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Antiretroviral drug use and HIV drug resistance among MSM and transgender women in sub-Saharan Africa

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Abstract

Objective: To analyze antiretroviral (ARV) drug use and HIV drug resistance among HIV-infected men who have sex with men (MSM) and transgender women who were screened for participation in the HIV Prevention Trials Network (HPTN) 075 study.

Methods: A qualitative assay was used to detect 20 ARV drugs in five drug classes; this assay is based on liquid chromatography coupled with high-resolution accurate-mass mass spectrometry. HIV viral load testing was performed using the RealTime HIV-1 Viral Load Assay. HIV drug resistance testing was performed using the ViroSeq HIV-1 Genotyping System. Logistic regression was used to evaluate factors associated with study outcomes.

Results: ARV drugs were detected in 63 (34.4%) of 183 participants who had confirmed HIV infection at screening; 11 (17.5%) of the 63 participants were not virally suppressed. Six (54.5%) of the 11 participants had drug-resistant HIV, including four who had multiclass resistance. Seven (63.6%) of the 11 were at risk of acquiring resistance to additional ARV drugs. In multivariate

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model, ARV drugs were more frequently detected in older participants, those recruited from Kisumu, Kenya, and those who reported ever having been in HIV care or on ART.

Conclusion: Most of HIV-infected persons screened for participation in HPTN 075 were not on antiretroviral treatment (ART), and many of those who were on ART were not virally suppressed. Many of those participants had drug-resistant HIV. These findings highlight the need for improved HIV care for African MSM and transgender women.

Keywords

HIV; antiretroviral drugs; HIV drug resistance; HPTN 075; viral suppression

INTRODUCTION

Men who have sex with men (MSM) are disproportionally affected by the global HIV epidemic [1–3]. Based on a survey from 2001–2006, the risk of HIV infection in low and middle-income countries was nearly 19 times higher among MSM compared to the general population [4]. African MSM are also at high risk of HIV infection [4–8]. HIV prevalence among MSM in sub-Saharan Africa was reported to be 3.6 fold higher than the prevalence in the general population [1]. Despite efforts to curb the HIV epidemic, HIV incidence remains high among African MSM [1, 9]. Compared to MSM, transgender women in Africa are at an even higher risk of HIV infection [10].

Antiretroviral therapy (ART) plays an essential role in achieving the “90–90–90” target to end the HIV/AIDS epidemic [11]. In sub-Saharan Africa, 7.5 million people living with HIV were receiving ART by the end of 2012 [12]. However, criminalization and social stigmatization have limited use of HIV prevention interventions and access to HIV treatment among MSM in many regions of sub-Saharan Africa [13]. There is little information about antiretroviral (ARV) drug use among HIV-infected MSM in Africa. As access to ART increases, the prevalence of HIV drug resistance is rising in sub-Saharan Africa [14]. HIV drug-resistance may lead to ART failure and worse health outcomes, compromising long-term control of the HIV/AIDS epidemic. There are limited data describing HIV drug resistance among African MSM and transgender women.

ARV drug testing provides an objective biomedical measure of ARV drug use. We developed a high-throughput assay for ARV drug detection that was used to assess ARV drug use in a large, cross-sectional survey of African adults [15] and other clinical trials and cohort studies [16–18]. HPTN 075 was a multi-site observational cohort study that assessed the feasibility of recruiting and retaining MSM and transgender women, to facilitate future HIV prevention studies in this high-risk population. In this study, we assessed ARV drug use and HIV drug resistance among men and transgender women who were screened for participation in HPTN 075.

METHODS

Study cohort

HPTN 075 screened MSM and transgender women at four study sites in three countries (Kisumu, Kenya; Blantyre, Malawi; Soweto and Cape Town, South Africa). Participants included in this analysis met the following study criteria: age 18 to 44 years, male sex assigned at birth, ever having had sex with a man, willingness to be tested for HIV infection, and confirmed HIV infection at screening.

