High prevalence of anal high-risk HPV infection among transwomen: estimates from a Brazilian RDS study

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Abstract

Introduction: As the leading sexually transmitted infection worldwide, human papillomavirus (HPV) may disproportionately affect transwomen. We aimed to estimate anal HPV prevalence, especially focusing on high-risk (hr)-HPV types and evaluate their associated factors among transwomen living in Rio de Janeiro, Brazil.

Methods: Transwomen enrolled in a respondent-driven sampling (RDS)-based survey conducted between August 2015 and January 2016 self-collected anal samples, which were promptly stored at minus 80°C. After DNA extraction, HPV detection and genotyping were performed using the PapilloCheck test. We estimated HPV prevalences and evaluated the correlates of anal hr-HPV infection using a regression logistic model.

Results: Out of 345 transwomen, 272 (78.8%) were included in this analysis (122 [44.9%] HIV-positive). No participant had ever received HPV vaccination. Among participants enrolled, 212 (77.9%) were positive for any anal HPV type and 165 (60.7%) for hr-HPV. Most common hr-HPV were as follows: HPV16 (17.6%), HPV68 (14.7%), HPV39 (14.3%), HPV56 (12.5%), HPV51 (11.4%) and HPV52 (11.0%). HIV-positive transwomen had three times the odds of having an hr-HPV compared to HIV-negative transwomen. Participants who had a current rectal Neisseria gonorrhoeae infection had 3.7 times the odds of being coinfected with hr-HPV. Among HIV-positive transwomen, neither antiretroviral therapy use, undetectable viral load, current and nadir CD4 counts were associated with anal hr-HPV infection.

Conclusions: Brazilian transwomen in our study exhibit some of the highest population-specific rates of HPV and hr-HPV. There is an urgent need to elucidate the burden of HPV infection, prevalence of HPV-related diseases and access to and uptake of HPV vaccination among transwomen, especially from low- and middle-income settings.

Keywords: prevalence; papillomavirus infections; transgender persons; sexually transmitted disease; anal cancer

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1 | INTRODUCTION

Human papillomavirus (HPV) is the leading sexually transmitted infection (STI) worldwide. Most sexually active people become infected with HPV at some point in their lives [1-3]. HPV types with an oncogenic potential are grouped as high-risk HPV (hr-HPV). HPV is a ubiquitous pathogen in the anogenital region of cisgender (i.e. non-transgender) individuals. The global cervical HPV prevalence is 11% to 12% among cisgender women without cytological abnormalities [4,5]; there has been a strong association between cervical and anal hr-HPV [6]. Nevertheless, it is higher among groups disproportionally impacted by STI, such as cisgender men who have sex with men (MSM) [7,8].

Besides a necessary factor to cervical oncogenesis [9], hr-HPV infection is also a causal factor of other cancers [10,11]. Almost 90% of anal cancers are attributable to HPV, particularly HPV16, which is the most carcinogenic type in the anus [6,12]. Although a rare outcome, there has been an increasing trend in anal cancer incidence worldwide [13]. This increase may be linked to a change in sexual behaviour effecting HPV transmission [14]. Anal cancer is more common among people living with HIV (PLHIV), a population growing in size as treatments continue to increase lifespan [15-17].

Transgender women (henceforth “transwomen”) experience numerous socio-economic factors that increase their vulnerability to HIV/STIs [18]. However, very little data exist on HPV infection among transwomen. A recent meta-analysis identified only four studies on anal HPV infection in Brazil, none among transwomen [8]. We aimed to estimate anal HPV and hr-HPV prevalences and to evaluate their associated factors among transwomen living in Rio de Janeiro, Brazil.

2 | METHODS

This is a secondary analysis of Transcender, a cross-sectional study that enrolled 345 transwomen using respondent-driven
sampling (RDS) at the Evandro Chagas National Institute of Infectious Diseases (INI)-FIOCRUZ, Rio de Janeiro, Brazil, between August 2015 and January 2016. RDS has been used to obtain robust and diverse samples of hard-to-reach populations [19]. Procedures have been described previously [20]. Briefly, eligible participants self-identified as transwomen, lived in Rio de Janeiro or metropolitan area, and were aged 18 + years. We selected 12 diverse seed participants in our formative phase to ensure that the sample did not over-represent groups by age, HIV status, or sex work. Participants recruited up to five peers until the target sample size was reached and the sample composition from one wave to the next differed by less than 2% (equilibrium).

We offered HIV/STIs testing to all participants. A trained staff member provided anal self-collection materials and explained how to perform the procedure using illustrated instructions [21]. In a private bathroom dedicated only for self-collection, participants were instructed to insert a sterile brush (Kolplast, Brazil) 3 to 4 cm into the anus in a comfortable position, to circle it three times, and to remove the brush and place it in a ThinPrep vial (18ml). Participants immediately disposed of their vials in a sealable plastic bag and delivered them to a team member. Samples were promptly stored at minus 80°C and shipped on dry ice to the Virology Laboratory at the Instituto de Medicina Tropical da Universidade de São Paulo. Analysis methods have been described elsewhere [22].

