Transgender populations and HIV: unique risks, challenges and opportunities

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Abstract

Due to unique social, behavioural, structural and biological issues, transgender (TG) populations, especially TG women, are at high risk for HIV acquisition. This increased risk is multifactorial, due to differing psychosocial risk factors, poorer access to TG-specific healthcare, a higher likelihood of using exogenous hormones or fillers without direct medical supervision, interactions between hormonal therapy and antiretroviral therapy, and direct effects of hormonal therapy on HIV acquisition and immune control. Further research is needed to elucidate these mechanisms of risk and to help design interventions to reduce HIV risk among transgender populations.

Keywords: transgender, HIV, sex steroid hormones

Introduction

Transgender men (TGM) and women (TGW) are populations that are often subsumed under other risk groups, such as men who have sex with men, in HIV studies, despite a number of significant differences. This review aims to characterise the social, behavioural and medical issues unique to transgender (TG) populations that may impact HIV transmission, pathogenesis and treatment.

TG individuals are generally defined as persons whose gender identity and/or gender expression differs from their biological sex assigned at birth. TG may identify as male-to-female (MTF) transwomen/transgender women or female-to-male (FTM) or transmen/transgender men; may identify with their gender expression (e.g. male, female); or may not adhere to the gender binary at all (e.g. gender queer). Moreover, various cultures may have their own locally produced or indigenous terms for transmen and transwomen, and may be rooted in specific socio-cultural roles (e.g. spiritual ceremonies) [1,2]. Further, TG individuals may engage in sexual activities with persons whose gender expression is similar or different from their own.

It is difficult to enumerate the total number of TG people in a given population since research studies have differing definitions that may or may not include transitioning experiences or diagnosis of gender dysphoria. Social and cultural factors, including social stigma and outright legal persecution in some countries, may prohibit individuals from self-identifying as TG. In the US and Asia, proposed estimates of TG individuals range from 0.3 to 0.5% of the total population [3,4]. According to the Diagnostic and Statistical Manual of Mental Disorder (DSM-5), gender dysphoria – a term used to replace gender identity disorder – is a formal diagnosis for persons whose gender at birth is different from the one with which they identify [5]. Data on gender dysphoria are usually based on surveys taken by parents, on adolescents and adults who accessed gender mental health clinics, and usually in the Global North [6]. Clinic-based studies in these environments suggest that TG prevalence ranges from 1 : 30,000 males and 1 :100,000 females to as high as 1 : 180 to 1 : 3000, respectively [6].

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HIV and sexually transmitted infection epidemiology among TG populations

The population of transgender women is disproportionately affected by HIV and members are in need of HIV prevention, treatment, care and support services. A meta-analysis conducted by Baral and colleagues [7] found that transgender women have a pooled HIV prevalence of 19.1% (95% confidence intervals [CI] 17.4–20.7); for high-income countries the prevalence was 21.6% (CI 18.8–24.3) and for middle- and lower-income countries the pooled prevalence was 17.7% (CI 15.6–19.8). Remarkably, the risk of being HIV infected among TGW in middle- and lower-income countries was 50 times (CI 26.5–94.3) that of all reproductive-age adults; in higher income countries, it was 46.3 times (CI 30.3–70.7).

For transgender women sex workers (TSW), HIV prevalence is even greater, estimated at 27.3% [8]. A recent review found that TSW have a unique combination of risks that are multi-level (e.g. biological, individual, interpersonal and structural), and that together may interact to increase HIV vulnerability [9]. Similar to studies of TGW being grouped with MSM, TSW may also be grouped into MSM and female sex worker categories, further underestimating prevalence estimates. Furthermore, studies of sex workers tend to be either brothel-based or street-based, in part because it is easy to reach/recruit them into studies [9]. However, sex work in the age of the internet and mobile technology goes beyond the brothel and the street. Transgender university students, for example, are engaging in sex work by using their smart phones to meet clients [10]. Future studies, including preventive interventions, will need to consider these factors.

