only and other gene variants with sex-discordant associations with set point viral load in potentially immune-active genes (125). Further work is needed to elucidate whether baseline or stimulated gene expression differences contribute to observed differences in immune response to HIV. In addition, another key gap in knowledge is the very limited body of work exploring immune cell function in transgender individuals with discordant sex chromosome complement and sex hormone exposure.

Sex differences in the context of ART

Treatment responses and comorbid conditions. In general, both women and men achieve viral load suppression with ART, as predicted for medications that target viral proteins. As with many types of medications, for some ART agents there is a higher level of reported adverse effects in women and there are pharmacokinetic differences (126, 127). Analyses have historically been limited by low representation of women in clinical trials, which, although improving, still does not proportionally represent the epidemic, particularly regarding the inclusion of African women (15). For current ART, a major challenge is management of weight (128). The ADVANCE trial, a prospective randomized trial of three ART regimens, identified specific regimens as being linked to weight gain that is most pronounced among women (129, 130). The mechanisms by which these ART regimens promote weight gain are incompletely understood, and the intersection with sex may provide a key leverage point for understanding how these medications are affecting metabolism (131). Emerging work in preclinical models suggests that there may be an interaction among dolutegravir, estradiol, and mitochondrial function that may contribute to weight changes (132). Other possibilities — including effects of ART on the gut microbiome, which at baseline has sex-specific features (133) — are still under investigation.

Outside of the adverse effects of ART lies the residual inflammation from HIV even with near complete viral suppression. This inflammation is thought to be a driver of comorbid conditions and remains a key target of novel treatment strategies developed to ameliorate the effect of chronic HIV. Notably, HIV confers a proportionally greater increase in risk of cardiovascular and cerebrovascular disease in women as compared with men (134–137). These findings are consistent with sex-specific features of the burden of comorbid conditions, with changes also noted through reproductive aging in women (138–140). Some of this may reflect gender, with specific health-related behaviors including smoking that contribute to outcomes in women living with HIV. In the sub-Saharan African setting, male mortality exceeds female mortality, again thought to be driven in part by gendered differences in access to testing and care (141, 142). To optimize preventive health interventions across cis- and transgender individuals and in a variety of settings, more studies are needed to identify the HIV- and non-HIV-related drivers of inflammation and associations with comorbid illness and to separate gender- and sex-related mechanisms for disparities in outcomes.

Cure. Aside from eliminating residual inflammation, the other frontier of modern HIV clinical science is the effort to develop a curative intervention. Cure is variably defined as elimination of all replication-competent virus (eradication) or functional cure, whereby individuals no longer require daily ART to suppress HIV replication. The latter is a model of inducing a controller status and refers to the models of spontaneous control and posttreatment control described above with the notable influence of sex (143). Interestingly, all three individuals in the anecdotal reports characterized as having undergone spontaneous cure — i.e., no recovered replication-competent virus despite extensive sampling — were female (144–146). This, along with data suggesting that females are more likely to have a delayed rebound time after treatment interruption (discussed above) suggest that female sex may be associated with greater propensity to have sustained control (Figure 2).

Given the differences in set point viral load, studies directly explored whether there are differences in the low level of residu-

