AIDS, Publish Ahead of Print

DOI: 10.1097/QAD.0000000000004225

# Sexually transmitted infections in men who have sex with men with tenofovir/emtricitabine- or cabotegravir-resistant HIV

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**Abstract**

**Objective:** Sexually transmitted infections (STIs) are associated with an increased risk of HIV transmission, raising concerns in case of virus resistant (R) to the drugs currently approved for pre-exposure prophylaxis (PrEP). We explored the incidence of STIs in men who have sex with men with HIV (MSMWH) and resistance to tenofovir/emtricitabine (TXF/FTC) and/or cabotegravir (CAB).

**Design:** Retrospective, cohort study on MSMWH on antiretroviral treatment (ART) with ≥1 genotyping resistance test (GRT) including integrase.

**Methods:** The following STIs were included in the analysis: *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma/Ureaplasma spp.* (only if symptomatic), early syphilis (primary, secondary, or early latent), and mpox infections. Poisson regression modeled incidence rates (IRs) and 95% confidence intervals (95%CIs).

**Results:** Overall, 638 MSMWH evaluated: 67 (10.5%) TXF/FTC-R, 4 (0.6%) CAB-R, and 13 (2.0%) TXF/FTC+CAB-R.

During a median follow-up of 9.6 (7.3-11.7) years [5908 person-years-of-follow-up (PY)], 307/638 (48.1%) individuals developed 744 STIs: IR=12.6 (95%CI=11.7-13.5)/100 PY. Among 307 MSMWH who developed STIs, 34 (11.1%) had ≥1 STI at HIV load ≥200 copies/mL [21 (6.8%) ≥1000 copies/mL].

Thirty-two (10.4%) of 307 individuals with ≥1 incident STI had TXF/FTC- and/or CAB-R strains; 5 (15.6%) of these developed STIs at HIV load ≥200 copies/mL (specifically, ≥1000 copies/mL). STI incidence was significantly lower in presence of drug resistance [either TXF/FTC- or CAB-R: IR=8.2 (95%CI=6.2-10.5)/100 PY and IRR=0.6 (95%CI=0.5-0.8); TXF/FTC+CAB-R: IR=2.9 (95%CI=0.8-7.3)/100 PY and IRR=0.2 (95%CI=0.1-0.5)].

**Conclusions:** In our cohort of MSMWH, STI incidence was non-negligible, although reduced, in presence of resistance to TXF/FTC and/or CAB. Discussion of HIV resistance test results should include the risk of sexual transmission uncontrolled by pre-exposure prophylaxis.

**Keywords**

HIV; drug resistance; sexually transmitted infections; STIs; men who have sex with men; pre-exposure prophylaxis



Curable sexually transmitted infections (STIs) are recognized as a global health problem, especially among vulnerable populations, including men who have sex with men (MSM) and individuals with human immunodeficiency virus (HIV) [1,2]. The most common STIs are estimated to account for ≥1,000,000 cases per day [1,2]; furthermore, a recent global outbreak of mpox has been described [3,4].

In addition to serving as a marker of high-risk sexual behavior, STIs are known to increase the risk of HIV transmission [5]; this is of particular concern in the case of HIV resistant (R) to the drugs currently approved for pre-exposure prophylaxis (PrEP) [6]. However, to our knowledge, no data on the incidence of STIs in people with HIV (PWH) and resistance to tenofovir (TXF)/emtricitabine (FTC) or cabotegravir (CAB) are available.

Therefore, the primary objective of the current study was to evaluate the incidence of STIs in MSM with HIV (MSMWH) and TXF/FTC and/or CAB resistance.

**Methods**

This is a retrospective, cohort study on MSMWH followed at HIV Clinic, IRCCS San Raffaele Scientific Institute (Milan, Italy). Individuals provided written informed consent for the use of their data in scientific analyses and for inclusion in the Centro San Luigi HIV Cohort (date of approval by IRCCS San Raffaele Scientific Institute Ethics Committee: December 4th, 2017; protocol n. 34). Recorded data were anonymized and managed according to the Good Clinical Practice.

Inclusion criteria were: 1) male sex-assigned-at-birth; 2) age ≥18 years; 3) living with HIV [antiretroviral treatment (ART)-naïve or -experienced]; 4) self-identification as MSM; 5) availability of ≥1 RNA-based genotyping resistance test (GRT) including integrase gene.