While HIV prevalence estimates are limited in TGW, there is even less information about HIV prevalence among TG men [11]. Some studies have shown that TGM and TGW are equally at risk for HIV acquisition and transmission, possibly because TG men may be the receptive anal partner with other men [12,13]. However, more research is needed to understand biological and social determinants of HIV risk in TG men.

Infection with sexually transmitted infections (STIs), including syphilis, gonorrhoea and chlamydia, has been associated with increased risk of HIV acquisition among MSM [14–16]. However, information on rates of STIs in TG is lacking. A study in a San Francisco STI clinic reported 5% of 69 TGM had had rectal chlamydia in the previous year [12]. One cross-sectional study in TGW in Peru looking at rates of gonorrhoea and chlamydia found 27.9% had prevalent anal infection and 14.4% had pharyngeal

infections; a study that took place in Indonesia found evidence of current or past syphilis in 47.5% of the 241 TGW sampled [17,18]. Sex work was significantly associated with STI diagnosis [11,19]. Little is known about the risk contexts associated with acquisition of STIs, especially STIs of the neovagina. There is one case report published of gonorrhoea detected in the neovagina [20]. It is possible that increased inflammation in the neovagina may predispose to higher STI risk, but larger studies are needed.

Transgender women who have undergone genital surgery may continue to practise both receptive anal and receptive neovaginal sex; some transgender men also report engaging in receptive anal sex with other male partners [12,13]. Unprotected receptive anal sex confers high risk for HIV acquisition compared to other sex acts, given trauma to the anal mucosa, but little is known regarding the risk of unprotected neovaginal sex [21]. For MSM, the US CDC 2015 Sexually Transmitted Diseases Treatment Guidelines recommend a minimum of annual testing for gonorrhoea and chlamydia rectally in men who have had receptive anal intercourse during the previous year, urethral testing for gonorrhoea and chlamydia in men who have had insertive anal intercourse during the previous year, and pharyngeal testing for gonorrhoea in men who have had receptive oral intercourse in the previous year [22]. In addition, a minimum of annual testing for HIV and syphilis should be conducted. There is no published guidance on testing intervals or sites of testing for STIs among TG persons, but the guidelines urge providers to assess risk based on current anatomy and sexual behaviour. Urgent research is needed to further characterise the rates of gonorrhoea and chlamydia in different anatomical sites for TG people in order to provide guidance on testing intervals, sites of testing, and appropriate methods of sampling to detect STIs in this population.

Social and behavioural factors affecting TG individuals across the HIV care continuum

Certain psychosocial conditions, including depression, anxiety, suicidal ideation, substance abuse and violence, are highly prevalent within TG populations [23–28]. In addition, TG individuals have decreased access to healthcare and regularly face gender-based discrimination [29–32]. Barriers to healthcare include lack of providers who are sufficiently knowledgeable about transgender healthcare, financial barriers, discrimination, lack of cultural competence by providers, and health systems barriers [24]. Stigma and discrimination occur regularly, even in countries known to be more tolerant of TG communities, such as Thailand [33,34]. Taken together, these factors contribute to HIV and STI vulnerabilities at multiple levels for TG individuals, and may help to explain the high prevalence of HIV in TG populations.

Information on correlates of testing for HIV and STI, how transgender persons access HIV or other medications, and factors impacting medication adherence are urgently needed, particularly in the Global South where the burden of HIV infection is greatest. Antiretroviral adherence for HIV-positive transgender women was lower than non-transgender men and women in a US-based sample, and TGW were less likely to achieve viral suppression in this study [35]. Related to this is social and behavioural research that provides important contextual insights for preventive interventions. Ethnographic studies are needed to understand how some persons may perceive, rationalise, or even produce or reproduce risks. For example, an ethnography found that kathoeis (Thai transgender women) regularly – as part of their everyday life – get together with one another for injection parties, injecting everything from vitamin C to placenta to hormones without medical supervision in the 'pursuit of beauty' [36]. In this example, the transgender women perceive risk as identification by authorities rather than seeing the behaviours as risks in themselves. Knowing this, public health practitioners can better design harm-reduction approaches to decrease 'risks'.

