ORIGINAL RESEARCH

An audit of the HIV drug resistance testing program in Malawi

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Abstract

Introduction

For persons failing on dolutegravir- and protease inhibitor-based antiretroviral therapy (ART) regimens, Malawi's HIV program requires confirmation of HIV drug resistance (HIVDR) before switching to next-line regimens. Approval of applications for HIVDR testing is determined by a national HIVDR committee that also provides management recommendations based on HIVDR test results. We audited HIVDR test applications for all ages in Malawi's national ART program to evaluate the HIVDR testing process and explore short-term outcomes, including viral suppression.

Methods

We conducted a retrospective review of routinely collected data from applications for HIVDR testing registered between July 2020 and December 2021. We determined drop-offs at steps of the HIVDR testing cascade: approval for genotyping, sample collection, receiving results, completion of genotypic sequencing, provision of management recommendations and implementation of recommendations. We assessed ART outcomes, including the first viral load (VL) result ≥6 months after recommendations from the HIVDR committee.

Results

228 HIVDR applications were received, of which 75% (172/228) were approved. Of these, 72% (124/172) had samples sent to laboratory and 122 genotyping results were obtained. 75% (92/122) of samples were successfully sequenced and 68% (65/92) sequences had ≥1 major drug resistance-associated mutation, including 17% with moderate or high-level dolutegravir resistance of individuals on dolutegravir-based regimens. Treatment outcomes were available for 90 clients: 65 were alive on ART, 3 had defaulted, 12 died, 9 transferred out and 1 stopped ART. Of 68 available follow-up VL results, 34 (51%) were <1,000 copies/mL.

Conclusions

This audit demonstrates gaps in Malawi's HIVDR testing cascade and concerning clinical outcomes among those with follow up results: considerable attrition from care and low VL suppression. These results suggest that improvements in HIVDR testing in the Malawi HIV program need to be considered, including in-country sequencing and more efficient procedures for applications, approvals, clinical recommendations and clinical follow up.

Keywords: HIV drug resistance mutations, Malawi, HIV viral load, treatment failure

Introduction

At the end of 2021, there were approximately 946,000 people living with HIV (PLHIV) in Malawi[1]. ART coverage has been increasing every year since the introduction of free ART in 2004. The Malawi Population-based HIV Impact Assessment 2020-2021 found that 92.0% of PLHIV knew their status, 97.9% were on ART and 96.9% of those on ART were virally suppressed[2]. Individuals aged <19 years constitute around 8% of Malawi's ART cohort and have lower viral suppression (around 80%)[1].

The Malawi HIV program started replacing non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line ART and protease inhibitor-based second-line ART with regimens containing dolutegravir in 2019. By June 2021, 98% of the national program's ART cohort was on a dolutegravir-based regimen. Many clients were transitioned without having recent VL tests results, making it likely that part of the cohort was transitioned with a detectable viral load (VL). A study in Chiradzulu district suggested that 5.3% of the clients were transitioned to DTG-based regimens while viremic[3]. These individuals may be at increased risk for development of HIV drug resistance (HIVDR) and ART failure.

https://dx.doi.org/10.4314/mmj.v37i1.3

While ART is highly effective, a substantial number of individuals still present with virological failure annually. The Malawi HIV clinical management guidelines state that all PLHIV on dolutegravir- or PI-based regimens with confirmed virological failure, defined as two consecutive VL results of ≥1,000 copies/mL and good adherence after intensive adherence counseling, need to have resistance testing to inform switching to next-line ART regimens[4]. To this effect, clinicians need to submit standardized forms to apply for HIVDR testing to a national HIVDR committee, introduced in 2017. This committee, comprised of specialist HIV clinicians, reviews HIVDR testing applications, approves or rejects testing, reviews HIVDR testing results, and recommends next-line regimens based on HIVDR test results and clinical information[5]. There is currently limited information about Malawi's ART program HIVDR testing cascade and on treatment outcomes of clients who received a recommendation from the HIVDR committee. We therefore did an audit to evaluate applications to the national HIVDR committee, identify gaps in the cascade, and understand the resulting treatment recommendations and subsequent short-term clinical outcomes.

Methods

Design and data collection

We conducted a retrospective analysis of routinely collected data from PLHIV with an application for HIVDR testing, registered at Malawi's HIVDR committee secretariate from 1 July 2020 to 31 December 2021. For approved applications for HIVDR testing, dried blood spot (DBS) samples were transported to the National Health Laboratory Service, Johannesburg, South Africa. Genotypic HIVDR testing was performed as described in detail elsewhere[6]. Interpretation of genotypic sequences was obtained from the Stanford HIV database, genotypic resistance system version 9.0, to generate detailed resistance reports. Here we report only mutations that are classified by the Stanford HIVDR website[7].

