

HIV and urethritis: time required for antiretroviral therapy to suppress HIV in semen

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Objectives: To examine the time required to suppress HIV in the genital tract with antiretroviral therapy (ART) in men with urethritis.

Design: An observational cohort study.

Methods: Men with HIV and urethritis not on ART were enrolled at an STI clinic in Malawi and offered to initiate ART. Blood and semen samples were collected pretreatment and at 1, 2, 4, 8, 12 and 24 weeks post-urethritis treatment. Median viral loads (VLs) were calculated by ART initiation groups: 'within 1 week', 'between 1 and 4 weeks' and 'no ART before 4 weeks', based on the men's choice about whether or not to initiate ART. The presence of ART at each visit was confirmed by bioanalytical methods.

Findings: Between January 2017 and November 2018, 74 men presented with urethritis and HIV and were confirmed ART naive. The median age was 32 years. Forty-one (55% of men) initiated ART within 1 week; 12 (16%) between 1 and 4 weeks; and 21 (28%) did not initiate ART by week 4. Within the 1 week group, median VL was suppressed within 4 weeks in both semen and blood. Among the 1–4 weeks group, VL was suppressed within 4 weeks in semen and 5 weeks in blood. Among the no ART before 4 weeks group, VL in semen declined within the first 4 weeks but remained unsuppressed through week 24, and there was no significant decline in blood HIV.

Conclusion: Treatment of urethritis and prompt initiation of ART with counseling for safer sex for at least one month is a critical measure to reduce transmission of HIV.

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Introduction

HIV concentration in blood [1] and semen [2] strongly correlate with the probability of HIV transmission. HIV concentration in semen is increased with the mucosal inflammation associated with urethritis [3,4], creating greater risk of viral transmission [2,3,5]. We recently demonstrated that treatment of gonococcal urethritis with an antibacterial agent among men already receiving antiretroviral therapy (ART) led to a decrease in transiently raised HIV viral load in semen to a baseline level over one month [6]. In the present study, we describe the velocity of reduction of HIV in blood and semen in men presenting with urethritis with initiation of ART. It is common to find untreated HIV infection among men who present with urethritis, and so understanding the timing and magnitude of benefit of initiation of ART is important for HIV prevention.

Methods

We conducted an observational cohort study of HIV-infected ART naïve men with acute urethritis, defined as presence of urethral discharge during clinical examination, at the Bwaila District Hospital STI clinic in Lilongwe, Malawi [6]. The Bwaila District Hospital is the largest public secondary care health facility under the Lilongwe District Health Office [6].

Men living with HIV who came for treatment of urethritis were recruited on the same day of their clinic visit. HIV diagnosis was confirmed using rapid point-of-care tests per Malawian HIV testing guidelines [7]. Blood and semen samples were collected for HIV viral load testing and syphilis serologies were performed (BD Macro-Vue RPR and Serodia TP-PA). Urethral swabs were collected at all episodes of urethritis for etiologic testing (*Neisseria gonorrhoea*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*) using GeneXpert (*N. gonorrhoeae* and *C. trachomatis*), culture (*N. gonorrhoeae*) or OSOM-Trichomonas 105 Rapid Test (*T. vaginalis*). All patients were treated for urethritis with gentamicin 240 mg i.m. single dose, doxycycline 100 mg orally twice daily for 7 days, and metronidazole 2 g orally as a single dose, and referred for ART initiation per Malawian syndromic STI treatment guidelines [8].

Follow-up study visits occurred at 1, 2, 4, 8, 12, 24, 36, and 48 weeks. If a participant initiated ART after their week 1 visit, the calendar reset to week 1 to optimize visit frequency around the time of ART initiation. At each follow-up visit, blood and semen were collected for HIV viral loads and any incident cases of urethritis were assessed. Viral suppression was defined as <400 copies/ml. Detectable viral load was 20 copies/ml.

In this analysis, we included men living with HIV who enrolled in the study and completed at least one follow-up visit. Participants who had ART detected in their blood at enrollment were excluded from this analysis. For our longitudinal analyses, participant follow-up was analytically censored at any repeat case of urethritis after 4 weeks (urethral discharge within 4 weeks of enrollment was considered persistent urethritis) [6]. Follow-up was also analytically censored at ART interruption for those who started within 4 weeks of urethritis diagnosis, and at ART initiation for those who started after 4 weeks post-urethritis diagnosis. Pre-ART follow-up data from the latter group was then included in the 'no ART before 4 weeks' analyses. We used descriptive statistics to characterize participants, as well as Fishers exact test (categorical variables) and the Mann-Whitney *U* test (continuous variables) to assess differences by ART initiation status ($\alpha=0.05$). Median viral loads and interquartile ranges (IQRs) were calculated by visit and ART initiation groups.