A subset of the participants described in this study were subsequently enrolled in the HPTN 075 study. HPTN 075 enrolled both HIV-infected and HIV-uninfected MSM and transgender women (age 18–44) who reported anal sex in the past 3 months. HIV-infected participants were excluded from enrollment in HPTN 075 if they reported that they were in HIV care or had been prescribed ART. Study staff were instructed not to disclose the enrollment criteria to the participants during the screening visit.

Laboratory testing

Participants were tested for HIV infection at the screening visit at study sites using either two HIV rapid tests or one HIV rapid test and one enzyme immunoassay. These tests were performed in parallel; at least one of the two tests was performed in a laboratory. Participants were considered to be HIV infected if both tests were reactive. Additional testing was performed retrospectively at the HPTN Laboratory Center (Baltimore, Maryland) using samples collected at the screening visit. This included further testing to confirm HIV status, ARV drug testing, HIV resistance testing, and HIV viral load testing.

ARV testing was performed using a multidrug assay that combines high performance liquid chromatography (HPLC) with high resolution mass mass spectrometry in five drug classes, including three non-nucleoside reverse transcriptase inhibitors (NNRTIs, efavirenz [EFV], nevirapine [NVP], and rilpivirine [RPV]), six nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs, abacavir [ABC], emtricitabine [FTC], lamivudine [3TC], stavudine, tenofovir [TFV], and zidovudine), nine protease inhibitors (PIs, amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir [NFV], ritonavir, saquinavir, and tipranavir), one integrase strand transfer inhibitor (raltegravir [RAL]), and one CCR5 receptor antagonist (maraviroc [MVC]) [17]. The limit of detection is 2 ng/mL for six of the 20 drugs (RAL, MVC, NVP, RPV, ABC and NFV), and 20 ng/mL for the other 14 drugs [17].

HIV drug resistance testing was performed for the subset of HIV-infected participants who had ARV drugs detected and had a HIV viral load > 400 copies/mL. This testing was performed using the ViroSeq HIV-1 Genotyping System, v3.0 (Abbott Diagnostics, Des Plaines, IL). HIV sequences were submitted to GenBank (accession numbers: MG597249–MG597259).

HIV viral load testing was performed with the RealTime HIV-1 Viral Load Assay (Abbott Molecular, Abbott Park, IL). A validated dilution method was used for testing because the volume of plasma available for testing was limited in some cases; this method has a lower

limit of quantification of 400 copies/mL HIV RNA. Viral suppression was defined as viral load <400 copies/mL.

Statistical analysis

Univariate and multivariate logistic regression were used to analyze the association of ARV drug detection and other factors (SAS, version 9.4).

Ethical Considerations

All study participants provided informed consent for screening for the HPTN 075 study (oral consent in Blantyre, Malawi; written consent at the other study sites). The study was approved by Institutional Review Boards at each site.

RESULTS

Study cohort

In HPTN 075, 624 MSM and transgender women were screened for study participation; 26 did not meet screening criteria and were excluded from analysis. The remaining 598 participants, included 168 from Kisumu, Kenya; 122 from Blantyre, Malawi; 170 from Soweto, South Africa; and 138 from Cape Town, South Africa. Overall, 183 (30.6%) of 598 participants had confirmed HIV infection at screening (Figure 1).

Detection of ARV drugs

Plasma samples collected at the screening visit were tested for the presence of ARV drugs. At least one ARV drug was detected in samples from 63 (34.4%) of the 183 HIV-infected participants, including 19 participants Kisumu, 10 from Blantyre; 11 from Cape Town, and 23 from Soweto (Figure 1, Table 1). NNRTIs and NRTIs were the only classes of ARV drugs detected (Table 1). Two NNRTIs were detected (59 were taking EFV; 5 were taking NVP), and four NRTIs were detected (52 were taking TFV; 31 were taking 3TC; 27 were taking FTC; one man was taking ABC). Two or more ARV drugs were detected in 57 (90.5%) of the 63 cases, consistent with use of a multi-drug regimen for ART; two of those participants had unusual combinations of ARV drugs that were not consistent with recommended treatment regimens (one had 2 NNRTIs + 2 NRTIs; one had 1 NNRTI + 3 NRTIs). The remaining six participants had a single ARV drug detected (all had EFV detected alone).