Table 1. Prevalence of anal HPV types, overall and according to HIV status, among transwomen enrolled in the Transcender study, Rio de Janeiro, 2015 to 2016

| HPV type                  | Overall (N = 272) | HIV-positive (N = 122) | HIV-negative (N = 150) | p-value |
|---------------------------|------------------|-----------------------|------------------------|---------|
| Any HPV type              | 212 (77.9)       | 105 (86.1)            | 107 (71.3)             | <0.01   |
| Any 2-valent vaccine types| 61 (22.4)        | 38 (31.1)             | 23 (15.3)              | <0.01   |
| Any 4-valent vaccine types| 101 (37.1)       | 55 (45.1)             | 46 (30.7)              | 0.01    |
| Any 9-valent vaccine types| 139 (51.1)       | 81 (66.4)             | 58 (38.7)              | <0.001  |
| Multiple HPV types        | 153 (72.2)       | 90 (85.7)             | 63 (58.9)              | <0.001  |
| hr-HPV                    |                  |                       |                        |         |
| Any hr-HPV types          | 165 (60.7)       | 92 (75.4)             | 73 (48.7)              | <0.001  |
| Multiple hr-HPV types     | 96 (58.2)        | 66 (71.7)             | 30 (41.1)              | <0.001  |
| HPV16                     | 48 (17.6)        | 27 (22.1)             | 21 (14.0)              | 0.08    |
| HPV18                     | 16 (5.9)         | 14 (11.5)             | 2 (1.3)                | <0.001  |
| HPV31                     | 16 (5.9)         | 12 (9.8)              | 4 (2.7)                | 0.01    |
| HPV33                     | 22 (8.1)         | 14 (11.5)             | 8 (5.3)                | 0.07    |
| HPV35                     | 17 (6.2)         | 14 (11.5)             | 3 (2.0)                | <0.01   |
| HPV39                     | 39 (14.3)        | 26 (21.3)             | 13 (8.7)               | <0.01   |
| HPV45                     | 14 (5.1)         | 11 (9.0)              | 3 (2.0)                | <0.01   |
| HPV51                     | 31 (11.4)        | 17 (13.9)             | 14 (9.3)               | 0.24    |
| HPV52                     | 30 (11.0)        | 17 (13.9)             | 13 (8.7)               | 0.17    |
| HPV56                     | 34 (12.5)        | 22 (18.0)             | 12 (8.0)               | 0.01    |
| HPV58                     | 29 (10.7)        | 23 (18.9)             | 6 (4.0)                | <0.001  |
| HPV59                     | 25 (9.2)         | 18 (14.8)             | 7 (4.7)                | <0.01   |
| HPV68                     | 40 (14.7)        | 23 (18.9)             | 17 (11.3)              | 0.08    |
| HPV73                     | 9 (3.3)          | 9 (7.4)               | 0 (0.0)                | <0.001  |
| HPV82                     | 28 (10.3)        | 19 (15.6)             | 9 (6.0)                | 0.01    |
| lr-HPV                    |                  |                       |                        |         |
| HPV6                      | 43 (15.8)        | 21 (17.2)             | 22 (14.7)              | 0.57    |
| HPV11                     | 21 (7.7)         | 11 (9.0)              | 10 (6.7)               | 0.47    |
| HPV40                     | 18 (6.6)         | 11 (9.0)              | 7 (4.7)                | 0.15    |
| HPV42                     | 42 (15.4)        | 27 (22.1)             | 15 (10.0)              | 0.01    |
| HPV43                     | 16 (5.9)         | 7 (5.7)               | 9 (6.0)                | 0.93    |
| HPV44                     | 64 (23.5)        | 39 (32.0)             | 25 (16.7)              | <0.01   |
| HPV53§                    | 35 (12.9)        | 24 (19.7)             | 11 (7.3)               | <0.01   |
| HPV55                     | 64 (23.5)        | 39 (32.0)             | 25 (16.7)              | <0.01   |
| HPV66§                    | 26 (9.6)         | 14 (11.5)             | 12 (8.0)               | 0.33    |
| HPV70                     | 24 (8.8)         | 16 (13.1)             | 8 (5.3)                | 0.02    |

HIV, human immunodeficiency virus; HPV, human papillomavirus; hr-HPV, high-risk HPV; lr-HPV, low-risk HPV.
*Positive for 1 + HPV type; HPV 16 or 18; HPV 6, 11, 16 or 18; HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82; *more than 1 HPV type (analysis restricted to those HPV positive; N = 212); HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82; *more than 1 hr-HPV (denominator restricted to hr-HPV-positive, N = 165); HPV 53 and 66 are currently considered as probable high-risk types.
In summary, we used the QIAamp DNA Mini Kit (Qiagen, Chatteris, UK) for DNA extraction. HPV detection and genotyping used the PapilloCheck HPV-Screening Test (Greiner Bio-One GmbH, Frickenhausen, Germany), which detects 15 hour-HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82), two probable hr-HPV genotypes (53 and 66) and seven low-risk (lr)-HPV genotypes (6, 11, 40, 42, 43, 44, 70).