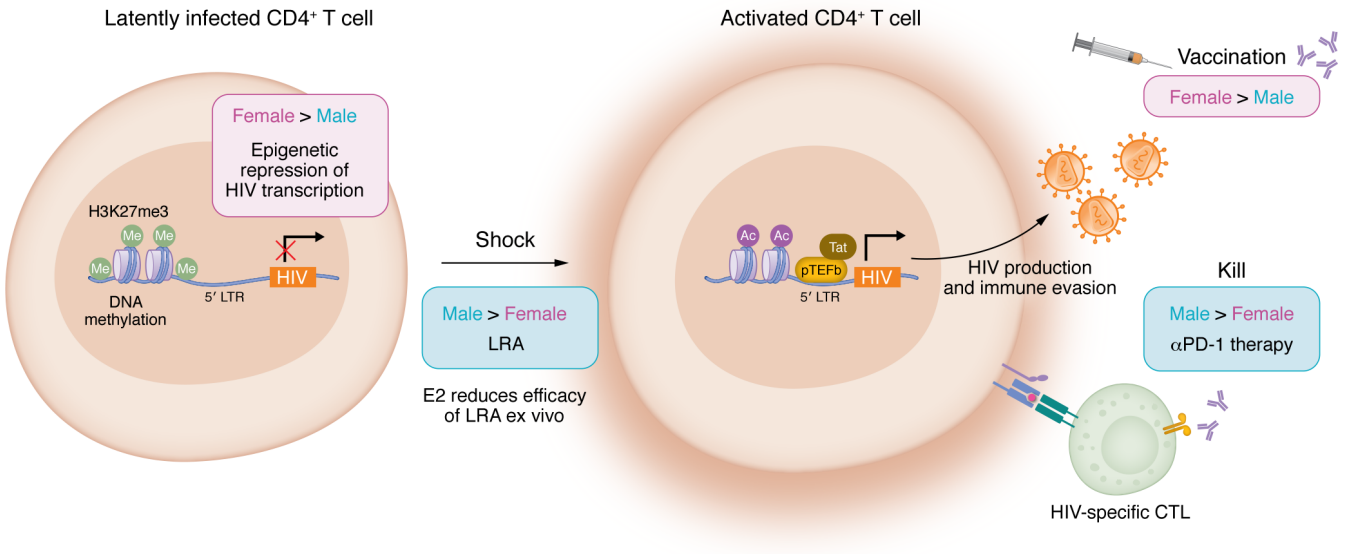

Figure 2. Sex differences in strategies for HIV cure. Female sex is associated with tighter control of latent HIV that may be a barrier to latency reversal. Mechanisms may include epigenetic repression and latency promotion via E2 signaling. Immune-enhancing strategies including checkpoint inhibition and vaccination may also have sex-differential efficacy. LRA, latency reversal agent; pTEFb, positive transcription elongation factor b; LTR, long terminal repeat; CTL, cytotoxic T lymphocyte.

al HIV expression observed under suppressive ART. In a cohort of matched reproductive-age men and women in the US, levels of HIV DNA were comparable, but levels of multiply spliced cell-associated HIV and low-level viremia by single-copy assay were lower in women (107). Lower levels of cell-associated HIV RNA in females were also observed in a retrospective analysis (147) and in a study of CMV/HIV coinfection (148). While some studies of peripheral blood mononuclear cells have suggested lower levels of total HIV DNA (149, 150), in the majority of studies, levels of HIV DNA (total and/or integrated) are comparable in men and women (107, 147, 148, 151, 152). This suggests tighter control of latent HIV expression in females as compared with males. It is unknown whether there is a difference in the replication competent reservoir; in one study, females had lower levels of ex vivo inducible HIV (152), but in another, there was no significant difference in measures of intact virus and outgrowth (151). These apparent differences in the stringency of latency maintenance are key to the feasibility of some curative strategies. Specifically, the approach of inducing HIV expression to allow identification and elimination of HIV reservoir–harboring cells, known as "shock and kill," would be predicted to have a higher barrier in females (153). Alternatively, the strategy of "block and lock," whereby integrated proviruses are maintained in a permanently silenced state of deep latency, might be easier to achieve in females (154). Given the challenges with achieving cure, even small differences in efficacy may be significant.

Potential mechanisms of sex differences in HIV latency. There is substantial interest in the potential mechanisms for sex-differential latency control. In an unbiased shRNA screen for host factors critical to maintenance of HIV latency, ERα emerged in three independent screens of a cell line model as a key latency regulator (155). This association was further tested using a primary cell model of latency and by assessing the effect of both estradiol and selective estrogen receptor antagonists designed to block or activate ERα. These studies consistently demonstrated that estrogen signaling blocked HIV latency reversal (155). In samples from PLWH, estradiol exposure blocked HIV RNA induction, and antagonists of ERα enhanced the latency reversal activity of other treatments, including the histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA, also known as vorinostat) (107, 155). A clinical trial in postmenopausal women testing whether the selective estrogen receptor modulator tamoxifen could augment latency reversal with SAHA failed to show an increase in HIV RNA expression (156). This study was limited by the relatively poor latency reversal efficacy of SAHA and also by the low levels of detectable HIV RNA in trial participants, with substantially more participants having undetectable HIV RNA than in prior studies of male participants (156). In addition, this trial enrolled only postmenopausal women due to genotoxocity concerns around the use of SAHA. Subsequent work has highlighted that there is a higher level of HIV reactivation potential as women move through menopause with waning exposure to estradiol (157), suggesting that estradiol and tamoxifen are likely less impactful in postmenopausal women. Taken together, data support a role for estrogen and ERα in the regulation of HIV transcription, with a changing magnitude across the reproductive lifespan. The precise mechanism of this effect remains unknown.

Another potential mechanistic pathway for differences in HIV latency is sex specificity in epigenetic regulators. HIV latency induction and maintenance is partially mediated through epigenetic marks that suppress transcription through repressive nucleosome arrangements, DNA methylation, and histone methylation (158). Women have globally higher levels of DNA methylation in whole blood (159), and analyses of sex-biased gene expression across tissues suggest sex-differential epigenetic marks as a mechanism of differential gene expression (160). Again there is evidence of hormone modulation of these effects, with a smaller

Table 2. Summary of sex differences in HIV acquisition, pathogenesis, and response to cure and treatment strategies; and identification of knowledge gaps and directions for future research