Eleven (17.5%) of the 63 participants who had ARV drugs detected were not virally suppressed (HIV viral load ≥ 400 copies/mL, Table 1). These 11 participants included six from Kisumu, Kenya; one from Blantyre, Malawi; three from Cape Town, South Africa; and one from Soweto, South Africa (Table 2). The median viral load for the 11 participants was 2,200 copies/mL (range: 430 to 31,650 copies/mL). These 11 cases included four where EFV was the only ARV drug detected and seven where two or three ARV drugs were detected (Table 2).

HIV drug resistance

HIV genotyping was performed for the 11 participants who had ARV drugs detected and were not virally suppressed. At least one major drug resistance mutation was detected in six

of the 11 cases (Table 2). One case had NNRTI resistance only (case 9), one case had NRTI resistance only (case 5), and four cases had multiclass resistant HIV (NRTI plus NNRTI resistance, cases 4, 6, 7, and 8). The most frequently detected mutations were M184V/I (N=5; associated with NRTI resistance) and K103N (N=3; associated with NNRTI resistance). Two participants had the K65R mutation, which confers resistance to tenofovir disoproxil fumarate, one of the components of Truvada®, which is used for HIV pre-exposure prophylaxis.

All five of the participants who had HIV with major NNRTI resistance mutations were taking EFV or NVP. Among the five participants who had HIV with major NRTI resistance mutations, two had 3TC detected, two had 3TC plus TFV detected, and one had no NRTIs detected. In seven (63.6%) of the 11 cases, ARV drugs were detected without detection of corresponding resistance mutations (Table 2). Some of these 11 participants were at risk of acquiring HIV resistance to additional ARV drugs over time. Four participants were at risk of acquiring NNRTI resistance (cases 1–3 and 5), and three were at risk of acquiring NRTI resistance (cases 9–11); in these cases, participants were taking NNRTIs (EFV or NVP) or NRTIs (various combinations of 3TC, TFV, and FTC) and were not virally suppressed.

Factors associated with detection of ARV drugs

We next evaluated the association of demographic and behavioral factors with ARV drug use (Table 3). In a multivariate model, ARV drugs were more frequently detected among participants who reported being engaged in HIV care or any current or prior ARV drug use, compared to those who did not report prior HIV care or ARV drug use (88.5% vs. 9.8%, $p<0.001$). ARV drugs were also detected more frequently among participants who were not asked these questions because they did not report a prior HIV positive test, compared to participants who did not report prior HIV care or ARV drug use (31.0% vs. 9.8%, $p=0.011$). Other factors that were statistically associated with detection of ARV drugs included older age (48.8% in participants >25 years vs. 22.8% in participants ≤25 years, $p=0.019$), and study site (67.9% in Kisumu, Kenya, 37.0% in Blantyre, Malawi, 25.0% in Cape Town, South Africa, and 27.4% in Soweto, South Africa; $p=0.003$, $p=0.022$, $p=0.016$, respectively, with Kenya as the reference). The univariate analysis also found more frequent detection of ARV drugs among those who reported ever having sex with women (43.8% participants who reported having sex with both women and men vs. 27.2% who reported having sex with men only, $p=0.020$), but this association was not significant in the multivariate model.