To confirm ART use, blood plasma from venipuncture specimens from each visit were qualitatively screened for the presence of 10 different ART drugs by adapting a previously described LC-MS/MS approach [9] for the following drugs; efavirenz, atazanavir, lopinavir, ritonavir, tenofovir, lamivudine, emtricitabine, abacavir, zidovudine and nevirapine.

This study was approved by the Malawi National Health Science Research Ethics Committee and the University of North Carolina Institutional Review Board. All participants provided written informed consent for study participation. Study funders had no role in study.

Results

Between January 2017 and November 2018, 74 men presented to the STI clinic with acute urethritis and HIV who were confirmed to not be taking ART and had ≥ 1 follow-up visit. (Table 1). Participants reported having urethritis a median of 4 days (IQR: 3, 7) before seeking treatment. Patients had varying degrees of delay of ART (Table 1). Sixty participants initiated a combination of tenofovir, lamivudine and efavirenz and two participants initiated tenofovir, lamivudine and nevirapine. Detailed information about the cause of urethritis and the participants is presented in the Table 1.

The concentration of HIV in blood and semen was measured at each visit and is summarized in Fig. 1. The time required to achieve viral suppression is provided in Table 2. Twenty-one subjects did not start treatment. Their median blood viral load at baseline (pretreatment) was 22 720 copies/ml (IQR: 9052–86 802) and the median semen viral load was 22 497 copies/ml (IQR:

Table 1. Participant characteristics of men with acute urethritis living with HIV and not taking ART at enrollment.

Characteristic	Total n (%)	Initiated ART n (%)	No ART n (%)
Total	74	62	12
Age (median, IQR)	32 (27, 37)	32 (27, 37)	32 (26, 38)
Days of urethritis (median, IQR)	4 (3, 7)	4 (3, 7)	4 (3, 11)
Urethritis etiologies at enrollment			
<i>Neisseria gonorrhoeae</i> (NG)	62 (84)	51 (82)	11 (92)
<i>Neisseria gonorrhoeae</i> (by NAAT)	62 (84)	51 (82)	11 (92)
<i>Neisseria gonorrhoeae</i> (by culture) ^a	53 (73)	44 (71)	9 (82)
<i>Chlamydia trachomatis</i> (CT)	10 (14)	8 (13)	2 (17)
<i>Trichomonas vaginalis</i> (TV)	2 (3)	1 (2)	1 (8)
Number of etiologies (of NG, CT, TV)			
0	8 (11)	7 (11)	1 (8)
1	59 (80)	50 (81)	9 (75)
≥2	7 (9)	5 (8)	2 (17)
Number of additional urethritis episodes (excluding enrollment)			
0	62 (84)	53 (85)	9 (75)
1	9 (12)	6 (10)	3 (25)
2	3 (4)	3 (5)	0 (0)
HIV diagnosis			
New HIV diagnosis	43 (58)	37 (60)	6 (50)
Previous HIV diagnosis	31 (42)	25 (40)	6 (50)
Syphilis ^b	7 (10)	5 (8)	2 (18)
ART use			
ART by week 1, no interruption ^c	26 (35)	26 (42)	0 (0)
ART by week 1, interrupted ^{c,d}	15 (20)	15 (24)	0 (0)
ART by weeks 2–4, no interruption ^c	6 (8)	6 (10)	0 (0)
ART by weeks 2–4, interrupted ^c	6 (8)	6 (10)	0 (0)
ART after 4 weeks	9 (12)	9 (15)	0 (0)
No ART initiation	12 (16)	0 (0)	12 (100)

CT, *Chlamydia trachomatis*; NAAT, Nucleic Acid Amplification Test; NG, *Neisseria gonorrhoeae*; TV, *Trichomonas vaginalis*.

^a*n* = 73; one *N. gonorrhoeae* culture result is missing. All participants with a positive *N. gonorrhoeae* culture tested positive for *N. gonorrhoeae* via NAAT.

^b*n* = 72; one syphilis result was unknown, one was indeterminate.

^cART interruption was defined as a visit with no ART detected in the blood, after ART initiation.

3357–402 355; Fig. 1). During follow-up of this group, the median blood viral load remained relatively stable and unsuppressed at 4 weeks (median: 37 696; IQR: 21 928–101 154), 12 weeks (median: 44 398; IQR: 23 602–114 936) and 24 weeks (median: 23 814; IQR: 10 243–33 520). In the semen however, the median viral load decreased during the first 4 weeks (median: 2534; IQR: 366–61 117) and then remained relatively stable but unsuppressed through 12 weeks (median: 2062; IQR: 102–20 390) and 24 weeks (median: 2250; IQR: 470–12 723). One third of participants experienced suppression of HIV in semen in the absence of ART.