The only exclusion criterion was the development of TXF/FTC and/or CAB resistance after the first available GRT including integrase gene: the exact time of resistance development was difficult to estimate, as it may have occurred at the time of failure prior to the GRT, potentially leading to the misclassification of some STIs. Only 13 MSMWH were excluded, as detailed in Table S1, http://links.lww.com/QAD/D552.

Baseline was defined as the date of the first available GRT including integrase gene for each individual: the first inclusion date in the current study was January 28th, 2008. Follow-up accrued from baseline until death, loss-to-follow-up, or censoring date (February 28th, 2024).

Resistance to a drug was defined as at least intermediate resistance according to the Stanford HIV database algorithm (version 9.6, hivdb.stanford.edu); resistance to TXF/FTC as resistance to TXF and/or FTC; resistance to a drug class as resistance to ≥1 drug in the class.

The primary study outcome was the incidence of STIs in TXF/FTC- and/or CAB-R MSMWH.

Considered STIs were: (1) *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections, defined as any positive nucleic acid amplification test (NAAT) or culture from urethral, anal, or oropharyngeal site; (2) symptomatic *Mycoplasma/Ureaplasma spp.* infections, defined as any positive NAAT or culture from urethral or anal site, in presence of symptoms; (3) mpox, defined as any positive NAAT from lesions, plasma, urethral, anal, or oropharyngeal site (beginning May 2022); (4) early syphilis, defined as primary, secondary, or early latent syphilis and diagnosed by clinical examination, a nontreponemal (rapid plasma reagin) and a treponemal (*Treponema pallidum* hemagglutination assay) test, according to European guidelines [7]. Late latent and tertiary syphilis, herpes simplex virus, and human papillomavirus infections were excluded from the analysis because of the impossibility of correctly dating their acquisition. STI testing was performed according to international and local guidelines: depending on the MSMWH's risk of contracting an STI, based on reported sexual behavior, testing was conducted either every 6 or 12 months with also the possibility of tailored screening as needed or in the presence of symptoms. HIV load testing was performed every 1-3 months for MSMWH who were ART-naïve, on virological failure or switching regimen, and every 3-12 months for virologically suppressed individuals on stable ART, according to international and local guidelines; HIV load testing could also have been additionally performed in conjunction with STIs, at the individual discretion of HIV care providers. The last HIV load prior to STI diagnosis (up to 3 months) was used to stratify STIs by viremia.

Individuals' characteristics, described using median (interquartile range) or frequency (percentage), were compared by Kruskall-Wallis or Mann-Whitney U test (continuous variables) and Chi-Square or Fisher's exact tests (categorical variables), as appropriate.

Incidence rates (IRs) of STIs among MSMWH (overall, either TXF/FTC- or CAB-R, and TXF/FTC+CAB-R) were calculated as the number of post-baseline episodes per 100 person-years-of-follow-up (PY); crude IRs and 95% confidence intervals (95%CIs) were estimated through univariable Poisson regression modeling.

Statistical analyses were performed at a two-sided 5% significance level using R Statistical Software, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

Overall, 638 MSMWH included in the analysis: at baseline, 67 (10.5%) with TXF/FTC-R strains, 4 (0.6%) with CAB-R, and 13 (2.0%) with TXF/FTC+CAB-R. Characteristics are reported in Table 1. Interestingly, TXF/FTC- and/or CAB-R MSMWH were older, characterized by a lower $CD4^+$ nadir, and more frequently had a positive hepatitis C virus (HCV) serostatus (Table 1). They were also characterized by a lower HIV load and a higher $CD4^+$ count, presumably attributable to a more frequent ART-experienced status (Table 1). In the 6 months immediately prior to baseline, 23 (3.6%) individuals developed STIs: 21/23 (91.3%) had ≥1 STI at HIV load ≥200 copies/mL (all ≥1000 copies/mL). Five (21.7%) of these 23 MSMWH with STIs in the 6 months pre-baseline showed TXF/FTC- or CAB-R strains at baseline: 4/5 (75%) had ≥1 STI at HIV load ≥200 copies/mL (all ≥1000 copies/mL).

During a median follow-up of 9.6 (7.3-11.7) years (5908 PY), 307/638 (48.1%) individuals developed 744 STIs for an IR of 12.6 (95%CI=11.7-13.5)/100 PY (Table S2, http://links.lww.com/QAD/D553). HIV load was available for the three months preceding each STI, with a time interval of 15 (0-77) days. Thirty-four (11.1%) of the 307 MSMWH who developed STIs had ≥1 event at HIV load ≥200 copies/mL; 21 (6.8%) had ≥1 STI at HIV load ≥1000 copies/mL.

