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HIV-Infected Transgender Women Frequently Take Antiretroviral Therapy and/or Feminizing Hormone Therapy Differently Than Prescribed Due to Drug-Drug Interaction Concerns

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Abstract

Purpose: Both hormone therapy (HT) and antiretroviral therapy (ART) can be lifesaving for HIV-infected (HIV+) transgender women (TW), but both have side effects and potential drug-drug interactions (DDI). We assessed how concerns for HT-ART interactions affected treatment adherence.

Methods: A cross-sectional survey of 87 TW in Los Angeles, CA.

Results: Fifty-four percent were HIV-infected and 69% used HT. Only 49% of HIV+ TW discussed ART-HT DDI with their provider; 40% reported not taking ART (12%), HT (12%), or both (16%) as directed due to DDI concerns.

Conclusion: This imperfect use and limited communication suggests a need for improved HT-ART integration.

Introduction

Feminizing hormone therapy (HT) is used to harmonize gender identity and secondary sex characteristics for transgender women (TW), and antiretroviral therapy (ART) is essential for HIV-infected individuals; both therapies can be lifesaving.[1] Despite a 34-fold higher likelihood of HIV infection among TW in the U.S. compared to the general population,[2] transgender people (approximately 0.4-0.6% of the U.S. population[3,4]) have comparatively low healthcare utilization rates[5] and may seek gender-affirming therapies (including HT and body modification services) outside of traditional, supervised medical settings.[6,7] Both HT and ART have potential side effects, and drug-drug interactions (DDI) may exist between some ART medications (such as non-nucleoside reverse transcriptase inhibitors [NNRTI] and protease inhibitors [PIs]) and HT (particularly ethinyl estradiol),[8] making unsupervised or uncoordinated HT and ART use potentially risky for TW.

However, limited data exist that address knowledge and consequences of ART and/or HT side effects and ART-HT DDIs among TW. Qualitative studies have identified fear among TW that ART limits the effect of hormones.[9] However, few studies have explored levels of adherence to either regimen resulting from these fears about interaction. Using survey data from a cross-sectional, community-based study, we assessed knowledge of and concern about HT and ART side effects and DDIs, including effects on treatment adherence, among HIV-infected and HIV-uninfected TW in Los Angeles, California.

Methods

Participants

From March-July 2016, self-identified TW were recruited from APAIT, a community-based AIDS service organization serving diverse communities in Los Angeles, CA, for a cross-sectional, pilot project to determine differences in biomarkers of inflammation and cardiovascular risk among HIV-infected TW, HIV-uninfected TW, and age- and race-matched HIV-infected and HIV-uninfected control cisgender men. For this trial, eligibility criteria included being assigned male sex at birth and age ≥ 18 years (or 17 years with parental consent). The study sought to enroll at least 40 participants per arm (total n=160, including a minimum of 80 TW). In our current analysis, we further restricted the sample to participants self-identifying as a TW.

Procedures

At the time of questionnaire administration, blood was collected for the parent study's assessment of cardiovascular risk, for which HIV-infected TW were required to be on ART and have HIV-1 RNA<50 copies/mL. Eligible participants self-reported sociodemographics, medical history, healthcare access, and knowledge of ART and HT side effects and ART-HT DDIs. HIV-infected participants were asked if concern about ART-HT DDIs had prevented them from taking either/both therapies as prescribed.

Consent/Permissions

The study was approved by the Institutional Review Board of the University of California, Los Angeles. Written informed consent was obtained from all study participants prior to performance of study procedures.

Data Analysis

The main outcome for this analysis was self-reported history of HT or ART use differently than prescribed due to concerns about ART-HT DDI (HIV-infected TW only), which we constructed as a dichotomous variable. We calculated descriptive summaries of participant characteristics, and self-reported beliefs and healthcare experiences. Significance was defined as $p<0.05$. All analyses were exploratory using chi-square and t-test, without adjusting for multiple testing. Prevalence ratios were calculated using generalized linear models to estimate the associations of participant clinical or sociodemographic characteristics with our main outcome of imperfect use of HT and/or ART. All analyses were performed using Stata 14.0 (StataCorp, College Station, TX, USA).

Results

Eighty-seven TW were enrolled, 47 (54%) of whom were living with HIV and on ART. Participants were predominately Hispanic (62%), black (17%), or multiracial (13%), with a mean age of 45 (Table 1). In our sample, HIV-infected TW were slightly older than HIV-uninfected TW (48 years vs 43 years, p=0.03) and more likely to report substance use during the last 90 days (47% vs 25%, p=0.04). Median $CD4^+$ T lymphocyte count among HIV-infected TW was 555 cells/□L. ART regimens included nucleoside reverse transcriptase inhibitors (98%, including 79% with tenofovir and 23% with abacavir), integrase inhibitors (40%), PIs (32%) and NNRTIs (28%).