Syphilis screening used Venerable Disease Research Laboratory (VDRL) tests, and positive results were confirmed by a microhaemagglutination assay for Treponema pallidum. We detected rectal Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (NG) infection by using the Abbott Real Time platform and the Amplification Reagent Kit (Abbott Molecular, Des Plains, IL, USA) in INI-FIOCRUZ Laboratory. Indeterminate results were repeated with the same tests on the same samples. All participants living with HIV collected CD4+ count (Becton Dickinson FACScan) and HIV viral load (VL). Previous CD4+ counts were retrieved from the Brazilian National Registry, which records most measures performed in the country. Participants self-reported antiretroviral therapy (ART) use.

We estimated prevalence of any anal HPV, at least one HPV type in the 2-valent (HPV16, 18), 4-valent (HPV6, 11, 16, 18) and 9-valent (HPV6, 11, 16, 18, 31, 33, 45, 52, 58) vaccines, hr-HPV (positive for 1+ hour-HPV detected by the test) and individual HPV types.

Continuous variables were reclassified as categorical. We defined active or recent syphilis as VDRL titers of at least 1/8 and a positive microhaemagglutination assay for T. pallidum. The nadir CD4+ count was defined as the participant’s lowest level ever recorded.

We used RDS-unadjusted data. Descriptive analysis used median and interquartile range (IQR) and absolute and relative frequencies. We compared participants according to HIV status using chi-square tests. We used a regression logistic model to evaluate the correlates of anal hr-HPV infection. Variables with p < 0.2 in the univariable logistic regression analysis and potential confounders were included in the initial multivariable model. A backward elimination procedure guided the removal of non-significant variables until we reached a final multivariable model where all variables had a p ≤ 0.05 or modified the effect of other variables. Statistical analysis was performed using R software version 3.4.3.

This study was approved by the INI-FIOCRUZ Institutional Review Board. All participants provided an informed consent form. This study received grants of the Brazilian Research Council (CNPq) and the National Institute of Allergy and Infectious Diseases (NIAID-NIH).

3 RESULTS AND DISCUSSION

Among 345 transwomen enrolled in the Transcender study, 341 (98.8%) agreed to and conducted anal specimen collection, 69 (20.0%) had invalid anal samples due to insufficient material and 272 (78.8%) had samples with valid results and were included in the present analysis. HIV-negative status was more common among participants with invalid samples than those with valid samples (72.9% vs. 55.1% respectively). Overall, participants were aged 30 years (IQR 24 to 37), 76.8% were non-white, and 48.9% were currently on hormones. Only 16 (5.9%) participants had gender-affirming surgery. Ever and currently doing sex work were reported by 79.0% and 48.9% respectively. No participant had received HPV vaccine. HIV-infection was present in 122 individuals (44.9%). Among those living with HIV, 83 were on ART, 43.7% were virologically suppressed, and median current and nadir CD4 count were, respectively, 631 cells/mm³ (IQR 384 to 833) and 380 cells/mm³ (IQR 196 to 756).

Out of 272 participants tested for anal HPV, 212 (77.9%) and 165 (60.7%) were positive for any HPV and hr-HPV respectively (Table 1).

The most common hr-HPV was HPV16 (17.6%). Only three people had both HPV16 and 18 (1.1%), and none were positive for all 4- and 9-valent vaccine types. Transwomen living with HIV had a significantly higher prevalence of most types of anal HPV than those HIV negative. HPV6 and HPV43 had decreasing prevalences according to age (Table 2). Transwomen aged 25+ years had higher prevalences of HPV44 and HPV55 as compared to those aged 18 to 24 years, whereas HPV56 had a lower prevalence among transwomen aged ≥35 years.

Younger participants had significantly higher odds of anal hr-HPV infection (Table 3). Transwomen living with HIV had three times the odds of anal hr-HPV infection compared to those without HIV.