Fillers: illicit injections with risk

Fillers are synthetic, injectable products that allow for feminisation of various areas of the body including face, hips, buttocks and breasts. Fillers have also been used to treat HIV-related lipodystrophy occurring with older generations of antiretroviral therapy such as stavudine. Use of fillers by TGW has ranged from 16.7% in a San Francisco-based sample to a high of 65% in a sample of Thai TG individuals [37,38].

Although liquid injectable silicone used for cosmetic purposes is sold, and injections can be performed by qualified health practitioners in countries like the United States, multiple studies have noted that many TGW engage in illicit injections of other substances purported to be medical grade silicone, including industrial silicone, olive oil, petroleum jelly, liquid paraffin, tyre sealant and automobile transmission fluid, with volumes ranging from two ounces to up to 8 litres having been reported [39–41]. While illicit injections are often more accessible and affordable, they may come with substantive risk. Allergic reactions or infections related to injecting foreign material have been described in the literature, including cellulitis, lymphadenitis and scarring. In some cases, large-volume injection has led to acute pulmonary haemorrhage, pneumonitis, multi-organ failure and death [39–41].

In cross-sectional studies of transwomen and fillers, most have reported no association between filler use and HIV [37,38]. However, if injections are not performed in a sterile manner or the injection equipment is contaminated, transmission of blood-borne infections, including HIV, hepatitis B and hepatitis C may occur. Although not yet studied, it is possible that chronic inflammation secondary to filler use could exacerbate the clinical complications of HIV infection, as soluble and cellular markers of inflammation in HIV-infected individuals have been associated with cardiovascular disease, depression, neurocognitive impairment, metabolic abnormalities and increased mortality [42–44].

Surgery

Transgender people may undergo a variety of surgical procedures to affirm their gender identities. Major categories and procedures

Table 1. Gender-affirming non-hormonal medical and surgical procedures

	Head and neck	Chest/breast	Genital removal	Genital construction
Transgender men (TGM)/ female-to-male (FTM)	Liposuction	Mastectomy or breast reduction Pectoral implants	Hysterectomy Salpingo-oophorectomy Vaginectomy	Phalloplasty Scrotoplasty Testicular implants
Transgender women (TGW)/ male-to-female (MTF)	Rhinoplasty Reduction thyroid chondroplasty	Mammoplasty • Silicone implants • Saline implants • Injection of fillers	Orchiectomy Penectomy	Vaginoplasty Clitoroplasty Labiaplasty

Table 2. Anti-androgens

Anti-androgen	Class	Mechanism of action	Route of administration	Risks
Spironolactone	Antihypertensive	Inhibits testosterone secretion Blocks androgen binding to androgen receptor	Oral	Hyperkalaemia Hypotension
Finasteride, dutasteride	5-alpha reductase inhibitor	Blocks conversion of testosterone to 5-alpha-dihydrotestosterone	Oral	
Goserelin	Gonadotropin-releasing hormone (GnRH) agonist	Blocks GnRH receptor Blocks release of follicle stimulating hormone (FSH) and luteinising hormone (LH)	Injectable, implants	
Cyproterone acetate (CPA)	Progestogen, anti-androgen	Progesterone receptor agonist Glucocorticoid receptor antagonist 21-hydroxylase inhibitor	Oral	Hepatotoxicity Adrenal insufficiency with abrupt withdrawal Depression

are listed in Table 1. Many transgender men may not undergo genital construction surgery as creation of a phallus may require multiple procedures and complications such as urinary stenosis, fistula formation and necrosis of the microphallus may occur. In TG women, vaginoplasty aims to create a functional vagina while maintaining sexual sensation, and can be accomplished through a variety of surgical techniques, including penile skin inversion, sigmoidal transplant, and free skin grafts to line the neovagina [45,46]. Postoperative complications described following creation of the neovagina include necrosis of the vagina and labia, fistulas from the bladder or bowel into the vagina, stenosis of the urethra, and vaginas that are either too short or too small for coitus [45]. In addition, as the neovagina is prone to stenosis, TGW who have had creation of a neovagina must practise regular dilatation or penetrative sex to keep the neovagina open.

