CONCISE COMMUNICATION

Prevalence of HIV drug resistance in Nigeria: results from a cross-sectional, population-based survey of Nigerian adults with unsuppressed viral load

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Background: HIV drug resistance (HIVDR) surveillance is an important tool to monitor threats to progress towards epidemic control. The characterization of HIVDR in Nigeria at the national level is needed to inform both clinical decisions and population-level HIV policy strategies. This study uses data obtained from the Nigeria HIV/AIDS Indicator and Impact Survey (NAIIS) to describe the prevalence and distribution of HIVDR in Nigeria.

Methods: NAIIS was a cross-sectional, population-based survey of households throughout Nigeria in 2018. NAIIS was designed to provide estimates of HIV prevalence and related health indicators from a nationally representative sample. The study population included participants aged 15–64 years who tested positive for HIV, had a viral load at least 1000 copies/ml, and had available HIV drug resistance genotypes. HIV isolates were genotyped to detect drug resistance mutations. Individual characteristics of study participants associated with HIVDR were identified using a weighted multivariable logistic regression model.

Results: Of 1355 respondents with available HIV genotypes, 293 (19%) had evidence of drug-resistant mutations (DRMs) that conferred resistance to at least one antiretroviral drug. The majority of DRMs observed conferred resistance to NNRTIs (17.6%) and NRTIs (11.2%). HIVDR was associated with being ART-experienced, longer duration on ART, and lower $CD4^+$ count but not sociodemographic characteristics.

Conclusion: The population level DRM prevalence in Nigeria was consistent with what would be expected in a mature HIV treatment landscape. The continued roll out of

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dolutegravir-anchored regimens should mitigate the impact of NNRTI resistance on population viral load suppression and progress towards epidemic control.

Introduction

Despite the expansion of antiretroviral therapy (ART) in Nigeria, the country has not achieved epidemic control [1]. Nigeria has one of the largest populations of people with HIV in the world, with approximately 2.2 million cases and an HIV incidence rate exceeding all-cause mortality among people with HIV [1,2]. Estimating the prevalence of HIV drug resistance (HIVDR) is important in countries like Nigeria with a large population in need of ART, limited availability of genotypic surveillance, and limited second-line and third-line treatment options [3].

HIVDR patterns in Nigeria are important to monitor as the nation moves forward with efforts to widen ART access. When sub-Saharan African countries were predominantly using non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line ART, the prevalence of HIVDR was shown to exceed 80% among individuals failing initial regimens [4−6] and increase over time with continued virologic failure [7,8]. Levels of pretreatment and transmitted HIVDR are also rising throughout sub-Saharan Africa [9−11]. In Nigeria, prior studies have reported drug resistance mutations (DRMs) in 50−99% of people failing first-line ART [11−16]. Among Nigerians with recent HIV infections, HIVDR levels beyond 20% have been recorded [15]. The reported prevalence of DRMs associated with resistance to protease inhibitors in Nigeria is especially concerning, as these mutations may reduce the efficacy of available second-line therapies [14,17,18].

Although prior assessments of HIVDR in clinical cohorts provide insight into the severity of this public health crisis in Nigeria, nationally representative estimates are needed to inform population-level treatment strategies. Identifying sociodemographic correlates of HIVDR among a representative sample of Nigeria will also be useful for targeting interventions such as viral load monitoring and HIV genotyping. In this study, we describe the prevalence and distribution of HIVDR among Nigerian adults with unsuppressed viral loads using data from the 2018 Nigeria HIV/AIDS Indicator and Impact Survey (NAIIS) [2,19].

Methods

Survey sampling and population
NAIIS was a cross-sectional survey of households throughout Nigeria conducted in 2018. The methodology of NAIIS has been previously described in detail [2,19]. Briefly, NAIIS was designed to provide estimates of HIV prevalence, HIV incidence, viral load suppression, and related health indicators from a nationally representative sample of the Nigerian population. The eligible survey population included members of targeted households who were aged 0−64 years and slept in the household the night before. Written informed consent was obtained from all participants.

