EDITORIAL COMMENT

Striving to characterize endocrine–metabolic and immune health risks among transgender women with HIV

Markella V. Zanni and Steven K. Grinspoon

See related paper on page 855

AIDS 2019, **33**:919–922

Keywords: HIV, immune, metabolic, transgender, women

HIV prevalence among transgender women has been estimated to range from 17.7% in low-income and middle-income countries [1] to 27.7% in high-income countries like the United States [2]. Sex-affirming hormonal therapy (including testosterone suppression and estrogen administration) represents an important component of comprehensive clinical care for transgender women [3], irrespective of HIV status. Importantly, studies assessing endocrine–metabolic and immune effects of sex-affirming hormonal therapy among transgender women (HIV status not reported) have yielded mixed results [4,5]. Among transgender women with HIV, a unique endocrine–metabolic and immune risk-profile may be expected, related to intertwined effects of sex-affirming hormonal therapy, chronic HIV infection, and combined antiretroviral therapy (ART). Improved understanding of specific endocrine–metabolic and immune health risks among transgender women with HIV will facilitate the development and implementation of rational strategies to maximize cardiometabolic health in this population.

In this issue of *AIDS*, Pommier *et al.* [6] present data from the MATTHIS-IMEA 045 study, comparing metabolic, hormonal, and immune parameters among transgender women with HIV and cisgender men with HIV. Participants prospectively recruited to this study included 100 transgender women with HIV and 192 age-matched cisgender men with HIV all receiving care at the Infectious Diseases Department of the Bichat Claude-Bernard University Hospital in Paris, France. All participants, recruited between 2013 and 2015, underwent history and physical examination, as well as fasting blood sampling for metabolic, hormonal, and immune parameters. Pommier *et al.* [6] primarily compared the prevalence of metabolic syndrome among transgender women with HIV and cisgender men with HIV. In addition, Pommier *et al.* [6] performed between-group comparisons of hormonal parameters reflecting adrenal/thyroid status, HIV-specific parameters (viral load, $CD4^+$ T-cell count), and ART bioavailability measurements. HIV-specific parameters and ART bioavailability measurements were also compared *within* the studied group of transgender women with HIV – specifically, among those reporting vs. not reporting present adherence to sex-affirming hormonal therapy.

Primary and secondary data analyses by Pommier *et al.* [6] yielded three key observations pertaining to the metabolic, endocrine, and immune health status of their studied cohort of transgender women with HIV vs. cisgender men with HIV. First, there were no statistically significant between-group differences in the prevalence of metabolic syndrome, and indeed, transgender women with HIV demonstrated a lower frequency of select metabolic risk parameters (e.g., elevated blood pressure, elevated fasting blood glucose). Second, transgender women with HIV demonstrated a higher frequency of

Program in Nutritional Metabolism, Division of Endocrinology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA.

Correspondence to Steven K. Grinspoon, MD, Program in Nutritional Metabolism, Division of Endocrinology, Massachusetts General Hospital, 5 Longfellow Place, Room 207, Boston, MA 02114, USA.

Tel: +1 617 724 9109; fax: +1 617 724 8998; e-mail: sgrinspoon@mgh.harvard.edu

Received: 19 December 2018; accepted: 2 January 2019.

DOI:10.1097/QAD.0000000000002153

abnormalities in morning cortisol levels and in levels of thyrotropin (TSH) as compared with cisgender men with HIV. Third, HIV-specific parameters (viral load, $CD4^+$ T-cell count) and ART bioavailability measures were comparable among transgender women with HIV and cisgender men with HIV. Moreover, these parameters and measures were also comparable among transgender women with HIV reporting vs. not reporting present adherence to sex-affirming hormonal therapy.