The impact of different surgical techniques on construction of the neovagina may impact HIV acquisition, although this has yet to be studied. In a study of neovaginal versus rectal secretions in transgendered women, IgG and IgA antibodies were detected in neovaginal secretions, but at lower total levels than in rectal secretions from the same individuals. However, IgG to IgA ratios were higher in neovaginal versus rectal secretions (N Karasavvas, personal communication). Use of the foreskin versus sigmoidal tissue or skin grafts may create differences in the immunological microenvironment at the site of HIV exposure in those transgendered women who practise receptive neovaginal sex.

Hormonal therapy

Goals of hormonal therapy in TGW include suppression of endogenous testosterone production or reduction of active forms of testosterone to minimise secondary sex characteristics generally associated with males and administration of exogenous oestrogen to increase female characteristics. If hormones are started after a person has gone through puberty, a combination of anti-androgens and oestrogen is likely to be needed to maximise feminisation. Expected physical changes may take up to 2 years, and include body fat redistribution, decreased muscle mass, decreased spontaneous erections, decreased testicular volume and sperm production, thinning and slowed growth of body and facial hair, and increased breast growth [45–48]. In TGM, testosterone administration through various routes (oral, intradermal, intramuscular) can increase masculine characteristics such as deepening of the voice, and reduce some female secondary sex characteristics such as suppression of menses; vaginal atrophy may also occur [47,49]. Risks of testosterone administration in TGM include polycythaemia, exacerbation of lipid abnormalities, and decreased bone density, which can be particularly pronounced following oophorectomy [47,50–53]. Although testosterone is associated with an increased number of cardiovascular events such as stroke and myocardial infarction in men, it is unclear whether this is also true in TGW [54,55]. Although various regimens and combinations have been described, there have been no randomised clinical trials comparing safety and efficacy of hormonal regimens [48,51].

Anti-androgens either reduce endogenous levels of testosterone or decrease testosterone activity. The benefit of anti-androgen administration is twofold: (1) the reduction in testosterone helps minimise masculine characteristics; and (2) as testosterone is decreased, the levels of exogenous oestrogen administration required for feminisation are also decreased. This decreases risks associated with long-term, high-dose oestrogen use. Table 2 details anti-androgens that are commonly available.

Oestrogens fall into two main categories, progestins and oestrogens. Progestin use continues to be controversial, with some clinicians advocating its use for breast development. However, others believe that the potential risks, including depression, weight gain, hypertriglyceridaemia, and likely increased cardiovascular and breast cancer risk, outweigh any benefits they may provide.

Oestrogens may be administered orally, sublingually, transdermally or parenterally. All forms of oestrogen increase the risk of venous thromboembolism, but certain forms of oestrogen, including ethinyl oestradiol and conjugated equine oestrogen, are not recommended for use in transgender women due to increased venous thromboembolic (VTE) risk compared to other forms [51]. Increased age (above 40), tobacco use, and prior history of hypercoagulable states further elevates VTE risk. For TG women with high baseline risk for VTE, transdermal oestrogen is recommended as its use confers less VTE risk than oral forms of oestradiol.

Other risks associated with oral oestrogen use include increased cardiovascular and cerebrovascular events in patients over 50 with underlying risk factors, hypertriglyceridaemia and other lipid abnormalities, potential hepatotoxicity, and cholelithiasis. For TGW who are co-infected with HIV, and are taking both antiretroviral therapy and hormonal therapy, drug–drug interactions and adverse effects need to be considered.