Field and laboratory testing
NAIIS survey personnel administered field-based testing for HIV infection and CD4$^+$ count, as previously described [2]. Blood specimens were obtained from participants who tested positive for HIV and sent to laboratories, where HIV status was confirmed and incidence testing was performed using the HIV-1 Lag-Avidity Assay, which categorized infections as either recent or long-term [20]. Serological evidence of ARV use was also evaluated in specimens from people with HIV at the University of Cape Town, South Africa. The assay was configured to detect first-line and second-line ART according to the Nigeria national treatment guidelines, including efavirenz (NNRTI), nevirapine (NNRTI), atazanavir (protease inhibitor), and lopinavir (protease inhibitor) [21,22].

HIV genotyping
Stored plasma samples with a detectable viral load at least 1000 copies/ml were HIV-1-genotyped at the Institute of Human Virology Nigeria's laboratory in Abuja and at the Nigerian Institute of Medical Research, Lagos using published methods [23]. Quality checks, confirmation of genotype findings, and drug resistance classification was provided by the HIVDR laboratory and the International Laboratory Branch, Division of Global HIV and TB at CDC, Atlanta, Georgia, USA.

Statistical analysis
We conducted descriptive analyses on each covariate in the full sample and in subsets stratified by HIVDR status, noting missing or extreme values. We then determined crude associations between HIVDR status and each covariate of interest using bivariate logistic regression. We used multivariable logistic regression to determine the adjusted odds of HIVDR associated with select covariates. Independent variables were considered for the multivariable model if they were independently associated with HIVDR at a significance threshold of *P* less

than 0.02. We started with a saturated model, then removed covariates with the highest *P* value one-by-one until each of the remaining model terms met a significance threshold of *P* less than 0.05. Descriptive statistics, HIVDR prevalence estimates, and regression analyses included survey weights to account for nonresponse. Absolute numbers are reported with associated weighted prevalence estimates. Statistical analyses were generated using SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Ethical considerations

Human subject review and approval for the NAIIS survey and secondary uses of the data were provided by the CDC Institutional Review Board (IRB), the University of Maryland Baltimore IRB, and the Nigerian National Health Research Ethics Committee (NHREC). Health facilities identified by the respondents were provided results for certain tests, including HIV status, HIV viral load, and $CD4^+$ count. Individuals who tested positive for HIV but were not on ART were offered linkage to care.

Results

Demographic and virologic characteristics of the sample

We evaluated data from 1355 adults with viral load at least 1000 copies/ml and successful viral genotypes. The sample was predominantly women (61%) and between the ages of 25 and 45 years (59%). Most were not aware of their HIV status (81%) nor on ART (86%). Of those who were on ART, 97% were taking an NNRTI and 3% were taking a protease inhibitor. The majority of HIV infections were classified as long-term (98%). The most prevalent HIV subtypes overall were CRF02_AG (52.8%) and G (35.5%). Socio-demographic, clinical, and virological characteristics of the sample are summarized in Table 1. We observed missing covariate information for 6% of participants.

HIV drug resistance mutations

Among 1355 HIV genotypes, 293 (19%) had evidence of DRMs to at least one ART class. We estimated a drug resistance prevalence (including pretreatment and acquired drug resistance) of 19.2% (286 of 1318 long-term infections) and a transmitted drug resistance prevalence of 13.8% (7 of 37 recent infections) (Table 1).

The majority of observed DRMs were associated with resistance to NNRTIs (17.6%) and nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) (11.2%). K103N was the predominant NNRTI-associated DRM (11.3%) and M184V was the most common NRTI-associated mutation (9.2%) (Table 2). Among participants with NNRTI-resistant infections, 53.4% were taking an NNRTI at the time of sample collection (data not

shown). PI DRMs were detected in just 1% of respondents. The most frequent protease inhibitor-associated DRM was M46I (0.5%) (Table 2).