Most TW (77%) had a regular healthcare provider, and 64% were currently using feminizing HT. Eighty-six percent of insured TW reported that their insurance covers HT fully or in part. Twenty-five percent of HT users (HIV-uninfected 13%, HIV-infected 34%, p=0.07) were

accessing HT outside of the medical system and obtaining non-prescription HT from: the street (9%), a friend (4%), a pharmacy without a prescription (4%), multiple (7%), or other (2%) sources. TW took HT in the form of pill only (40%), injection only (28%), patch only (2%), or multiple delivery routes (30%), and took estrogen (67%), progesterone (2%), anti-androgen (4%) or combination (26%) HT. While most (78%) took their hormones regularly, those that did not commonly reported fears of side effects (31%), financial difficulties (23%), limited access to a prescribing clinician (8%), multiple (31%), or other challenges (8%)[1] as barriers to taking HT as directed.

Only 68% of TW (HIV-uninfected 78%, HIV-infected 61%, p=0.12) discussed potential HT side effects with their provider, including the risks of blood clots (71%), heart attacks (69%), stroke (55%), or other side effects (24%). Fifty-seven percent of HIV-infected TW reported concern for ART-HT interactions, and 40% cited this concern as a reason for not taking ART (12%), HT (12%), or both (16%) as directed, although only 49% reported discussing these concerns with their provider. Of note, taking ART differently than prescribed was not associated with significantly lower $CD4^+$ T lymphocyte counts (not as directed: 493 cells/μL vs as directed: 563 cells/μL, p=0.45) among this group with an undetectable plasma HIV-1 RNA.

In bivariate models, no clinical or sociodemographic factors were significantly associated with our main outcome of taking HT or ART differently than prescribed, although our outcome frequency was small (n=17). We observed suggested associations between this outcome and recent (last 90 days) substance use (crude Prevalence Ratio [cPR] 1.92, 95% confidence interval [CI] 0.87–4.25, p=0.10) or alcohol use (cPR 1.92, 95% CI 0.87–4.25, p=0.10). We also observed a trend that current HT users were more likely to take HT and/or ART as directed (cPR 1.81, 95% CI 0.90–3.64, p=0.10).

[1] Percentages may not total 100 due to rounding.

Discussion

In this cohort of 87 TW in Los Angeles, we noted high rates of concern about ART-HT DDIs and side effects, but insufficient communication on this topic with healthcare providers. We also found high rates of taking HT, ART, or both differently than prescribed because of these concerns. These results support previous research demonstrating TW's concern that adverse ART-HRT DDIs delay the desired effects of hormones.[9] Our findings are concerning for numerous reasons: for HIV-infected TW, sub-optimal ART adherence increases the risk of developing ART resistance and virologic failure.[10–13] Sub-optimal adherence also increases HIV transmission risk to sexual partners during periods of uncontrolled viremia,[14–16] and possibly increases risk of transmission of drug-resistant virus. While incompletely studied, decreased HT adherence or intermittent use may cause sub-optimal feminization and/or increased risk of side effects or adverse outcomes of HT.[17]

These data affirm the importance of generating evidence-based data on ART-HT DDIs, as well as educating patients and providers on perceived versus actual risks. These findings also extend to ART for pre-exposure prophylaxis (PrEP) to prevent HIV acquisition, as TW may have concerns about possible DDIs between PrEP and feminizing HT.[18]

In looking at the evidence for DDIs, published studies predominantly address HT-ART DDI between ART (typically NNRTI/PI-based regimens) and ethinyl estradiol, a synthetic estrogen used in contraception but not recommended for feminizing HT due to increased thrombotic risk.[19] A recent systematic review found that the most noteworthy interactions occurred for cisgender women using NNRTIs, and particularly efavirenz, although these outcomes were predominantly pharmacokinetic in nature and assessed interactions at doses used for

contraception rather than feminizing HT.[20] No studies have specifically addressed interactions between ART and the estrogen regimens/doses used for feminizing HT. Thus, there are insufficient data to fully understand the risk of DDIs between ART and HT for TW.[21] However, even relatively minor or rare interactions warrant attention, as both HT and ART may be long-term or lifelong medications. In addition, HIV-infected TW have a baseline cardiovascular disease risk influenced by both traditional risk factors (smoking, obesity, etc.) and HIV-specific risk factors (independent of ART),[22,23] so the additive risk of ART/HT DDIs is worth defining. Evidence-based guidance for feminizing HT for TW living with HIV or taking PrEP is needed.

Considering the recent findings that 1) TW may have sub-optimal ART adherence,[24,25] and 2) higher HT adherence and access to other transgender-specific healthcare factors is associated with higher ART adherence,[26] opportunities exist to utilize this synergy to ensure greater participation in HIV care by TW. Given our results that current HT users may report higher rates of HT or ART adherence, our findings support previous data[25,26] suggesting that gender-affirming healthcare, including clinical integration of HT and ART services, may improve engagement in HIV care for TW.