Notably, 32 (10.4%) of 307 individuals with ≥1 incident STI had TXF/FTC- and/or CAB-R strains [28 (9.1%) TXF/FTC-R, 1 (0.3%) CAB-R, 3 (1.0%) TXF/FTC+CAB-R]. Five (15.6%) of the 32 TXF/FTC- and/or CAB-R MSMWH with STIs [4/28 (14.3%) TXF/FTC-R, 1/1 (100%) CAB-R, and 0/3 (0%) TXF/FTC+CAB-R] had ≥1 event at HIV load ≥200 copies/mL (all with ≥1 event at ≥1000 copies/mL; Figure 1; Figure S1, http://links.lww.com/QAD/D551; Table S3, http://links.lww.com/QAD/D554). However, the incidence of STIs was significantly lower in the presence of drug resistance (Table 2).

**Discussion**

Our findings showed that 10.4% of MSMSWH who developed STIs were characterized by resistance to TXF/FTC and/or CAB, with an STI incidence of 8.2/100 PY for resistance to one compound, 2.9/100 PY for resistance to both.

Although these incidence rates were significantly lower than that observed in the group without TXF/FTC and/or CAB resistance and the proportions of individuals who developed STIs during follow-up followed the same trend, these results are noteworthy: first, in our study, TXF/FTC- and/or CAB-R MSMWH were older than those without resistance; second, $CD4^+$ nadir was lower in the TXF/FTC- and/or CAB-R groups, suggesting a higher disease burden, as previously reported in PWH with drug resistance [8,9]. Despite these aspects, the occurrence of STIs in TXF/FTC- and/or CAB-R MSMWH suggests an active sexual life with unprotected sex, consistent with our previous findings in the 4-class drug-resistant population [10]. This hypothesis is further supported by the high HCV seroprevalence among TXF/FTC- and/or CAB-R MSMWH; the increased value compared to MSMWH without resistance is probably related to the older age of the TXF/FTC- and/or CAB-R groups, reflecting the global decline in HCV diagnoses [11].

Interestingly, among TXF/FTC- and/or CAB-R MSMWH who developed incident STIs, 5 had ≥1 STI diagnosis at HIV load ≥200 (and specifically ≥1000) copies/mL; even if this number may seem low, mainly thanks to the numerous and effective ART alternatives available, it represents between 1 in 10 and 1 in 20 of the overall group with resistance to at least one compound. The risk of sexual HIV transmission is well established at viremia ≥1000 copies/mL, while it is debated between 200 and 999 copies/mL [12]. In these cases, drug-resistant virus transmission might not be prevented by PrEP: breakthrough HIV infections have been described in highly oral PrEP-adherent individuals due to acquisition of TXF- and/or FTC-R strains [6]. The recent approval of injectable CAB for PrEP is particularly promising, not only because of its long-acting mechanism, but also for the currently lower prevalence of integrase inhibitor-R strains [13]. However, we highlighted 2 cases of MSM with a pre-ART genotype characterized by resistance to CAB and a case of a CAB-R MSMWH with ≥1 STI at HIV load ≥1000 copies/mL, suggesting the possibility of uncontrolled HIV transmission even with injectable PrEP. Therefore, in case of TXF/FTC and/or CAB resistance, achieving an HIV load <1000 (or better <200) copies/mL [12,14] through ART and adherence optimization, together with careful transmission prevention counseling, becomes mandatory.

Finally, the risk of HIV transmission is increased in case of co-occurring STIs [5]: HIV compartmentalization in genital tract appears to be increased in presence of STIs and some STIs have been shown to be associated with increased plasma viral load. In case of STIs, the risk of HIV acquisition is also higher in individuals at risk for HIV [5,12]: according to high-

quality data in MSM, this risk is doubled with chlamydia, quadrupled with syphilis or gonorrhea [15]. This further highlights the need to prioritize virological suppression in TXF/FTC- or CAB-R MSMWH with an active sexual life.

The current investigation has some limitations that need to be mentioned. First, the study design was retrospective, with a possible underestimation of the number of STIs. Second, the number of TXF/FTC- and/or CAB-R MSMWH may appear limited, but it represented >10% of the total study population. Finally, another constraint is the HIV load used to classify STIs: it was measured within the previous 3 months, possibly leading to an inaccurate estimation of the risk of concomitant HIV transmission, despite the generally more limited time span.