Table 2. Prevalence of anal HPV types according to age among transwomen enrolled in the Transcender study, Rio de Janeiro, 2015 to 2016

| 18 to 24 years (N,%) | 25 to 35 years (N,%) | >35 years (N,%) | p-value |
|---------------------|---------------------|----------------|---------|
| HPV6                | 18 (24.7)           | 18 (15.4)      | 7 (8.5) | 0.02    |
| HPV11               | 7 (9.6)             | 9 (7.7)        | 5 (6.1) | 0.72    |
| HPV16               | 13 (17.8)           | 24 (20.5)      | 11 (13.4) | 0.43 |
| HPV18               | 6 (8.2)             | 6 (5.1)        | 4 (4.9) | 0.66    |
| HPV31               | 6 (8.2)             | 6 (5.1)        | 4 (4.9) | 0.70    |
| HPV33               | 7 (9.6)             | 11 (9.4)       | 4 (4.9) | 0.44    |
| HPV35               | 5 (6.8)             | 8 (6.8)        | 4 (4.9) | 0.83    |
| HPV39               | 13 (17.8)           | 14 (12)        | 12 (14.6) | 0.53 |
| HPV40               | 6 (8.2)             | 5 (4.3)        | 7 (8.5) | 0.40    |
| HPV42               | 15 (20.5)           | 20 (17.1)      | 7 (8.5) | 0.10    |
| HPV43               | 7 (9.6)             | 9 (7.7)        | 0 (0)   | <0.01   |
| HPV44               | 10 (13.7)           | 34 (29.1)      | 20 (24.4) | 0.05 |
| HPV45               | 2 (2.7)             | 5 (4.3)        | 7 (8.5) | 0.23    |
| HPV51               | 11 (15.1)           | 13 (11.1)      | 7 (8.5) | 0.44    |
| HPV52               | 7 (9.6)             | 13 (11.1)      | 10 (12.2) | 0.87 |
| HPV53               | 10 (13.7)           | 12 (10.3)      | 13 (15.9) | 0.49 |
| HPV55               | 10 (13.7)           | 34 (29.1)      | 20 (24.4) | 0.05 |
| HPV56               | 11 (15.1)           | 19 (16.2)      | 4 (4.9) | 0.04    |
| HPV58               | 4 (5.5)             | 12 (10.3)      | 13 (15.9) | 0.11 |
| HPV59               | 6 (8.2)             | 13 (11.1)      | 6 (7.3) | 0.62    |
| HPV66               | 9 (12.3)            | 12 (10.3)      | 5 (6.1) | 0.40    |
| HPV68               | 15 (20.5)           | 17 (14.5)      | 8 (9.8) | 0.17    |
| HPV70               | 5 (6.8)             | 14 (12)        | 5 (6.1) | 0.28    |
| HPV73               | 1 (1.4)             | 6 (5.1)        | 2 (2.4) | 0.44    |
| HPV82               | 8 (11)              | 15 (12.8)      | 5 (6.1) | 0.3     |

HPV, human papillomavirus.
Table 3. Correlates of anal hr-HPV infection among transwomen in Transcender study, Rio de Janeiro, 2015 to 2016