Care for TW can also be improved through active engagement by healthcare providers and both professional and community-based organizations. While more data are needed before providing specific clinical recommendations to providers on preferred HT and ART regimens/doses for HIV-infected TW, professional organizations (such as the World Professional Association for Transgender Health) could help by issuing expert consensus statements. Clinicians serving transgender patients should be attentive to possible HT-ART DDI and address them similarly to other DDIs, if such concerns arise.

Several limitations to our pilot study exist. First, our small sample size, although common among studies of TW, limits generalizability to larger populations of TW. Replication of this study with participants of more varied ethnicities and ages may be necessary as our sample was predominantly Hispanic with a mean age of 45, possibly limiting generalizability to other groups. In addition, the study site was a community center that did not provide medical care. Therefore, we were unable to capture whether the participant's hormones (when prescribed and not acquired on the black market) were provided within an informed consent framework, a model of HT provision that addresses the medical and social benefits and risks of HT, including potential side effects.

The parent study, a community-based assessment, was not focused exclusively on HIV-infected TW, and therefore did not address other topics that may influence ART adherence, such as stigma or discrimination. Finally, HIV-infected TW were required to have undetectable plasma HIV-1 RNA, which limits our ability to examine adherence. However, our racially diverse sample of TW and the limited number of studies addressing transgender-specific issues in HIV care make these data an important contribution to the field.

Conclusion

Our data suggest a need for comprehensive care programs for HIV-infected TW. Future research will address ART-HT DDIs and side effect profiles for TW, including cardiovascular disease risk, and investigate approaches to mitigate risk. An improved understanding of these interactions will likely improve engagement and retention in healthcare for TW, and may increase clinician comfort discussing TW's concerns regarding ART-HT side effects and DDIs.

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Author Disclosure Statement

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Table 1: Demographics and Self-Reported Treatment Regimens of Transgender Women (n=87); Los Angeles, CA; 2016[a]

	All (n=87)	HIV Serostatus	
		HIV-uninfected (n=40)	HIV-infected (n=47)
Age (years)*	45.3 (SD 10.8)	42.6 (SD 11.6)	47.5 (SD 9.7)
Living with HIV	47 (54%)	N/A	N/A
Race/Ethnicity			
Hispanic	54 (62%)	26 (65%)	28 (60%)
Black/African American	15 (17%)	5 (13%)	10 (21%)
Multiracial	11 (13%)	3 (8%)	8 (17%)
Asian, Alaskan Native/American Indian, White, Other	7 (8%)	6 (15%)	1 (2%)
Health Insurance Coverage			
MediCal (California's Medicaid Program)	39 (45%)	14 (35%)	25 (53%)
Medicare	5 (6%)	4 (10%)	1 (2%)
Dual MediCal-Medicare coverage or Private plan	20 (23%)	9 (23%)	11 (23%)
No healthcare insurance	23 (26%)	13 (33%)	10 (21%)
Feminizing HT Use			
Current use	56 (64%)	25 (63%)	31 (66%)
HT acquisition outside of medical system (n=55; n=23 HIV- and n=32 HIV+)	14 (25%)	3 (13%)	11 (34%)
Planning future use	17 (20%)	10 (25%)	7 (15%)
No current or planned use	14 (16%)	5 (13%)	9 (19%)
Substance Use (last 90 days)*	32 (37%)	10 (25%)	22 (47%)
Alcohol Use (last 90 day)	43 (49%)	19 (48%)	24 (51%)
Current Tobacco Use	31 (36%)	12 (30%)	19 (40%)
Past Tobacco Use	14 (16%)	9 (23%)	5 (11%)
Unsupervised Injections for Body Modification (n=81; n=38 HIV- and n=43 HIV+)	11 (14%)	5 (13%)	6 (14%)
Antiretroviral Therapy			
NRTI	-	1 (2.5%) [PrEP]	46 (98%)
Tenofovir[b]	-	1 (2.5%)	37 (79%)
Abacavir[b]	-	-	11 (23%)
NNRTI	-	-	13 (28%)
PI	-	-	15 (32%)
INSTI	-	-	19 (40%)
Current $CD4^+$ T lymphocyte count (cells/μL, median [IQR], n=44)	-	-	555 (320, 763)
HT and/or ART taken differently than prescribed due to DDI concern (n=43)	-	-	17 (40%)
ART (only) taken differently than prescribed due to DDI concern	-	-	5 (12%)
HT (only) taken differently than prescribed due to DDI concern	-	-	5 (12%)
Both HT and ART taken differently than prescribed due to DDI concern			7 (16%)

[a]Mean (standard deviation) or number (percent), unless specified. Percentages may not total 100 due to rounding.

*$p < 0.05$ for HIV-infected compared with HIV-uninfected transgender women

[b]Participants were able to report therapy with both tenofovir and abacavir.

HT, hormone therapy; ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; PrEP, pre-exposure prophylaxis; NNRTI, non-NRTI; PI, protease inhibitor; INSTI, integrase inhibitor; DDI, drug-drug interactions.