Effects of hormonal therapy on antiretroviral therapy

For HIV-positive transgender women who take hormones as part of gender-affirming medical therapy, drug–drug interactions with antiretroviral therapy may impact the efficacy of both antiretroviral therapy and hormonal therapy. No studies focused on the interaction of hormone therapy with antiretroviral therapy in transgendered women have been published. However, there has

been an increasing number of studies detailing interactions between oral contraceptives and antiretrovirals in HIV-positive women. Although a large range of oral contraceptive pills is available globally, the two broad categories are combination pills (generally ethinyl oestradiol co-formulated with progesterone), and progesterone-only pills. Ethinyl oestradiol is generally not recommended for transgender women due to increased risk of thromboembolism. However, many transgender women only have access to hormonal therapy through off-label use of oral contraceptive pills that are purchased without a prescription or guidance from a healthcare provider and may take doses of between three and four times those given for oral contraceptive purposes. This may increase known drug–drug interactions between hormonal therapy and antiretrovirals [29,38,46].

Significant drug–drug interactions exist between ethinyl oestradiol and two main classes of antiretroviral medications: non-nucleoside reverse transcriptase inhibitors (NNRTIs) and ritonavir-boosted protease inhibitors (PIs), largely due to the metabolism of hormonal contraception by the cytochrome P450 system (CYP3A4) [56]. Little research has focused on interactions between nucleoside reverse transcriptase inhibitors (NRTIs) and oral contraception, as NRTIs are not metabolised by the CYP450 system. Small pharmacokinetic studies have noted no interaction between ethinyl oestradiol administered as oral contraception and tenofovir [57]. However, one *in vitro* study conducted in peripheral blood lymphocyte cultures showed an inhibition of stavudine by beta-oestradiol [58].

Among NNRTIs, nevirapine is an inducer of CYP3A4 and can potentially decrease levels of hormonal contraception; the package insert for nevirapine lists a significant interaction between nevirapine and oral contraception. However, the published literature shows mixed results, with some small pharmacokinetic studies showing reduction of oestrogen levels with concomitant use of nevirapine [59,60]. A recent cohort study comparing HIV-positive women who were ART naïve and taking oral contraception to those who were taking nevirapine-containing regimens with oral contraception did not show a reduction in contraceptive effectiveness or ovulation rates as measured by weekly progesterone levels [61]. Efavirenz, often used as first-line therapy in resource-limited settings, is also a CYP3A4 inducer. A pharmacokinetic study, where HIV-positive women took both oral contraceptives containing ethinyl oestradiol and efavirenz, showed that levels of both progesterone and efavirenz were decreased below therapeutic levels when compared to nevirapine [59].

The newer NNRTIs etravirine and rilpivirine do not appear to affect levels of oestrogen or progesterone when co-administered with oral contraception and could be an alternative for HIV-positive transgender women on hormonal therapy [62,63].

Ritonavir, a CYP3A4 inhibitor, is generally co-administered with protease inhibitors to boost levels and maximise drug efficacy. By decreasing metabolism through CYP3A4, the potential for significant interactions exists by increasing levels of medications metabolised through this pathway. Conversely, many protease inhibitors cause oestrogen levels to decrease, thereby making it difficult to determine how overall oestrogen levels will be impacted in individual patients. Specifically, boosted atazanavir, boosted lopinavir, and boosted darunavir have all been shown to decrease oestrogen levels in healthy volunteers when taken with ethinyl oestradiol, and concomitant administration of oral contraception with these medications is not recommended [64–67]. No interactions have been noted between oral contraceptives and the integrase inhibitors raltegravir and dolutegravir or with the CCR5 entry inhibitor maraviroc [68–70].

For HIV-positive TGW, the potential reduction in oestrogen by NNRTIs and boosted protease inhibitors may lead to decreased antiretroviral medication adherence or self-prescribed increases in exogenous oestrogen administration [71]. Clinicians treating HIV-positive TGW should take an accurate history of hormonal therapy, including medication dosages, and assess for interactions with antiretroviral therapy to facilitate maintenance of feminisation while also suppressing viral replication.