| Characteristic                      | hr-HPV-positive (N = 165), % | Crude OR | p-value | Adjusted OR | p-value |
|-------------------------------------|-----------------------------|----------|---------|-------------|---------|
|                                     |                             | Univariable |        | Multivariable |        |
|                                     |                             | Crude OR   | p-value | Adjusted OR | p-value |
| Agea                               |                             |            |         |             |         |
| 18 to 24                            | 48 (65.8)                   | 1.5 (0.8 to 2.9) | 0.22 | 2.4 (1.1 to 5.2) | 0.03 |
| 25 to 35                            | 71 (60.7)                   | 1.2 (0.7 to 2.1) | 0.52 | 1.9 (1.0 to 3.8) | 0.06 |
| >35                                 | 46 (56.1)                   | 1         |         | 1           |         |
| Race/color                          |                             |            |         |             |         |
| Black                               | 38 (58.5)                   | 1         |         | 1           |         |
| Mixed/other                         | 95 (66.0)                   | 1.4 (0.8 to 2.5) | 0.30 |             |         |
| White                               | 32 (50.8)                   | 0.7 (0.4 to 1.5) | 0.38 |             |         |
| Monthly incomea,b                   |                             |            |         |             |         |
| ≤$130                               | 66 (58.4)                   | 1         |         | 1           |         |
| $131 to 260                         | 51 (62.2)                   | 1.1 (0.6 to 2.0) | 0.59 |             |         |
| >$260                               | 34 (59.6)                   | 1.2 (0.7 to 2.1) | 0.88 |             |         |
| Years of schoolinga                 |                             |            |         |             |         |
| <4                                  | 9 (52.9)                    | 1         |         | 1           |         |
| 4 to 8                              | 57 (67.1)                   | 1.8 (0.6 to 5.2) | 0.27 |             |         |
| >8                                  | 99 (58.2)                   | 1.2 (0.4 to 3.4) | 0.67 |             |         |
| Smoking                             |                             |            |         |             |         |
| Never                               | 51 (58.6)                   | 1         |         | 1           |         |
| Former                              | 22 (51.2)                   | 0.7 (0.4 to 1.5) | 0.42 |             |         |
| Current                             | 92 (64.8)                   | 1.3 (0.7 to 2.2) | 0.35 |             |         |
| Binge drinkingc                     |                             |            |         |             |         |
| No                                  | 55 (59.8)                   | 1         |         | 1           |         |
| Yes                                 | 110 (61.1)                  | 1.1 (0.6 to 1.8) | 0.83 |             |         |
| Any illicit drug use in the last 12 months |                       |            |         |             |         |
| No                                  | 64 (56.6)                   | 1         |         | 1           |         |
| Yes                                 | 101 (63.5)                  | 1.3 (0.8 to 2.2) | 0.25 |             |         |
| Current hormone use                 |                             |            |         |             |         |
| No                                  | 89 (64.0)                   | 1         |         | 1           |         |
| Yes                                 | 76 (57.1)                   | 0.7 (0.5 to 1.2) | 0.25 |             |         |
| Previous reassignment surgery       |                             |            |         |             |         |
| No                                  | 159 (62.1)                  | 1         |         | 1           |         |
| Yes                                 | 6 (37.5)                    | 0.4 (0.1 to 1.0) | 0.06 |             |         |
| Sex work                            |                             |            |         |             |         |
| Never                               | 35 (61.4)                   | 1         |         | 1           |         |
| Former                              | 44 (53.7)                   | 0.7 (0.4 to 1.4) | 0.37 |             |         |
| Currently                           | 86 (64.7)                   | 1.2 (0.6 to 2.2) | 0.67 |             |         |
| N. male sex partners in the last six monthsa |                       |            |         |             |         |
| 0 to 4                              | 38 (54.3)                   | 1         |         | 1           |         |
| 5 to 9                              | 15 (60.0)                   | 1.3 (0.5 to 3.3) | 0.62 |             |         |
| 10+                                 | 103 (64.0)                  | 1.5 (0.8 to 2.6) | 0.17 |             |         |
| Condomless anal sex with last 3 partners |                        |            |         |             |         |
| No                                  | 48 (67.6)                   | 1         |         | 1           |         |
| Yes                                 | 102 (57.0)                  | 0.6 (0.4 to 1.1) | 0.12 | 0.6 (0.3 to 1.2) | 0.16 |
| Condomless anal sex with main partner |                      |            |         |             |         |
| No                                  | 54 (58.1)                   | 1         |         | 1           |         |
| Yes                                 | 104 (61.5)                  | 1.2 (0.7 to 1.9) | 0.58 |             |         |
| Consistent condom use               |                             |            |         |             |         |
| No                                  | 132 (60.6)                  | 1         |         | 1           |         |
| Yes                                 | 26 (59.1)                   | 0.9 (0.5 to 1.8) | 0.86 |             |         |

(Continued)
those HIV-negative. Participants with a rectal NG infection had 3.9 times the odds of hr-HPV coinfection. Among transgender women living with HIV, including MSM and those with low socio-economic status (MWSW) had anal HPV. A Brazilian meta-analysis found that anal HPV prevalences compared to HIV-negative participants, consistent with previous findings. MSM have the highest population-specific HPV rates reported to date, especially among those living with HIV [31,33,34]. Any anal HPV prevalence was higher among MSM and MWSW aged 18 to 24 years in three countries, including Brazil [31]. Finally, contrasting findings observed that anal HPV prevalence increased from 24.5% among Chinese MSM aged ≤19 years to 55.8% among those aged 40+ years [32].

Transwomen living with HIV had a higher HPV and hr-HPV prevalences compared to HIV-negative participants, consistent with previous findings. MSM have the highest population-specific HPV rates reported to date, especially among those living with HIV [31,33,34]. Any anal HPV prevalence was higher among MSM with HIV (81%) as compared to HIV-negative MSM (47%), MWSW living with HIV (44%) and HIV-negative MWSW (12%) [34]. Anal HPV prevalence among MSM was 4 to 10 times higher than among MWSW [31]. A meta-analysis identified substantially higher pooled prevalence of any anal HPV and hr-HPV in MSM living with HIV (92.6% and 73.5%) than in those HIV-negative (63.9% and 37.2%) [33].