Summary	Knowledge gap/research directions
Acquisition risk	
Anatomical differences at mucosal sites: Microbiome and local inflammation condition risk of acquisition	• Interventions to optimize the vaginal microbiome • Optimize vaccine-elicited mucosal immune responses to prevent HIV acquisition in both rectal and vaginal mucosa
Vertical transmission: Female infants have a higher risk of intrauterine acquisition of HIV	• Delineate the interaction between interferon resistance, replication capacity, and transmission efficiency • Identify features of the developing immune system that enhance risk
Pathogenesis	
Viral set point: Females have a lower viral set point level	• Are there sex-specific genetic determinants of set point viremia? • How is set point viral load determined?
Spontaneous control: Females are more likely to spontaneously control	• What accounts for the female predominance of spontaneous control; is this linked to posttreatment control?
Immune activation: Females have ↑T cell activation per viral load, ↑production of IFN-α, and ↑levels of interferon-stimulated genes per viral load	• Do higher innate immune responses lead to control, to more chronic inflammation, or both? • Can they be deactivated during chronic HIV?
Cure and treatment strategies	
Antiretroviral therapy: Equally effective at achieving suppression of viral load in males and females, some sex differential adverse effects	• What is the mechanism of disproportionate weight gain in females associated with ART?
Residual inflammation/excess comorbidities: Females have higher HIV-associated risk of cardiovascular disease, and there are differences in patterns of residual inflammation	• Are there sex-specific pathways leading to risk of comorbid conditions, and can they be targeted for therapeutic blockade?
Shock and kill: Females have tighter control of residual virus expression, and E2 blocks latency reversal	• What happens to latency control across the reproductive lifespan? • Is the E2 effect a significant block to in vivo latency reversal treatment?
Lock and block: Females have higher global levels of DNA methylation and sex-stratified epigenetic marks	• Are there sex-specific features of the HIV integration landscape?
Immune modulation: Females have lower bulk T cell expression of PD-1, and there are sex-differential response to checkpoint blockade in cancer therapy	• Adequately evaluate checkpoint blockade, TLR agonism, and therapeutic vaccination for sex-differential efficacy

difference observed in postmenopausal women relative to men (161), highlighting the need to consider multiple features as potential mediators of differences.

A novel regulator of HIV infection susceptibility and reservoir maintenance lies in the metabolic state of the immune cell (162). HIV infection is less efficient in $CD4^+$ T cells in glucose-deprived conditions, highlighting the importance of metabolic balance on HIV replication (163–165). Differences in metabolism between cisgender men and women are well appreciated, with women having higher body fat percentages than men and different adipose storage distribution, but there is limited exploration of the impact of sex on immunometabolism (166). The potential role of sex in metabolic control of immune cell function has not yet been explored in the context of HIV, but it may be identified as contributor to reservoir maintenance and anti-HIV responses.

Curative therapies that may have sex-specific effects. As highlighted in the previous section, sex differences in epigenetic regulation may lead to differences in therapeutic responses to latency reversal agents in this class of drugs. Another area of interest for latency reversal is TLR agonism, with a dual goal of boosting HIV expression and inducing immune responses to promote reservoir clearance (167, 168). Nonhuman primate studies had promising results, and several small clinical trials have explored the effect of TLR7 and TLR9 agonism on induction of HIV expression and reduction of reservoir size, with variable results (169–173). Representation of females was limited in these trials, insufficient to allow sex-specific analyses, but the abundant data on sex-specific features of TLR7 regulation and function suggest that this should be carefully considered.

Another potential source of variation is in strategies aimed at enhancing endogenous immune responses to more efficiently eliminate the reservoir. One approach is the use of immune checkpoint blockade therapies used in cancer therapy with the goal of reinvigorating the T cell response to eliminate HIV-infected cells (174, 175). In the prospective cohort of ART-suppressed participants exploring sex differences in reservoir activity, immunophenotyping showed lower expression of programmed cell death 1 (PD-1) on bulk $CD4^+$ and $CD8^+$ T cells from women as compared with men, although these measures do not provide information on antigen-specific responses (107). In cancer therapeutics, there are sex-specific patterns of response to checkpoint therapies across different tumors (176, 177). Taken together, "kill" strategies leveraging checkpoint blockade may be less effective in women. Conversely, other "kill" strategies may be more effective in women; therapeutic vaccines designed to augment and redirect the immune response to eliminate HIV reservoir cells are another potential immune-modulating strategy. A broad range of literature demonstrates generally more robust vaccine responses in females

(reviewed in refs. 5, 178), arguing that these "kill" strategies may perform better in females.

Opportunities

Sex differences in HIV acquisition and pathogenesis and their consequences for comorbidities and HIV cure efforts highlight multiple levels of the immune response to HIV (Table 2). They also highlight the risks of narrow representation in clinical trials and importance of testing interventions against population variation. Comparisons by sex remain a rich source of scientific discovery. Moving forward, further work is still necessary to clarify the role of sex steroid hormones and genetic and epigenetic controls in mediating differences in phenotype by sex. Work is needed to increase representation of cisgender women across the spectrum of clinical research and to investigate the unique setting of transgender individuals to allow the development of personalized care approaches. Deconvoluting the overall mechanisms of differences by sex in outcomes of HIV will be critical to developing prevention, treatment, and cure strategies that are efficacious across all people.

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