In conclusion, the current study provides evidence of the occurrence of sexually transmitted infections in MSM with HIV and resistance to TXF/FTC and/or CAB. Given the risk of transmission of a drug-resistant virus uncontrolled by currently available PrEP strategies, careful discussion of HIV resistance test results and their individual and public health implications should be guaranteed.

**Notes**

**Acknowledgements.** We thank all MSMWH enrolled in this study and all doctors and nurses working at HIV Clinic, Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy.

Preliminary results of this work were presented at ICAR 2024: the 16th Italian Conference on AIDS and Antiviral Research (Rome, June 19th-21st, 2024) and HIVR4P 2024, the 5th HIV Research for Prevention Conference (Lima, October 6th-10th, 2024).

**Author Contribution.** T.C. and V.S. conceived the study, contributed to data collection, interpreted the findings, and drafted the manuscript. A.R.R. and S.N. contributed to study design and data collection and reviewed the manuscript. M.B., R.L., and S.D. performed statistical analysis, contributed to data collection, and reviewed the manuscript. R.P.B., C.M., M.N., G.T., E.M., and S.B. contributed in data collection and reviewed the manuscript. A.C. coordinated activities and contributed to the reviewing of the article.

**Data availability.** The datasets used and analyzed during the current study may be available from the corresponding author upon reasonable request.

**Financial support.** This work did not receive funding from any specific government or private entities.

**Potential conflicts of Interest.** We declare no competing interests related to this work. T.C. has received personal fees for speaker panels from Gilead Sciences. A.R.R. has received personal fees for speaker panels from Gilead Sciences. E.M. has received personal fees for speaker panels from Gilead Sciences. A.C. has received personal fees for advisory boards, speaker panels and educational materials from Gilead Sciences, ViiV Healthcare, Janssen-Cilag, Merck Sharp & Dohme, and Theratechnlogies. S.N. has received personal fees for advisory boards from Gilead Sciences and ViiV Healthcare, for speaker panels from Gilead Sciences, ViiV Healthcare, and Merck Sharp & Dohme, for meeting attendance from Gilead Sciences and Pfizer, payments to her institution for consultancies from Gilead Sciences and ViiV Healthcare. V.S. has received grants from Gilead Sciences, personal fees for speaker panels from Gilead Sciences, ViiV Healthcare and Merck Sharp & Dohme. All other authors: no potential conflicts.

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**Figure 1.** Proportion of men who have sex with men with HIV who developed incident sexually transmitted infections according to their HIV resistance profile.

Abbreviations: CAB: cabotegravir; FTC: emtricitabine; HIV: human immunodeficiency virus; MSM: men who have sex with men; STI: sexually transmitted infection; TXF: tenofovir

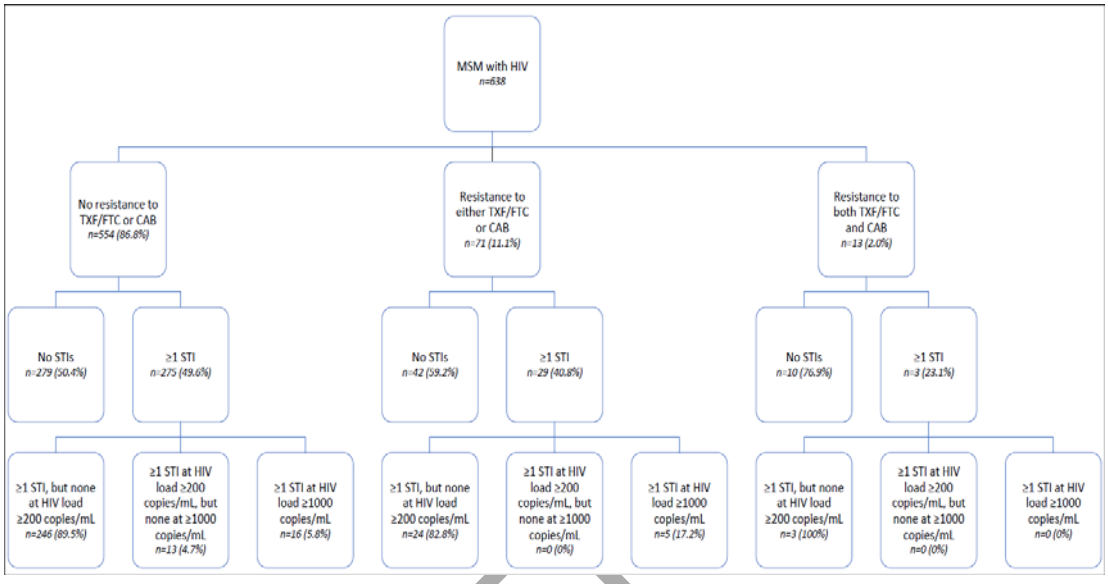

**Table 1.** Baseline characteristics of men who have sex with men with HIV included in the analysis.

Abbreviations: ART: antiretroviral therapy; CAB: cabotegravir; FTC: emtricitabine; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; TXF: tenofovir.