The 4-valent HPV vaccine, available at no cost in Brazil since 2014, is currently offered to girls aged 9 to 14 years, boys aged 9 to 14 years and people living with HIV aged 9 to 26 years (regardless of gender identity) [35]. Nevertheless, HPV vaccine uptake according to HIV status, nor other gender identities. In Canada, HPV vaccine uptake was low among male individuals living with HIV, including MSM and those with low socio-economic status [27]. Nevertheless, this association is conflicting in the anus. Previous studies in MSM demonstrated high, stable HPV prevalence across different age groups. An US study observed that 26% of 1,400 MSM had any anal hr-HPV with no difference in age groups [28]. Among Australian MSM, there was no consistent trend in HPV prevalence with increasing age [29]. A Chinese study on 578 MSM (50 with HIV) identified a decreasing trend in anal HPV prevalence with increasing age: 71% (≤19 years), 62% (20 to 29 years), 64% (30 to 39 years) and 54% (40+ years) [30]. Nevertheless, Nyitray et al. identified decreasing age-specific anal HPV prevalence with the highest rates among MSM and MWSW aged 18 to 24 years in three countries, including Brazil [31]. Finally, contrasting findings observed that anal HPV prevalence increased from 24.5% among Chinese MSM aged ≤19 years to 55.8% among those aged 40+ years [32].
economic status [37]. In Brazil, a highly discriminatory setting hinders sexual/gender minorities from accessing healthcare services [38,39]. Transphobia in Brazilian healthcare services has been previously described as the most prominent barrier to reduced willingness to seek HIV prevention or healthcare in general [39]. Although HPV-related diseases occur independently of sociodemographic characteristics, their distribution is unequal among individuals with different socio-economic status [40,41]. As a highly disadvantaged group, transwomen bear synergistic vulnerabilities that may ultimately lead to low vaccine uptake and disproportionate risk for anal HPV-related lesions.

This study has several limitations. First, although RDS survey is commonly used for hard-to-reach populations, its results may not be generalizable. In addition, the cross-sectional design does not allow us to establish causal inference. We also did not evaluate anal cytology or histopathology data, which could ultimately reinforce the burden of anal HPV infection among transwomen. Syphilis definition only included laboratory results and did not consider clinical data. Finally, the high proportion of invalid samples may be due to user error. Two rectal samples had to be collected (for HPV and CT/NG), which may create burden on participants and interfered with the process. Although self-collection has been described as an acceptable tool, including for anal samples, the proportion of invalid samples varied from 5% up to 37% across studies [21,24,42,43]. Transwomen without HPV results (refusal or invalid samples) more frequently were HIV-negative, which may have led to an overestimation of HPV prevalence among transwomen living with HIV. As PLHIV commonly access health services, they may be more familiar with performing laboratory exams including self-collection, which could have skewed results for this group. Despite limitations, our data fill an important gap in the limited information on HPV among transwomen and is consistent with other studies showing high HPV prevalence among this population.

4 | CONCLUSIONS

Our extremely high rates of HPV and hr-HPV among transwomen show that this group is disproportionately affected by HPV and may be at a high risk for cancer. HPV16 was the most prevalent anal hr-HPV type. Prevalence of hr-HPV was higher among younger participants, those living with HIV and concomitant rectal NG infection. There is an urgent need to elucidate the burden of HPV infection and to increase access to and uptake of HPV vaccination among transwomen, especially from low- and middle-income settings.

AUTHORS’ AFFILIATIONS

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COMPETING INTERESTS

The authors declare no conflict of interests.