Factors associated with HIV drug resistance

We examined individual factors associated with HIVDR in long-term infections. In unadjusted analyses, 51% of respondents with HIVDR had serological evidence of antiretroviral drugs versus 4% among those without HIVDR ($P < 0.01$). $CD4^+$ count was less than 100 cells/μl for 16% of those with HIVDR compared with 3% of those without. Viral subtype G was more likely to have at least one DRM than subtype CRF02_AG ($P = 0.04$). HIVDR was also associated with NNRTI use ($P < 0.001$), ART duration ($P < 0.001$), knowledge of HIV status ($P < 0.001$), and geopolitical zone ($P = 0.01$) analyses (Table 1).

After multivariable adjustment, the odds of HIVDR were significantly higher for participants with $CD4^+$ counts less than 100 cells/μl [adjusted odds ratio (aOR): 3.44; 95% confidence interval (CI): 1.51−7.85] and between 100 and 200 cells/μl (aOR: 1.84; 95% CI: 1.02−3.34) compared with those with $CD4^+$ counts greater than 500 cells/μl. Being on ART (aOR: 14.9; 95% CI: 8.4−26.6) and taking antiretroviral drugs for less than a year (aOR: 4.27; 95% CI: 1.54−11.8) were also associated with HIVDR after adjustment (aOR: 4.27; 95% CI: 1.54−11.8) (Table 1).

Discussion

Nearly one in five virally unsuppressed Nigerian adults had a drug-resistant HIV infection. However, our data indicate lower HIVDR rates compared with earlier studies, which showed that up to 99% of ART-experienced people failing first-line therapy had HIV DRMs [11−16]. Prior studies were smaller and were not population-based, which may explain their higher HIVDR prevalence estimates. We also observed HIVDR in 14% of recent infections, which roughly coincides with a recent report of a 20.5% prevalence of TDR in MSM and transgender women [15].

NNRTI-resistant infections were the most common type of inhibitor-specific HIVDR in our sample, driven primarily by the K103N mutation. NRTI resistance was also common, led by the M184V mutation. The predominance of these two mutations is consistent with several previous reports in Nigeria [11,14,15], whereas other studies noted a stronger predominance of Y181C [13,16,18]. Although the prevalence of NNRTI DRMs in our sample supports the move to dolutegravir-based combinations as first-line ART in Nigeria, resistance to NRTIs may still threaten initial treatment regimens. DRMs conferring resistance to protease inhibitors were

Table 1. Sociodemographic, clinical, and virological characteristics of participants aged 15–64 with HIV and viral load at least 1000 copies/ml, Nigeria HIV/AIDS Indicator and Impact Survey 2018.