Effects of hormonal therapy on pre-exposure prophylaxis (PrEP)

In a subgroup analysis of transgendered women in the iPreX trial comparing tenofovir-emtricitabine to placebo for HIV prevention, the authors found that in comparison to MSM, transgendered women randomised to take daily PrEP were less likely to have detectable levels of tenofovir in their blood [72]. Low adherence was likely to have contributed to the reported hazard ratio of 1.1 for HIV seroconversion in TGW randomised to take PrEP compared to placebo; in all TGW who seroconverted, tenofovir levels in the blood were undetectable at the seroconversion visit. TGW in this trial were more likely than MSM to report increased risk behaviour, including transactional sex, unprotected anal intercourse, and greater number of sex partners. Unfortunately, unlike the MSM included in the study who were more likely to be adherent to PrEP if they engaged in more risk behaviours, TGW's self-reported HIV risk behaviour did not predict adherence to PrEP.

Pharmacokinetic studies have shown that tenofovir diphosphate concentrations are 100-fold higher in colonic *vs* vaginal tissue; however, exogenous oestrogen could affect this concentration as it has been shown to regulate tenofovir diphosphate and creatine kinase, which are responsible for phosphorylation of tenofovir in colonic tissue [71,73,74]. Future studies need to establish whether TGW taking exogenous hormones need to take different PrEP dosing compared to MSM.

Hormonal effects on HIV acquisition and progression

The effect of exogenous androgens in HIV has been reported in the context of treatment of hypogonadism in HIV-infected men and women. In HIV-infected men, supraphysiological testosterone replacement therapy has been associated with improved mental health, quality of life scores and fat-free mass [75]. In HIV-infected women, low-dose testosterone therapy has resulted in significant improvements in body composition, bone mineral density and quality of life indices [53,76]. For TGM who take testosterone, vaginal thinning and atrophy often occur, and could predispose to increased HIV acquisition through vaginal mucosa depending on sexual behaviour.

While systematic studies on the effects of exogenous hormones on HIV acquisition in transgendered populations have not been reported, effects of oestrogen and progesterone have been studied *in vitro* or in the context of hormonal contraception. Figure 1 summarises the effect of oestrogen and progesterone on the vaginal epithelium. Progesterone is known to increase HIV susceptibility through three separate mechanisms. First, it induces thinning of HIV vaginal epithelium, which allows for greater mechanical disruption of the mucosal barrier during intercourse or in an inflammatory state such as a concurrent STI. Second, medroxyprogesterone acetate inhibits cytokine and chemokine secretion from T cells, vaginal mononuclear cells, macrophages and dendritic cells, effectively blunting the innate and adaptive immune response [77]. Third, use of progestin-only contraceptives increases expression of CCR5 co-receptors on CD4+ T cells in the