DISCUSSION

This report evaluated ARV drug use, viral suppression, and HIV drug resistance in a cohort of MSM and transgender women with confirmed HIV infection who were screened for participation in a clinical trial. In this cohort, approximately one third of the participants (34.4%) were taking ARV drugs at the time of study screening. The most common combinations of ARV drugs detected were EFV+3TC+TFV and EFV+FTC+TFV. This combination of drugs is consistent with first-line ART regimens in Kenya, Malawi and South Africa [19–21]. Four participants had one NNRTI detected with one NRTI, and six had EFV alone detected; six of these 10 participants were not virally suppressed. Failure to detect two

NRTIs in these cases may reflect sub-optimal adherence to an ART regimen; alternatively, one or both of the NRTIs may not have been detected because of the short half-lives of these drugs. In the cases where EFV was detected alone, it is also possible that the participants were taking EFV for recreational purposes [22, 23]. Two (3.2%) of the 63 participants in this cohort who were taking ARV drugs had unusual combinations of ARV drugs detected; in contrast, 29 (48.3%) of the men in HPTN 061 who were taking ARV drugs had unusual combinations of drugs detected [16]. This indicates that the African MSM and transgender women recruited for participation in HPTN 075 were more likely to be taking recommended ART regimens than men recruited into HPTN 061, which was conducted at six cities in the United States.

The frequency of ARV drug use varied among the HPTN 075 study sites. The highest frequency of ARV drug detection was in Kisumu, Kenya, where ARV drugs were detected in 68% of the HIV-infected participants; the frequency ranged from 25% to 37% at the other three study sites. These regional differences may reflect differences in the availability of ART or other factors. Regional differences in ART coverage among MSM have been observed globally, from 2% (Jamaica and Kyrgyzstan) to 73% (Denmark) [24]. In Kenya, the ART coverage among gay men and other men who have sex with men was reported to be 69.9% in 2017, which is similar to the coverage reported here (67.9%) [25]. As a result of stigma, discrimination and criminalization, it has been difficult to determine the proportion of MSM in sub-Saharan African countries who are HIV infected and on ART [26, 27]. According to a report published in 2015, ART coverage ranged from 0% to 25% among MSM at different sites in Cameroon, which was much lower than the 57% coverage observed in the general population [28]. In Kenya, Malawi and South Africa, estimated ART coverage among the general population was 64%, 66% and 56% in 2016, respectively [29].

In this study, older age was associated with ARV drug detection. A higher frequency of ART has been reported among older MSM compared to younger men in the United States (US) [30]. Higher rates of ART adherence were also observed in older adults in the US and other countries [31–33]. In our study, sexual partner type (men and women vs. men only) was also associated with ARV drug use, but that association was only observed in univariate analysis. Not surprisingly, in our cohort, participants who reported that they were ever engaged in HIV care and/or on ART were more likely to be using ARV drugs. Participants who reported that they were on ART at the time of screening were not eligible for enrollment in HPTN 075. It is notable that 19 of the participants who enrolled in the study were taking ARV drugs, but did not report this to study staff; in these cases, ARV drug use was revealed through retrospective ARV drug testing. These 19 participants represented 27.1% of the 70 HIV-infected participants enrolled in HPTN 075. In seven (36.8%) of the 19 cases, the participants were not virally suppressed; for this reason, HIV viral load would not have been a useful surrogate marker for undisclosed ARV drug use.

Eleven (17.5%) of the 63 participants who were taking ARV drugs at the screening visit were not virally suppressed. More than half (55%) of those participants had drug-resistant HIV, and about one third (36.3%) had HIV that was resistant to two classes of HIV drugs (multiclass resistance). Furthermore, seven (63.6%) of the 11 participants were at risk of acquiring additional resistance mutations, further limiting their treatment options. One

limitation of this study is that the assay used for ARV drug detection only reflects recent ARV drug use, and drugs present at low levels may not be detected. Also, because population sequencing was used to assess HIV drug resistance, low-frequency drug resistance mutations were not detected; low-frequency mutations can impact ART outcomes [34]. For these reasons, the frequencies of ARV drug use and HIV drug resistance reported in this study should be considered to be minimum estimates.