		Total (N = 1355) [n (weighted %)]	No HIVDR (N = 1062) [n (weighted %)]	HIVDR (N = 293) [n (weighted %)]	uOR (95% CI)	aOR (95% CI)
Age (years)						
	15–24	196 (14.7)	156 (15.0)	40 (13.3)	Reference	
	25–34	422 (30.2)	338 (30.2)	84 (30.3)	1.3 (0.8–2.2)	
	35–44	398 (28.6)	303 (28.1)	95 (30.7)	1.4 (0.8–2.4)	
	45–54	237 (18.3)	185 (18.5)	52 (17.3)	1.1 (0.6–2.0)	
	55–64	102 (8.3)	80 (8.2)	22 (8.4)	1.4 (0.6–3.2)	
Sex						
	Male	445 (39.2)	358 (40.6)	87 (33.4)	Reference	
	Female	910 (60.8)	704 (59.4)	206 (66.6)	1.3 (0.9–1.8)	
Highest education level						
	Not completed primary	196 (13.5)	156 (13.9)	40 (11.8)	Reference	
	Primary	380 (27.1)	307 (27.7)	73 (24.5)	1.2 (0.7–2.1)	
	Secondary	583 (43.4)	461 (43.5)	122 (43.0)	1.3 (0.7–2.2)	
	Tertiary	160 (12.2)	117 (11.9)	43 (13.3)	1.5 (0.8–2.8)	
	Other	35 (3.6)	21 (3.0)	14 (6.2)	**3.3 (1.4–7.7)**	
	Missing	1 (0.2)	0 (0.0)	1 (1.1)		
Marital status						
	Never married	296 (23.4)	228 (23.5)	68 (22.7)	Reference	
	Married or living together	761 (56.2)	609 (56.7)	152 (54.3)	1.1 (0.7–1.7)	
	Divorced or separated	128 (8.7)	102 (8.9)	26 (8.1)	1.1 (0.6–2.0)	
	Widowed	165 (11.3)	119 (10.6)	46 (14.4)	1.6 (1.0–2.8)	
	Missing					
Number of sexual partners (last 12 months)						
	None	448 (32.5)	320 (30.0)	128 (43.0)	**3.5 (2.0– 6.3)**	**2.8 (1.5–5.2)**
	One	724 (51.4)	583 (51.9)	141 (49.3)	**2.3 (1.3–4.1)**	**1.9 (1.0–3.4)**
	Two or more	173 (15.4)	151 (17.4)	22 (6.8)	Reference	Reference
	Missing					
Geopolitical zone						
	Northwest	84 (10.0)	62 (9.2)	22 (13.2)	2.4 (1.0–6.1)	
	Northeast	186 (10.3)	121 (9.2)	65 (14.8)	**2.6 (1.2–5.7)**	
	Northcentral	207 (10.7)	150 (9.8)	57 (14.9)	**2.4 (1.1–5.3)**	
	Southeast	268 (17.0)	215 (16.7)	53 (18.5)	1.7 (0.8–3.7)	
	South-south	439 (34.4)	361 (36.0)	78 (27.5)	1.3 (0.6–2.7)	
	Southwest	171 (17.6)	153 (19.1)	18 (11.1)	Reference	
Knowledge of HIV status[a]						
	Aware	255 (16.7)	84 (7.4)	171 (56.3)	**17.3 (11.3–26.2)**	
	Unaware	1075 (81.4)	957 (90.6)	118 (42.1)	Reference	
	Missing	25 (1.9)	21 (2.0)	4 (1.6)		
CD4 count (cells/μl)						
	Below 100	81 (5.8)	41 (3.3)	40 (16.4)	**7.8 (4.1–14.7)**	**3.4 (1.5–7.9)**
	100–199	148 (11.0)	105 (10.0)	43 (15.1)	**2.7 (1.5–4.6)**	**1.8 (1.0–3.3)**
	200–349	324 (23.2)	254 (23.0)	70 (24.0)	1.6 (1.0–2.5)	1.6 (0.9–2.7)
	350–500	296 (22.1)	240 (23.4)	56 (16.6)	1.0 (0.6–1.6)	1.1 (0.6–1.8)
	Above 500	484 (36.3)	407 (38.8)	77 (25.9)	Reference	Reference
	Missing	22 (1.6)	15 (1.5)	7 (1.9)		
Viral load (copies/ml)		150 426	144 741	174 582	1.0 (1.0–1.0)	
Recency of infection[b]	Recent Infection	37 (3.1)	30 (3.3)	7 (2.3)	N/A	
	Long-term Infection	1318 (96.9)	1032 (96.7)	286 (97.7)		
Viral subtype[c]	CRF02_AG	719 (52.8)	578 (54.3)	141 (46.1)	Reference	
	G	469 (35.5)	353 (34.0)	116 (41.7)	**1.5 (1.0–2.2)**	
	A	76 (5.5)	59 (5.5)	17 (5.8)		
	CRF06_cpx	56 (4.1)	42 (3.9)	14 (5.0)		
	CRF09_cpx	6 (0.4)	5 (0.4)	1 (0.2)		
	CRF11_cpx	6 (0.4)	6 (0.5)	0 (0.0)		
	C	5 (0.2)	5 (0.3)	0 (0.0)		
	Other A, G or AG-related recombinants	5 (0.3)	4 (0.3)	1 (0.3)		
	B	4 (0.2)	3 (0.2)	1 (0.3)		
	D	3 (0.2)	2 (0.1)	1 (0.3)		
	F2	3 (0.1)	3 (0.2)	0 (0.0)		
	K	1 (0.1)	1 (0.1)	0 (0.0)		
	CRF18_cpx	1 (0.1)	1 (0.2)	0 (0.0)		