AUTHORS’ CONTRIBUTIONS

BG, EMJ, ECW and VGV conceived the analysis and interpreted the findings. BG, EMJ, ECW and VGV drafted the manuscript. LSV and EMJ performed the statistical analyses. JEL supervised the biological analysis, interpreted the results and provided biological inputs. EMJ, LM, LSV and ACFG helped with data acquisition, interpretation of the results and drafting the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. U.S. Centers for Disease Control and Prevention. Human Papillomavirus (HPV): HPV fact sheet [Internet]. 2019. Available from: https://www.cdc.gov/std/hpv/stdfact-hpvh.htm
2. Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, et al. Global burden of human papillomavirus and related diseases. Vaccine. 2017;39:F12–23
3. Bossert W, Aasland OA, Kjaer SK, Mørkholm S, Thorning E, Wiis J. Human papillomavirus infection in a national cohort of women with cervical cancer. J Natl Cancer Inst. 2010;102(15):1155–63
4. Reisner SL, Poteat T, Keatly J, Cabral M, Mothopeng T, Durham E, et al. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. Clin Infect Dis. 2012;54(7):1026–34
5. Reimer CL, Poteat T, Keatly J, Cabral M, Mothopeng T, Durham E, et al. Global health burden and needs of transgender populations: a review. The Lancet. 2016;388(10042):412–36
6. Lin C, Franceschi S, Clifford GM. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis. Lancet Oncol. 2009;10(4):321–2
7. Bruni L, Diaz M, Castellsague X, Ferrer E, Bosch FX, de Sanjosé S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cervical cytology findings. J Infect Dis. 2010;202(12):1789–99
8. Guan P, Howell-Jones R, Li N, Bruni L, de Sanjosé S, Franceschi S, et al. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. Int J Cancer. 2012;131(10):2349–59
9. Lin C, Franceschi S, Clifford GM. Human papillomavirus types from infection to cancer in the anus, according to sex and HIV status: a systematic review and meta-analysis. Lancet Infect Dis. 2018;18(2):198–206
10. D’Souza G, Wiley DJ, Li X, Chmiel JS, Margolick JB, Cranston RD, et al. Incidence and epidemiology of anal cancer in the multicenter AIDS cohort study. J Acquir Immune Defic Syndr. 2008;48(4):491–9
11. Colpani V, Soares Falcetta F, Bacelo Bidinotto A, Kops NL, Falavigna M, Serpa Hammes L, et al. Prevalence of human papillomavirus (HPV) in Brazil: a systematic review and meta-analysis. Consolario MEL, editor. PLoS One. 2020;15:e0229154
12. Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Shera KA, Wurscher MA, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12
13. Koutsky L. The epidemiology behind the HPV vaccine discovery. Annu Epidemiol. 2009;19(4):239–44
14. Krzewska-Firych J, Lucas G, Lucas C, Lucas N, Pietrzyk Ł. An overview of Human Papillomavirus (HPV) as an etiological factor of the anal cancer. Journal of Infection and Public Health. 2019;12(1):1–6
15. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012;13(6):e67–15
16. Islami F, Ferlay J, Lortet-Tieulent J, Bray F, Jemal A. International trends in anal cancer incidence rates. Int J Epidemiol. 2016;45(3):924–38
17. Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Sherer KA, Wachsmuth MA, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. Cancer. 2004;101(2):270–80
18. Chatuverdi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. J Natl Cancer Institute. 2003;95(11):1120–30
19. Clifford GM, Polesel J, Rickenbach M, on behalf of the Swiss HIV Cohort Study. Dal Maso L, Keiser O, et al. Cancer risk in the Swiss HIV cohort study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Institute. 2005;97(6):425–32
20. Silverberg MJ, Lau B, Justice AC, Engels E, Gill MJ, Goedert JJ, et al. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. Clin Infect Dis. 2012;54(7):1026–34
21. Reisner SL, Poteat T, Keatly J, Cabral M, Mothopeng T, Durham E, et al. Global health burden and needs of transgender populations: a review. The Lancet. 2016;388(10042):412–36
22. Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, et al. Global burden of human papillomavirus and related diseases. Vaccine. 2017;39:F12–23
23. Bossert W, Aasland OA, Kjaer SK, Mørkholm S, Thorning E, Wiis J. Human papillomavirus infection in a national cohort of women with cervical cancer. J Natl Cancer Inst. 2010;102(15):1155–63
24. Reisner SL, Poteat T, Keatly J, Cabral M, Mothopeng T, Durham E, et al. Global health burden and needs of transgender populations: a review. The Lancet. 2016;388(10042):412–36
19. Heckathorn DD. Respondent-driven sampling ii: deriving valid population estimates from chain-referral samples of hidden populations. Sociol. Probl. 2002;49(1):11–34.

20. Grinsztejn B, Jalil EM, Monteiro L, Velasque L, Moreira RI, Garcia ACF, et al. Unveiling of HPV dynamics among transgender women: a respondent-driven sampling study in Rio de Janeiro, Brazil. Lancet HIV. 2017;4(4):e169–76.

21. Lampinen TM, LaTulippe L, van Niekerk D, Schilder AJ, Miller ML, Anema A, et al. Illustrated instructions for self-collection of anorectal swab specimens and their adequacy for cytological examination. Sexually Transmitted Diseases. 2006;33(6):386–8.

22. Cambou MC, Luz PM, Lake JE, Levi J, Coutinho JR, de Andrade A, et al. Analy human papillomavirus (HPV) prevalences and factors associated with abnormal anal cytology in HIV-infected women in an Urban Cohort from Rio de Janeiro, Brazil. AIDS Patient Care STDS. 2015;29(1):4–12.

23. Nyitray AG, Carvalho da Silva RJ, Baggio ML, Lu B, Smith D, Abrahamsen M, et al. Age-specific prevalence of and risk factors for anal human papillomavirus (HPV) among men who have sex with women and men who have sex with men: the HPV in men (HIM) study. J Infect Dis. 2011;203(1):49–57.

24. Machalek DA, Poynten M, Jin F, Fairley CK, Farsworth A, Garland SM, et al. Human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. Lancet Oncol. 2012;13(5):487–500.

25. BRAZIL. Informe Técnico sobre a Vacina Papilomavírus Humano (HPV) na Atenção Básica [Internet]. 2014 [cited 2021 Jan 17]. Available from: https://portalarquivos2.saude.gov.br/images/pdf/2018/marco/14/Informe-T--cnico-Introducao-ao-vacina-HPV-18-2-2014.pdf

26. Wilson EC, Jalil EM, Moreira RI, Velasque L, Castro CV, Monteiro L, et al. High risk and low HIV prevention behaviours in a new generation of young trans women in Brazil. AIDS Care. 2020;1–5.