The remainder of subjects initiated treatment within one week or four weeks of urethritis.

Among participants who initiated ART within 1 week of acute urethritis diagnosis and treatment (*n* = 41), the baseline median blood viral load was 70 617 copies/ml (IQR: 22 995–271 400) and 82 071 copies/ml (IQR: 4926–233 022) in semen. The median blood viral load was suppressed by week 4 (<400 copies/ml) and remained suppressed through 24 weeks. The median seminal viral load experienced a rapid decrease to <1000 copies/ml by week 1 and was suppressed (<400 copies/ml) by week 4 and remained suppressed through week 24.

Among those who delayed ART and initiated treatment between 1 and 4 weeks (*n* = 12), the baseline median blood viral load was 44 258 copies/ml (IQR: 22 623–140 366) and the median semen viral load was 56 698 copies/ml (IQR: 3625–231 045). The seminal viral load remained above 10 000 copies/ml through the first week of treatment but was suppressed (<400 copies/ml) by 4 weeks and remained suppressed through 24 weeks. The median viral load in the blood reached suppression (<400 copies/ml) by week 5 after treatment and remained low through week 24. Assessment of adherence to treatment as demonstrated by detection of ART in blood samples is provided in Table 1.

Discussion

While there has been some reduction in HIV incidence worldwide [10], the burden of STIs remains very high [11] and STIs are frequently detected in people living with HIV [12–14]. ART leads to reduction of HIV transmission [15–18]. Untreated people living with HIV who develop an STI present increased risk for HIV transmission because of increased concentration of HIV in the genital tract [4]. Even on ART, urethritis causes transient increase in HIV in the male genital tract