Table 1 (*continued*)

		Total (N = 1355) [n (weighted %)]	No HIVDR (N = 1062) [n (weighted %)]	HIVDR (N = 293) [n (weighted %)]	uOR (95% CI)	aOR (95% CI)
ART status[d]						
	On ART	205 (13.2)	49 (4.2)	156 (51.3)	**24.9 (15.6–39.9)**	**14.9 (8.4–26.6)**
	Not on ART	1107 (86.0)	1008 (94.8)	137 (48.7)	Reference	Reference
	Missing	5 (0.8)	5 (1.0)	0 (0)		
NNRTI detection[f]						
	On NNRTI[g]	197 (96.8)	47 (94.8)	150 (97.5)	**23.7 (14.5–38.7)**	
	Not on NNRTI	8 (3.2)	2 (5.2)	6 (2.5)	Reference	
PI detection[f]						
	On PI	8 (3.2)	2 (5.2)	6 (2.5)	3.4 (0.5–234)	
	Not on PI	197 (96.8)	47 (94.8)	150 (97.5)	Reference	
Duration on ART[e,f]						
	Not on ART	96 (50.1)	30 (68.7)	66 (43.6)	Reference	Reference
	<12 months	20 (9.2)	7 (9.3)	11 (6.1)	**51.1 (22.4–117.0)**	**4.3 (1.5–11.8)**
	12–23 months	4 (2.0)	1 (1.0)	3 (2.4)	**41.3 (4.1–419.1)**	3.1 (0.4–22.9)
	≥24 months	70 (32.4)	9 (18.2)	63 (40.6)	**6.3 (2.4–16.9)**	0.6 (0.2–1.6)
	Missing	15 (6.2)	2 (2.7)	13 (7.4)		

Variable frequencies and weighted column percentages are displayed unless otherwise noted. Odds ratios denote crude (uOR) and adjusted (aOR) associations between HIVDR and each covariate. Only complete-case observations with long-term infections (N = 1235) were included in logistic regression analyses. Statistically significant odds ratios are bolded. ART, antiretroviral therapy; HIVDR, HIV drug resistance; PI, protease inhibitor.
[a]Combining self-report and ARV biomarker.
[b]Assessed via Limiting Antigen-Avidity enzyme immunoassays [19].
[c]Only majority HIV subtypes G and CRF02_AG were compared in regression analyses.
[d]Detection of efavirenz, lopinavir, atazanavir, and nevirapine in blood specimens at the time of sample collection [21].
[e]Self-reported.
[f]ART-related statistics were calculated among participants with serological evidence of antiretroviral drugs at the time of sample collection.
[g]Non-nucleoside reverse transcriptase inhibitor.

Table 2. HIV-1 drug resistance mutations among participants aged 15–64 with HIV and viral load at least 1000 copies/ml, Nigeria HIV/AIDS Indicator and Impact Survey 2018.