The findings reported by Pommier *et al.* [6] on cardiometabolic risk factors among studied transgender women with HIV (vs. cisgender men with HIV) may not be widely generalizable to the broader population of transgender women with HIV. Among transgender women with HIV who elected to take part in this prospective research study, 97% reported ART adherence and 81% evidenced viral suppression. By contrast, retrospective studies suggest markedly lower rates of ART adherence and viral suppression among population-based samples of transgender women with HIV [7,8]. For example, Mizuno *et al.* [7] analyzed data from an HIV surveillance system designed to yield reliable estimates representing the demographic/clinical characteristics of US people with HIV (PHIV). In this study, 78.4% of transgender women with HIV-reported ART adherence and only 50.8% evidenced durable viral suppression [7]. Indeed, several studies have shown that stigma impedes access to and utilization of quality healthcare both among transgender individuals [9] and PHIV [10]. How might ART adherence in the studied cohort of transgender women with HIV be expected to influence measured cardiometabolic risk parameters? To begin, sustained ART adherence likely reduces cumulative exposure to HIV-associated systemic immune activation and inflammation [11], potentially protecting against the development of select cardiometabolic complications [12]. Second, ART adherence likely reflects robust engagement in clinical care, which could track with cardiometabolic preventive health counseling/therapy and cardiometabolic health-promoting behaviors. For these reasons, cardiometabolic risk may be expected to be heightened in a more population-representative sample of transgender women with HIV. These observations notwithstanding, the study by Pommier *et al.* [6] adds substantively to the medical literature, as few other studies to date have compared endocrine–metabolic and immune parameters among transgender women with HIV and cisgender men with HIV.

Findings on abnormal hypothalamic–pituitary–adrenal (HPA) axis hormones among transgender women with HIV in the study by Pommier *et al.* [6] deserve careful consideration. A higher proportion of studied transgender women with HIV vs. cisgender men with HIV were noted to have adrenal insufficiency as defined by morning cortisol levels less than 82 nmol/l. Determination of the cause of adrenal insufficiency relies on *paired* values of morning cortisol and adrenocorticotropic hormone (ACTH) – data which are not presented in this study. We do note that in multivariate modeling among the group of transgender women with HIV, probable adrenal insufficiency was associated with low levels of ACTH, pointing toward secondary or tertiary causes. Low cortisol among transgender women – a significant proportion of whom are on oral estrogens – represents a potentially unexpected finding, as oral estrogen administration results in increased levels of cortisol binding globulin and, in turn, cortisol levels [13]. Pommier *et al.* [6] speculate that among transgender women with HIV, there may be higher rates of intermittent, nondisclosed exogenous corticosteroid use, resulting in HPA axis suppression. Of note, other exogenous agents which may induce HPA axis suppression include cyproterone acetate [14], medroxyprogesterone acetate [15], and various opioids [16]. These considerations highlight that clinical providers should engage all patients in candid discussion about use of both prescribed and nonprescribed medicinal agents. Patients deemed to be at risk for HPA axis dysfunction should undergo formal assessment for adrenal insufficiency, which, if untreated, can be fatal – particularly in the context of intercurrent illness [17].

Pommier *et al.* [6] also make interesting observations regarding hypothalamic–pituitary–thyroid (HPT) axis hormones among transgender women with HIV. A higher proportion of transgender women with HIV vs. cisgender men with HIV were noted to have TSH levels more than 4 mUI/l. However, free T4 hormone (FT4) levels did not differ significantly between groups. Overall, an increased percentage of transgender women with HIV vs. cisgender men with HIV were noted to have elevated TSH levels coupled with normal FT4 levels, possibly consistent with subclinical primary hypothyroidism. Of note, no transgender woman with HIV and elevated TSH levels exhibited positive thyroid peroxidase-antibodies, which are typically correlated with Hashimoto's thyroiditis – a common cause of primary hypothyroidism. Pommier *et al.* [6] hypothesize that among transgender women with HIV (vs. cisgender men with HIV), differences in ART exposure may explain abnormal thyroid function tests. Indeed, previous studies suggest relationships between select antiretroviral therapeutics and measures of thyroid disfunction [18,19]. However, additional possible explanations for elevated TSH levels coupled with normal FT4 levels among transgender women with HIV abound. First, among cisgender women with HIV, use of oral estrogen-containing hormonal preparations has been associated with increased levels of thyroid binding globulin and mildly increased levels of TSH, but not with reduced levels of FT4 [20]. Second, among transgender women without HIV, antiandrogen therapy with cyproterone acetate has been shown to reduce the ratio of T3 (the bioactive form of thyroid hormone) to T4 [21], which might also

potentially prompt TSH levels to rise. Third, small studies have suggested a relationship between adrenal insufficiency and TSH excess [22,23]. Additional work is needed to fully elucidate relationships between prescribed and nonprescribed medications and both HPA axis and HPT axis function among transgender women with HIV.