| **Baseline characteristics** | **Overall (n=638)** | **No resistance to TXF/FTC or CAB (Control group; n=554)** | **Resistance to either TXF/FTC or CAB (Group 1; n=71)[1]** | **Resistance to both TXF/FTC and CAB (Group 2; n=13)** | **Group 2 vs 1 vs control p-value[2]** |
|---|---|---|---|---|---|
| **Age (years)** | 38.1 (30.8-45.2) | 37.2 (30.0-43.7) | 46.4 (40.4-52.1) | 51.4 (44.1-53.9) | **<0.001** |
| **ART-naïve** | 501 (78.5%) | 489 (88.3%) | 12 (16.9%)[3] | 0 (0%) | **<0.001** |
| **HIV load (copies/mL)** | 44010 (8459-140462) | 57000 (13491-159100) | 4195 (742-21286) | 3570 (1127-12006) | **<0.001** |
| **HIV load <50 copies/mL** | 3 (0.5%) | 2 (0.4%) | 1 (1.4%) | 0 (0%) | 0.463 |
| **$CD4^+$ T-cell count ($cells/mm^3$)** | 393 (260-566) | 385 (252-550) | 506 (302-686) | 392 (328-538) | **0.011** |
| **$CD8^+$ T-cell count ($cells/mm^3$)** | 998 (750-1359) | 992 (746-1336) | 1058 (771-1567) | 1163 (974-1380) | 0.237 |
| **$CD4^+/CD8^+$ ratio** | 0.38 (0.23-0.57) | 0.37 (0.23-0.56) | 0.43 (0.26-0.67) | 0.26 (0.19-0.55) | 0.074 |
| **$CD4^+$ nadir ($cells/mm^3$)** | 338 (195-495) | 359 (229-510) | 200 (55-340) | 137 (64-202) | **<0.001** |
| **Positive HBsAg** | 29 (4.5%) | 23 (4.2%) | 6 (8.5%) | 0 (0%) | 0.261 |
| **Positive HCV serostatus** | 40 (6.3%) | 26 (4.7%) | 9 (12.7%) | 5 (38.5%) | **<0.001** |

[1] 67 with resistance to TXF/FTC and 4 with resistance to CAB

[2] by Kruskal-Wallis test (continuous variables), chi-square test (categorical variables), as appropriate

[3] 10/67 (14.9%) with resistance to TXF/FTC and 2/4 (50.0%) with resistance to CAB

**Table 2.** Incidence of sexually transmitted infections in men who have sex with men with HIV according to their HIV drug resistance profile.

Abbreviations: CAB: cabotegravir; FTC: emtricitabine; IR: incidence rate; IRR: incidence rate ratio; MSMWH: men who have sex with men with HIV; NA: non-available; PY: person-years-of-follow-up; STI: sexually transmitted infection; TXF: tenofovir; 95%CI: 95% confidence interval.

| | **No resistance to TXF/FTC or CAB (Control group)** | **Resistance to either TXF/FTC or CAB (Group 1)** | **Resistance to both TXF/FTC and CAB (Group 2)** | **Group 1 vs control** | **Group 2 vs control** |
|---|---|---|---|---|---|
| **Proportion of MSMWH with ≥1 STI** | 275/554 (49.6%) | 29/71 (40.8%) | 3/13 (23.1%) | p=0.168[§] | p=0.089[§] |
| **Number of STIs** | 710 | 60 | 4 | NA | NA |
| **Incidence of STIs** | IR=13.5 (95%CI=12.5-14.6)/100 PY | IR=8.2 (95%CI=6.2-10.5)/100 PY | IR=2.9 (95%CI=0.8-7,3)/100 PY | IRR=0.6 (95%CI=0.5-0.8) **p<0.001**[§§] | IRR=0.2 (95%CI=0.1-0.5) **p<0.001**[§§] |

[§] by Fisher's exact test

[§§] by Poisson regression