27. Avni-Singer LR, Yakely A, Sheth SS, Shapiro ED, Niccolai LM, Oliveira CR. Assessing sociodemographic differences in human papillomavirus vaccine impact studies in the United States: a systematic review using narrative synthesis. Public Health. 2020;178:137–50.

28. Yared NF, Horvath KJ, Baker JV, Thyagarajan B, Waterboer T, Kulasingam S. Concordance of self- and clinician-collected anal swabs to detect human papillomavirus in a sample of HIV-negative men. J Lower Genital Tract Dis. 2019;23(3):200–4.

29. Gilbert M, Kwag M, Mei W, Rank C, Kropp R, Severini A, et al. Feasibility of incorporating self-collected rectal swabs into a community venue-based survey to measure the prevalence of HPV infection in men who have sex with men. Sex Transm Infect. 2011;8(10):964–9.

30. Singh V, Gratzer B, Gorbach PM, Crosby RA, Panicker G, Steinau M, et al. Transgender women have higher human papillomavirus prevalence than men who have sex with men—two U.S. cities, 2012–2014. Sex Transm Dis. 2019;46(10):657–62.

31. dos Ramos Farías MS, García MN, Reynaga E, Romero M, Vaulet MLG, Fermin MR, et al. First report on sexually transmitted infections among trans (male to female transvestites, transsexuals, or transgender) and male sex workers in Argentina: high HIV, HPV, HBV, and syphilis prevalence. Int J Infect Dis. 2011;15(9):e35–40.

32. Brown B, Galea JT, Byraiah G, Poteat T, Leon SR, Calvo G, et al. Anogenital human papillomavirus infection and HIV infection outcomes among peruvian transgender women: results from a cohort study. Transgender Health. 2016;1(1):94–9.

33. Loverro G, Di Naro E, Carigliana AM, De Robertis AL, Loconsole D, Chironna M. Prevalence of human papillomavirus infection in a clinic sample of transsexuals in Italy. 1. Table. Sex Transm Infect. 2016;92(1):67–9.

34. Herrero R, Hildesheim A, Bratti C, Shermer ME, Hutchinson M, Morales J, et al. Population-based study of human papillomavirus infection and cervical neoplasia in rural Costa Rica. J Natl Cancer Inst. 2000;92(6):464–74.

35. Chin-Hong PV, Vittinghoff E, Cranston RD, Buchbinder S, Cohen D, Colfax G, et al. Age-specific prevalence of anal human papillomavirus infection in HIV-negative sexually active men who have sex with men: the EXPLORE study. J Infect Dis. 2004;190(12):2070–6.

36. Vajdic CM, van Leeuwen MT, Jin F, Prestage G, Medley G, Hillman RJ, et al. Anal human papillomavirus genotype diversity and co-infection in a community-based sample of homosexual men. Sex Transm Infect. 2009;85(5):330–5.

37. Gao L, Zhou F, Li X, Yang Y, Ruan Y, Jin Q. Anal HPV Infection in HIV-Positive Men Who Have Sex with Men from China. Kaul R, editor. PLoS One. 2010;5:e15256.

38. Zhou Y, Lin Y-F, Meng X, Duan Q, Wang Z, Yang B, et al. Anal human papillomavirus among men who have sex with men in three metropolitan cities in southern China: implications for HPV vaccination Vaccine. 2020;38(13):2849–58.

39. Marra E, Lin C, Clifford GM. Type-specific anal human papillomavirus prevalence among men, according to sexual preference and HIV status: a systematic literature review and meta-analysis. J Infect Dis. 2019;219(4):590–8.

40. BRAZIL. Boletim Informativo Vacinação contra o HPV [Internet]. 2018 [cited 2021 Jan 17]. Available from: https://portalarquivos2.saude.gov.br/images/pdf/2018/maio/14/Informe-T--cnico-HPV-MENINGITE.pdf

41. Grrewal R, Grewal T, Gillis JL, Ogilvie G, Gaspar M, Grace D, et al. Low human papillomavirus (HPV) vaccine uptake among men living with human immunodeficiency virus (HIV): cross-sectional findings from a clinical cohort. Prev Med. 2020;143:106329.

42. Wilson EC, Jalil EM, Castro C, Martinez Fernandez N, Kamel L, Grinsztejn B. Barriers and facilitators to PrEP for transwomen in Brazil. Global Public Health. 2019;14(2):300–5.

43. Brisson M, Drolet M, Malagon T. Inequalities in human papillomavirus (HPV)-associated cancers: implications for the success of HPV vaccination. J Natl Cancer Institut. 2013;105(3):158–61.