Separately, Pommier *et al.* [6] note that ART bioavailability is comparable among their studied cohorts of transgender women with HIV reporting vs. not-reporting sex-affirming hormonal therapy. However, more work is required to test for possible drug–drug interactions between specific sex-affirming hormonal therapy regimens and specific antiretroviral therapeutics [24]. This type of rigorous research would help provide necessary reassurance for patients and providers alike – indeed, a previous study suggested that *perceptions* of drug–drug interactions between sex-affirming hormone therapy and ART can prompt medication nonadherence among transgender women with HIV [25]. Research is also needed to elucidate ways in which underlying HIV infection, select ART, and select sex-affirming hormonal therapy may each independently – or synergistically – promote a common pathophysiologic condition – for example, thrombosis [26–28]. Such work would facilitate informed, shared-decision-making amongst available options for antiretroviral care and sex-affirming hormonal therapy.

Characterizing endocrine–metabolic and immune health risks among transgender women with HIV represents an urgent research priority [29]. Work by Pommier *et al.* [6] highlights potential unrecognized health risks while also raising new questions. Clearly, key knowledge gaps remain. Additional research engaging the community of transgender women with HIV will help yield much-needed scientific evidence to guide the provision of quality healthcare. In parallel, systems-based improvements involving sex affirmation and healthcare access will be crucial [30]. Moreover, clinicians may benefit from dedicated training in the provision of culturally specific care for transgender women with HIV. Such training may be expected to facilitate relationships built on mutual respect and trust, nonjudgmental conversations about adherence with prescribed medication and use of nonprescription medication, and shared healthcare decision-making synthesizing patient perspectives and best available medical evidence.

Acknowledgements

M.V.Z. is the Principal Investigator of an Investigator-Initiated Grant from Gilead to her institution, unrelated to this article. S.K.G. has received research funding from Kowa Pharmaceutical, Gilead, Theratechnologies, and Navidea and has served as a consultant to Theratechnologies.

Conflicts of interest

There are no conflicts of interest.

References

1. Baral SD, Poteat T, Stromdahl S, Wirtz AL, Guadamuz TE, Beyrer C. **Worldwide burden of HIV in transgender women: a systematic review and meta-analysis.** *Lancet Infect Dis* 2013; **13**:214–222.
2. Herbst JH, Jacobs ED, Finlayson TJ, McKleroy VS, Neumann MS, Crepaz N. **Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review.** *AIDS Behav* 2008; **12**:1–17.
3. Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, *et al*. **Endocrine treatment of gender-dysphoric/gender-incongruent persons: an endocrine society clinical practice guideline.** *J Clin Endocrinol Metab* 2017; **102**:3869–3903.
4. Maraka S, Singh Ospina N, Rodriguez-Gutierrez R, Davidge-Pitts CJ, Nippoldt TB, Prokop LJ, Murad MH. **Sex steroids and cardiovascular outcomes in transgender individuals: a systematic review and meta-analysis.** *J Clin Endocrinol Metab* 2017; **102**:3914–3923.
5. Auer MK, Ebert T, Pietzner M, Defreyne J, Fuss J, Stalla GK, T'Sjoen G. **Effects of sex hormone treatment on the metabolic syndrome in transgender individuals: focus on metabolic cytokines.** *J Clin Endocrinol Metab* 2018; **103**:790–802.
6. Pommier J-D, Laouénan C, Michard F, Papot E, Urios P, Boutten A, *et al*. **Metabolic syndrome and endocrine status in HIV-infected transwomen.** *AIDS* 2019; **33**:855–865.
7. Mizuno Y, Frazier EL, Huang P, Skarbinski J. **Characteristics of transgender women living with HIV receiving medical care in the United States.** *LGBT Health* 2015; **2**:228–234.
8. Gogia S, Coromilas A, Regan S, Stone L, Fourman LT, Triant VA, *et al*. **Cardiovascular risk profile of transgender women with HIV: a US healthcare database study.** *J Acquir Immune Defic Syndr* 2018; **79**:e39–e41.
9. White Hughto JM, Reisner SL, Pachankis JE. **Transgender stigma and health: a critical review of stigma determinants, mechanisms, and interventions.** *Soc Sci Med* 2015; **147**:222–231.
10. Rueda S, Mitra S, Chen S, Gogolishvili D, Globerman J, Chambers L, *et al*. **Examining the associations between HIV-related stigma and health outcomes in people living with HIV/AIDS: a series of meta-analyses.** *BMJ Open* 2016; **6**:e011453.
11. Wada NI, Jacobson LP, Margolick JB, Breen EC, Macatangay B, Penugonda S, *et al*. **The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation.** *AIDS* 2015; **29**:463–471.
12. Bourgi K, Wanjalla C, Koethe JR. **Inflammation and metabolic complications in HIV.** *Curr HIV/AIDS Rep* 2018; **15**:371–381.
13. Qureshi AC, Bahri A, Breen LA, Barnes SC, Powrie JK, Thomas SM, Carroll PV. **The influence of the route of oestrogen administration on serum levels of cortisol-binding globulin and total cortisol.** *Clin Endocrinol (Oxf)* 2007; **66**:632–635.
14. Panesar NS, Herries DG, Stitch SR. **Effects of cyproterone and cyproterone acetate on the adrenal gland in the rat: studies in vivo and in vitro.** *J Endocrinol* 1979; **80**:229–238.
15. Hellman L, Yoshida K, Zumoff B, Levin J, Kream J, Fukushima DK. **The effect of medroxyprogesterone acetate on the pituitary–adrenal axis.** *J Clin Endocrinol Metab* 1976; **42**:912–917.
16. Donegan D, Bancos I. **Opioid-induced adrenal insufficiency.** *Mayo Clin Proc* 2018; **93**:937–944.
17. Bancos I, Hahner S, Tomlinson J, Arlt W. **Diagnosis and management of adrenal insufficiency.** *Lancet Diabetes Endocrinol* 2015; **3**:216–226.
18. Beltran S, Lescure FX, El Esper I, Schmit JL, Desailloud R. **Subclinical hypothyroidism in HIV-infected patients is not an autoimmune disease.** *Horm Res* 2006; **66**:21–26.
19. Silva GA, Andrade MC, Sugui Dde A, Nunes RF, Pinto JF, Eyer Silva WA, *et al*. **Association between antiretrovirals and thyroid diseases: a cross-sectional study.** *Arch Endocrinol Metab* 2015; **59**:116–122.
20. Raps M, Curvers J, Helmerhorst FM, Ballieux BE, Rosing J, Thomassen S, *et al*. **Thyroid function, activated protein C resistance and the risk of venous thrombosis in users of hormonal contraceptives.** *Thromb Res* 2014; **133**:640–644.