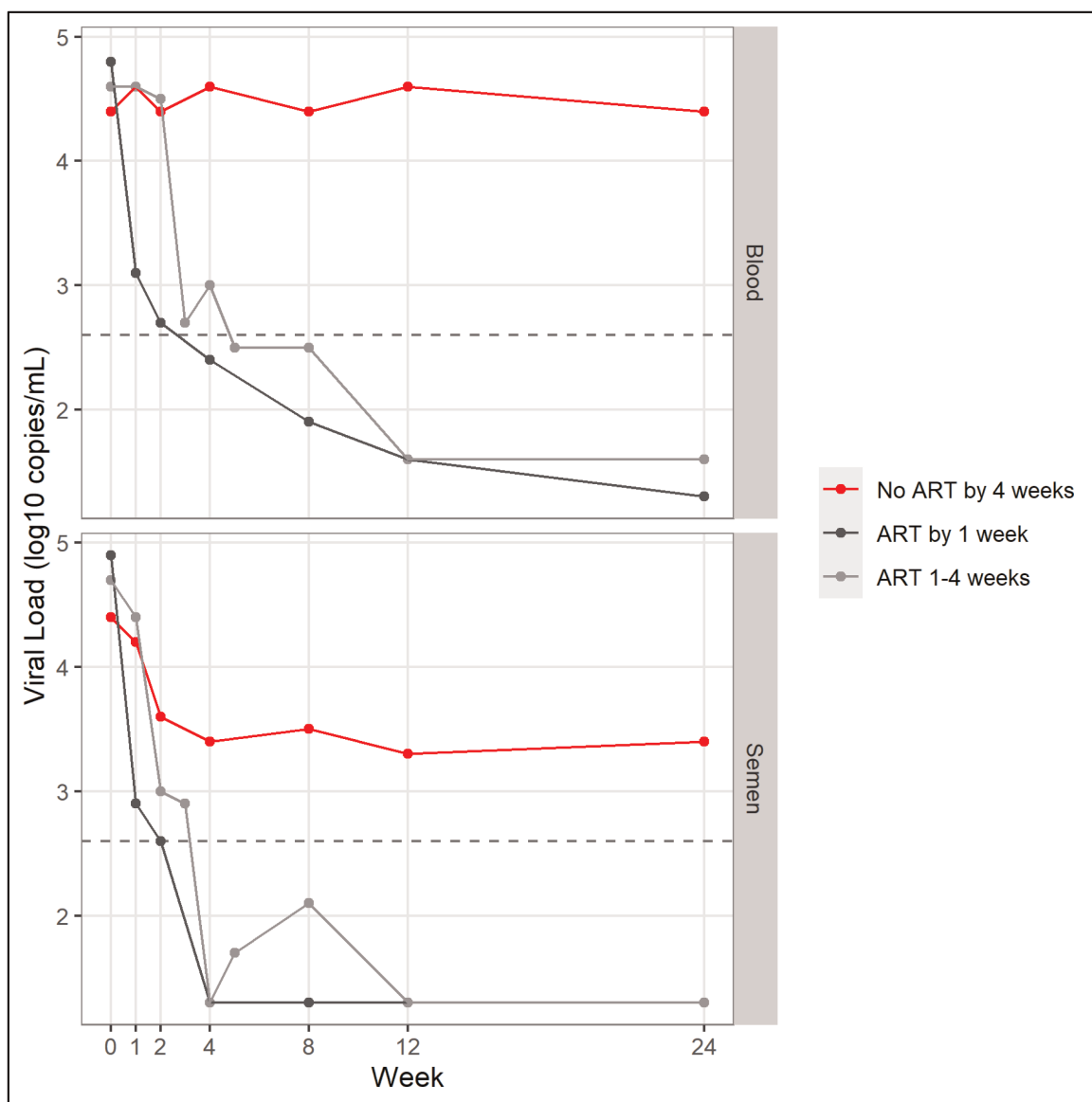


Fig. 1. Median viral load in blood and semen by visit across ART initiation groups. Group included if there were at least six data points in a given week.

Table 2. Viral suppression (<400 copies/ml) by visit across ART group.

	Enroll	Week1	Week 2	Week 3	Week 4	Week 5	Week 8	Week 12	Week 24
<i>Blood</i>									
ART by 1 week	1/41 (2)	10/39 (26)	17/41 (41)	–	24/36 (67)	–	22/31 (71)	23/26 (88)	21/25 (84)
ART 1–4 weeks	0/12 (0)	0/11 (0)	1/12 (8)	1/6 (17)	2/8 (25)	3/6 (50)	3/6 (50)	8/8 (100)	6/7 (86)
No ART by 4 weeks	2/21 (10)	2/20 (10)	2/20 (10)	–	1/16 (6)	–	1/14 (7)	1/12 (8)	0/13 (0)
<i>Semen</i>									
ART by 1 week	7/40 (18)	17/39 (44)	19/39 (49)	–	19/35 (54)	–	27/31 (87)	20/26 (77)	21/25 (84)
ART 1–4 weeks	2/12 (17)	0/11 (0)	4/11 (36)	3/6 (50)	4/7 (57)	4/6 (67)	3/6 (50)	7/8 (88)	7/7 (100)
No ART by 4 weeks	4/21 (19)	3/19 (16)	5/20 (25)	–	4/16 (25)	–	3/13 (23)	4/12 (33)	3/13 (23)

Because those who initiated ART after 1 week had visits added 1, 2, and 4 weeks after reported ART initiation, participants in the ART 1–4 week group were seen at different weeks than the other groups and had varying denominators on those weeks. Only those weeks with ≥5 participants are included (e.g. week 3 and week 5).

that is reversed over a month with additional antibiotic therapy that decreases inflammation and breakthrough of HIV [6]. The present study was undertaken to examine the time required to suppress HIV in the genital tract after first initiation of ART in men with urethritis [19–22].

Some men did not choose to initiate ART. While replication of gonorrhoea abates only hours after antibiotic initiation [23] such treatment of urethritis reduces but generally does not eliminate HIV in semen [3,4]. In our earlier study of men with urethritis before ART was available, we found persistence of HIV of greater than 10^4 copies/ml in semen 2 weeks after antibiotic treatment of urethritis [4], suggesting considerable risk for HIV transmission [5,16].

In the present study, most men started ART at or shortly after detection of urethritis. The treatment regimens used including agents initiated have been shown to be detected in seminal plasma and effective in suppressing HIV in blood and semen [15,20,21]. Participants with immediate or delayed initiation of ART experienced gradual reduction in HIV in blood and semen during recovery from urethritis.

ART can be expected to prevent HIV transmission when semen [5] and blood (Broyles *et al.*, in press, *Lancet* 2023) viral load is reduced below 1000 copies/ml [5]. In the absence of a vaccine, treatment of HIV as prevention (TasP) is widely considered the most important strategy for HIV prevention [18,24]. HIV will be detected in a substantial number of men with urethritis, regardless of ART status [6]. The current study emphasizes the critical importance of rapid HIV testing for men with urethritis, and concomitant initiation of ART. The ability of ART to virtually eliminate HIV transmission [10,15–18] has rightly led to the U=U campaign [25], but it is worth noting that U=U is not instant as shown in this study and Mujugira *et al.* [26] that transmission risk persists for a period of time after ART initiation.

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analysis. A.K., M.L.C., A.P.S., B.V.H. and L.A.T. were responsible for antiretroviral drug testing and manuscript review. G.T., G.B., I.T. and A.J.L. were responsible for laboratory testing and manuscript review. All authors reviewed and approved the manuscript.

Conflicts of interest

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