Conclusion

The overall rate of AIDS-related deaths in sub-Saharan Africa dropped 39% between 2005 and 2013 due to the scale-up of ART [35]. However, the impact of ART scale-up may have had less impact on survival among HIV-infected MSM, because they may have been less likely to access HIV care due to stigma, criminalization, or other factors. Only about one third of the HIV-infected participants who were screened for HPTN 075 were on suppressive ART. Some participants who were not on ART may not have been aware that they were HIV infected [36]. This finding, and our finding that many participants who were taking ARV drugs had drug-resistant HIV, underscores the need for additional interventions for HIV treatment in this high-risk population.

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Fig. 1. Proportion of participants with different study outcomes.

The figure shows a summary of data from the 183 HIV-infected participants who were screened for participation in HPTN 075. ARV drug testing was performed for all 183 participants using samples collected at the screening visit. Sixty-three participants had ARV drugs detected. Eleven of those participants were not virally suppressed (viral load ≥ 400 copies/mL); six of the participants who were not virally suppressed had drug-resistant HIV. Abbreviations: ARV: antiretroviral.

Table 1.

Antiretroviral drugs detected in HIV-infected participants at study screening.*

	VL <400 copies/mL (N=52)	VL 400 copies/mL (N=11)	Total (N=63)
1 ARV drug			
EFV	2	4	6
2 ARV drugs			
NVP+3TC	0	2	2
EFV+3TC	1	0	1
EFV+FTC	1	0	1
3 ARV drugs			
NVP+3TC+TFV	1	1	2
EFV+3TC+TFV	21	3	24
EFV+FTC+TFV	23	1	24
EFV+ABC+3TC	1	0	1
4 ARV drugs*			
EFV+NVP+TFV+FTC	1	0	1
EFV+3TC+TFV+FTC	1	0	1

The table summarizes the results of antiretroviral drug testing for 63 HIV-infected participants who had ARV drugs detected in samples collected from the HPTN 075 screening visit. This group includes 19 participants who were subsequently enrolled in the study. Numbers in the table indicate the number of participants with each drug or combination of drugs detected.

*These combinations of antiretroviral drugs are not recommended for HIV treatment.

Abbreviations: VL: HIV viral load; ARV: antiretroviral; EFV: efavirenz; NVP: nevirapine; 3TC: lamivudine; TFV: tenofovir; FTC: emtricitabine; ABC: abacavir.

HIV drug resistance detected in samples from HIV-infected participants who had one or more antiretroviral drug detected at screening but were not virally suppressed.

Table 2.

Case	ARV drug(s) detected		Viral load (copies/mL)	Study site	HIV drug resistance mutations ^b		
	NNRTI	NRTI			NNRTI mutations	NRTI mutations	PI mutations
1 ^a	EFV		2,930	Kisumu, Kenya	None	None	None
2 ^a	EFV		430	Cape Town, South Africa	None	None	None
3 ^a	EFV		570	Cape Town, South Africa	None	None	None
4 ^a	EFV		17,520	Cape Town, South Africa	K103N, V106M, E138A	M184I	None
5	NVP	3TC	10,230	Kisumu, Kenya	<i>V90I, V106I, E138G, H221Y</i>	<i>D67N, K70R, M184I, V75I/M, K219Q</i>	<i>L10I</i>
6 ^a	NVP	3TC	18,900	Kisumu, Kenya	K103N, H221Y, P225H	<i>K70R, M184V, D67G, K219Q</i>	None
7 ^a	NVP	3TC+TFV	31,650	Kisumu, Kenya	Y181C, G190A, V90I, K101E	<i>K65R, M184I, M41L</i>	None
8	EFV	3TC+TFV	2,200	Blantyre, Malawi	V106M, V179D	<i>K65R, M184V, Y115F</i>	None
9 ^a	EFV	3TC+TFV	480	Kisumu, Kenya	K103N	None	<i>L10I, V11I</i>
10	EFV	3TC+TFV	1,730	Kisumu, Kenya	None	None	None
11	EFV	FTC+TFV	490	Soweto, South Africa	<i>E138A</i>	None	<i>I54T</i>

^aSeven of the 11 participants were enrolled in HPTN 075.