21. Bisschop PH, Toorians AW, Endert E, Wiersinga WM, Gooren LJ, Fliers E. **The effects of sex-steroid administration on the pituitary-thyroid axis in transsexuals.** *Eur J Endocrinol* 2006; **155**:11–16.
22. Topliss DJ, White EL, Stockigt JR. **Significance of thyrotropin excess in untreated primary adrenal insufficiency.** *J Clin Endocrinol Metab* 1980; **50**:52–56.
23. Abdullatif HD, Ashraf AP. **Reversible subclinical hypothyroidism in the presence of adrenal insufficiency.** *Endocr Pract* 2006; **12**:572.
24. Radix A, Sevelius J, Deutsch MB. **Transgender women, hormonal therapy and HIV treatment: a comprehensive review of the literature and recommendations for best practices.** *J Int AIDS Soc* 2016; **19**:20810.
25. Braun HM, Candelario J, Hanlon CL, Segura ER, Clark JL, Currier JS, *et al*. **Transgender women living with HIV frequently take antiretroviral therapy and/or feminizing hormone therapy differently than prescribed due to drug–drug interaction concerns.** *LGBT Health* 2017; **4**:371–375.
26. Baker JV. **Chronic HIV disease and activation of the coagulation system.** *Thromb Res* 2013; **132**:495–499.
27. Toorians AW, Thomassen MC, Zweegman S, Magdeleyns EJ, Tans G, Gooren LJ, Rosing J. **Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people.** *J Clin Endocrinol Metab* 2003; **88**:5723–5729.
28. Satchell CS, O'Halloran JA, Cotter AG, Peace AJ, O'Connor EF, Tedesco AF, *et al*. **Increased platelet reactivity in HIV-1-infected patients receiving abacavir-containing antiretroviral therapy.** *J Infect Dis* 2011; **204**:1202–1210.
29. Gianella S, Sonya Haw J, Blumenthal J, Sullivan B, Smith D. **The importance of human immunodeficiency virus research for transgender and gender-nonbinary individuals.** *Clin Infect Dis* 2018; **66**:1460–1466.
30. Reisner SL, Poteat T, Keatley J, Cabral M, Mothopeng T, Dunham E, *et al*. **Global health burden and needs of transgender populations: a review.** *Lancet* 2016; **388**:412–436.