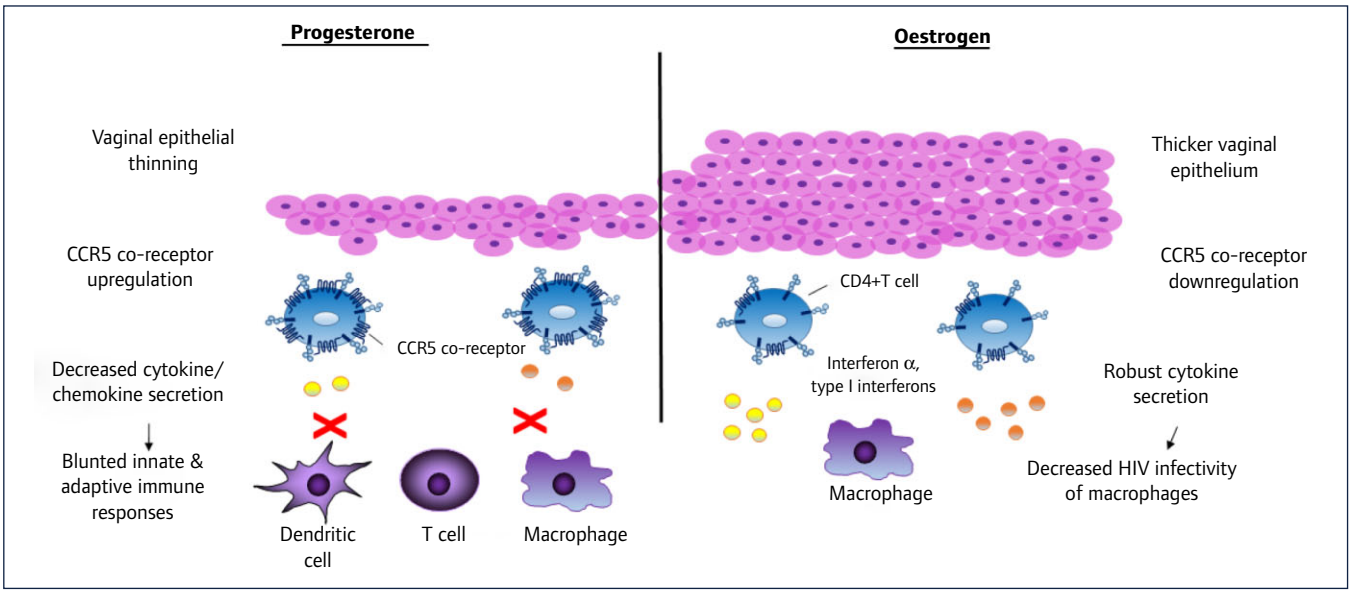

Figure 1. Effects of oestrogen and progesterone on vaginal HIV infection.

peripheral blood and the vaginal mucosa, thereby increasing the availability of target cells for HIV infection [78,79]. However, the effect of clinical high-dose progestin on risk of HIV acquisition remains controversial, as large systematic reviews have not revealed robust evidence to warrant policy recommendations against their use, so more definitive evidence is needed [80,81].

Conversely, oestrogen may have a protective effect through reduction of CCR5 expression, induction of interferon-alpha, and other entry-mediated and transcriptional mechanisms [82–84]. Both hormones can also influence expression of integrin alpha 4 beta 7 on CD4+ T cells, which is a gut homing marker associated with increased susceptibility to HIV infection. In a study of the female genital tracts in macaques, hormonal influence varied by anatomic location, as upregulation of alpha 4 beta 7 differed in the endocervical and vaginal tissue [85]. Hormonal effects on the neovagina and rectum/anus may therefore differ, and have yet to be characterised. Finally, the endogenous hormonal state can have a direct role on HIV transcription within cells. In a study by Asin *et al.*, high concentrations of oestradiol and progesterone directly reduced activation of the HIV long terminal repeat (LTR), corresponding to decreased HIV-1 replication *in vitro*, whereas low concentrations increased HIV-LTR activation, resulting in increased HIV-1 replication [86]. Because transgender women often use much higher doses of hormones than those used for contraception by natal women, further research is needed to optimise regimens that may reduce risk for HIV and other medical complications.

Conclusions

Although TG people are among the most at-risk populations for HIV acquisition globally, little is known regarding the biological mechanisms of HIV transmission, including the effect of hormonal therapy, at various anatomical locations. In addition, data on social determinants of risk for STI and HIV acquisition among TG people is limited. For HIV-positive TG, the safety and efficacy of concomitant hormonal therapy and antiretroviral therapy is an important treatment concern. Urgent attention is needed to increase access to TG-specific healthcare and to optimise HIV prevention and treatment programmes among TG people.

Acknowledgements

The authors thank Nittaya Phanupak for guidance. The opinions expressed herein are those of the authors and should not be construed as representing the views of the US Department of Defense or the Department of the Army.

Funding

This work was supported by intramural funding from the US Army Medical Research and Materiel Command (MRMC) and from the National Institutes of Allergy and Infectious Diseases (Y1-AI-2642-16) via a cooperative agreement between MRMC and the Henry M Jackson Foundation (W81XWH-07-2-0067).

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