NRTI resistance mutations (N = 1355)		NNRTI resistance mutations (N = 1355)		PI resistance mutations (N = 1355)	
Mutation	n (weighted %)	Mutation	n (weighted %)	Mutation	n (weighted %)
Any NRTI	181 (11.2)	Any NNRTI	274 (17.6)	Any PI	18 (1.0)
M41L	38 (2.1)	L100I	8 (0.5)	L24I	5 (0.2)
K65R	25 (1.3)	K101E	22 (1.1)	M46I	10 (0.5)
D67N	19 (1.4)	K101P	4 (0.3)	M46L	4 (0.3)
D67G	9 (0.4)	K103N	178 (11.3)	I50V	2 (0.1)
T69D	4 (0.2)	K103S	8 (0.6)	I50L	2 (0.0)
K70R	27 (1.6)	V106M	2 (0.0)	F53L	1 (0.1)
K70E	7 (0.3)	V106A	13 (1.0)	I54V	5 (0.2)
L74V	1 (0.1)	Y181C	50 (2.9)	I54L	1 (0.0)
L74I	10 (0.6)	Y181V	4 (0.2)	G73S	1 (0.1)
V75M	6 (0.3)	Y188L	9 (0.5)	L76V	3 (0.2)
F77L	2 (0.1)	Y188H	2 (0.0)	V82A	3 (0.1)
Y115F	8 (0.6)	Y188C	3 (0.1)	V82F	1 (0.1)
M184V	152 (9.2)	G190A	53 (3.0)	V82M	4 (0.1)
M184I	13 (0.8)	G190S	3 (0.1)	N83D	1 (0.0)
L210W	8 (0.6)	G190E	1 (0.0)	I84V	2 (0.1)
T215Y	26 (1.4)	P225H	28 (2.3)	L90M	1 (0.1)
T215F	21 (1.3)	M230L	5 (0.3)		
T215I	3 (0.1)				
T215S	2 (0.1)				
T215C	1 (0.1)				
T215E	2 (0.2)				
K219Q	14 (0.6)				
K219E	16 (1.2)				
K219N	5 (0.3)				
K219R	2 (0.1)				

Frequency and weighted prevalence of specific HIV-1 drug resistance mutations among NAIIS participants aged 15–64 with viral load at least 1000 copies/ml. NAIIS, Nigeria HIV/AIDS Indicator and Impact Survey; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

rare in our sample (1%). Protease inhibitor usage was uncommon in NAIIS, which may suggest a weak selective pressure for protease inhibitor resistance. Earlier studies report varying levels of protease inhibitor resistance in Nigeria, possibly because of significant heterogeneity in sample sizes and ART experience [14,17,18]. Two recent studies by Crowell *et al.* [11,15] did not detect any protease inhibitor-associated DRMs.

Despite low-ART uptake overall, more than half of the people with HIVDR were taking antiretroviral drugs at the time of sample collection. These people were considered to be failing treatment. Our observation is in agreement with canonical knowledge of HIVDR, as the most common scenarios that give rise to DRMs are poor adherence to treatment and maintenance of a failing ART regimen [7,9,10,24,25].

We acknowledge certain limitations in this study. It is challenging to accurately estimate acquired and transmitted drug resistance based on infection recency testing alone, as we cannot definitively determine if long-term drug-resistant infections were developed because of ART exposure or transmitted from another individual. Similarly, our ability to differentiate pretreatment HIVDR was limited by the absence of complete ART history data because of nondisclosure of HIV status to survey staff. Serological evidence of ARV metabolites was assessed at the time of sampling for the NNRTI and protease inhibitors that constituted the most common first-line and second-line treatment options in Nigeria. Respondents were not tested for presence of resistance to integrase inhibitors, such as dolutegravir, as it was just beginning scale-up in Nigeria. Future surveillance efforts should prioritize this gap, as a high prevalence of the integrase inhibitor-associated DRM L71I in Nigeria was recently reported prior to treatment [26].

In conclusion, population-level DRM prevalence in Nigeria was consistent with what would be expected in a mature HIV treatment landscape. The continued rollout of dolutegravir-based regimens may mitigate the impact of NNRTI resistance on population-level viral load suppression. Routine care visits including viral load monitoring for people with HIV surveillance is recommended to preserve the efficacy of NRTIs and protease inhibitors.

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Conflicts of interest

There are no conflicts of interest.

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