^bMajor resistance mutations are shown in bold; accessory mutations are shown in italics.

Abbreviations: ARV: antiretroviral; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; EFV: efavirenz; NVP: nevirapine; 3TC: lamivudine; TFV: tenofovir; FTC: emtricitabine.

Table 3.

Factors associated with detection of antiretroviral drugs among HIV-infected men who were screened for participation in HPTN 075.*

Variables	Total (N=183)	Any drug detected (N, %)	Univariate		Multivariate	
			OR (95% CI)	p-value	aOR (95% CI)	p-value
Age						
18–25 years	101	23 (22.8%)	ref		ref	
26–44 years	82	40 (48.8%)	3.23 (1.71–6.10)	<0.001	2.65 (1.18–5.98)	0.019
Study site						
Kisumu, Kenya	28	19 (67.9%)	ref		ref	
Blantyre, Malawi	27	10 (37.0%)	0.28 (0.09–0.85)	0.024	0.13 (0.03–0.50)	0.003
Cape Town, South Africa	44	11 (25.0%)	0.16 (0.06–0.45)	<0.001	0.22 (0.06–0.80)	0.022
Soweto, South Africa	84	23 (27.4%)	0.18 (0.07–0.45)	<0.001	0.24 (0.07–0.77)	0.016
Previous participation in an HIV Study						
No	172	57 (33.1%)	ref			
Yes	10	6 (60.0%)	3.03 (0.82–11.15)	0.096		
Reported prior HIV diagnosis^a						
No	93	30 (32.3%)	ref			
Yes	67	27 (40.3%)	1.42 (0.74–2.73)	0.296		
Unknown	23	6 (26.1%)	0.74 (0.27–2.07)	0.568		
Reported engagement in HIV care or current or prior ARV drug use						
No	41	4 (9.8%)	ref		ref	
Yes	26	23 (88.5%)	70.92 (14.54–346.0)	<0.001	98.25 (17.54–550.4)	<0.001
N/A ^b	116	36 (31.0%)	4.16 (1.38–12.56)	0.011	4.66 (1.43–15.24)	0.011
Gender identification^c						
Male	125	41 (32.8%)	ref			
Transgender	58	22 (37.9%)	1.25 (0.65–2.40)	0.497		
Immigrant						
No	173	57 (32.9%)	ref			
Yes	10	6 (60.0%)	3.05 (0.83–11.25)	0.094		

Variables	Total (N=183)	Any drug detected (N, %)	Univariate		Multivariate	
			OR (95% CI)	p-value	aOR (95% CI)	p-value
Ever had sex with women						
No	103	28 (27.2%)	ref		ref	
Yes	80	35 (43.8%)	2.08 (1.12–3.87)	0.020	1.77 (0.74–4.24)	0.198
Had sex in past 3 months						
No	8	2 (25.0%)	ref			
Yes	175	61 (34.9%)	1.60 (0.31–8.19)	0.570		
Had anal sex with men in past 3 Months						
No	18	5 (27.8%)	ref			
Yes	165	58 (35.2%)	1.41 (0.48–4.15)	0.533		

* ARV drug testing was performed for 183 HIV-infected persons who were screened for participation in HPTN 075. This testing was performed using samples collected at the screening visit. One or more ARV drug was detected in samples from 63 of those participants. The table shows factors associated with ARV drug detection. Data for variables shown in the table were collected at the screening visit. P values <0.05 are bolded.

^aThe 23 participants with unknown HIV status included 17 who reported no prior HIV testing; five who reported having a previous HIV test, but did not know their HIV status; and one who did not provide information on prior HIV testing.

^bN/A: The questions about engagement in care and ever being prescribed ART were only asked if participants reported that they were HIV infected.

^cParticipants who identified as female, male and female, and/or transgender were classified as transgender.

Abbreviations: N: number; OR: odds ratio; aOR: adjusted odds ratio; CI: confidence intervals; ARV: antiretroviral; ref: reference.