We characterized the HIVDR testing cascade by counting applications received, applications reviewed by the committee, application disposition (approved or rejected for testing), samples sent to laboratory of clients whose application was approved, HIVDR test results received of these samples, treatment recommendations made based on the HIVDR results, and finally, treatment recommendations implemented, in particular any changes to ART regimens. Demographic and clinical information was extracted from HIVDR testing application forms, HIVDR testing result forms, Electronic Medical Records (EMR) systems, individual clients' ART charts ("mastercards") and VL sample logbooks. The clinical information included standardized ART outcomes, as defined in national ART guidelines[4], as follows: death, defaulted (no clinic visits or other contact with a client who was known to have run out of medication 60 days after a scheduled clinic appointment or longer), transferred out to another ART clinic, and stopped ART.

Table 1: Clinical characteristics of clients with an HIVDR application

	Total	Males	Females
HIVDR applications, n (%)	228 (100)	93 (41)	135 (59)
Under-19 years, n (%)	96 (42)	45 (48)	51 (38)
Median age at ART initiation, n (IQR)	18 (7-34)	14 (6-35)	22 (7-33)
Median age at HIVDR application, n (IQR)	27 (15-41)	21 (15-44)	30 (16-40)
Median duration on ART*, years, n (IQR)	7 (4-11)	8 (4-12)	7 (4-11)
Initiated ART on a DTG-based regimen, n (%)	10 (4)	3 (3)	7 (5)
Categories of regimens at time of HIVDR application			
PI-based regimens, n (%)	101 (44)	44 (47)	56 (42)
INSTI-based regimens, n (%)	128 (56)	49 (53)	79 (59)
Regimens at HIVDR application, n (%)			
TDF/3TC/DTG	98 (43)	37 (40)	61 (45)
AZT/3TC+DTG	10 (4)	3 (3)	7 (5)
ABC/3TC+DTG	19 (8)	8 (9)	11 (8)
ABC/3TC+RAL	1 (0)	1 (1)	0 (0)
AZT/3TC+ATV/r	44 (19)	15 (16)	29 (21)
ABC/3TC+LPV/r	31 (14)	14 (15)	17 (13)
TDF/3TC+ATV/r	18 (8)	10 (11)	8 (6)
ABC/3TC+ATV/r	3 (1)	2 (2)	1 (1)
TDF/3TC+LPV/r	2 (1)	2 (2)	0 (0)
AZT/3TC+LPV/r	2 (1)	1 (1)	1 (1)
AZT/3TC+EFV	1 (0)	0 (0)	1 (1)

*At the time of HIVDR application. HIVDR, Human Immunodeficiency Virus Drug Resistance; ART, Antiretroviral Therapy; DTG, Dolutegravir; PI, Protease Inhibitor; INSTI, Integrase Strand Inhibitor; ABC, Abacavir; 3TC, Lamivudine; ATV, Atazanavir; r, ritonavir; LPV, Lopinavir, RAL, Raltegravir; AZT, Zidovudine; EFV, Efavirenz; TDF, Tenofovir disoproxil

Table 2: HIVDR testing results

Genotyping outcomes	N	D	%
Samples sent to the laboratory (n)	124		
HIVDR results received	122	124	98
Successful amplification	92	122	75
Samples without NRTI & NNRTI mutations and without major PI & DTG mutations	29	92	32
Samples with any NRTI, NNRTI mutation and/or major PI, DTG mutation	63	92	68
Samples with ≥1 NRTI mutation	38	92	41
Samples with ≥1 NNRTI mutation	58	92	63
Samples with ≥1 major PI mutation	31	43^	72
Samples with ≥1 major DTG mutation	8	46#	17
Samples with 1 class mutations	18	92	17
Samples with 2 class mutations	18	92	20
Samples with 3 class mutations	22	92	24
Samples with 4 class mutations	5	92	5

HIVDR, Human Immunodeficiency Virus Drug Resistance; DTG, Dolutegravir; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-NRTI; PI, Protease Inhibitor ^number of successfully sequenced samples from individuals on a PI-based regimen; # number of successfully sequenced samples from individuals on a DTG-based regimen

Table 3: HIVDR related mutations

	N	%
Successfully sequenced samples (denominator)	92	
NRTI		
M184V/I	36	39
T215/Y/A/V/D^, D67N/H^, K70D/R/T^, K219Q/E^, M41L^, L210W^	19	21
T69D	4	4
L74I	4	4
K65R	2	2
NNRTI		
K103N	40	43
Y181C/V	21	23
G190A	12	13
K101E	6	7
V106I	4	4
PI		
Successfully sequenced samples of individuals on PI-based regimens (denominator)	43	
M46L/I	8	19
V82A	8	19
L33F	5	12
I54V/L	4	9
I50L	3	7
L90M	2	55
INSTI		
Successfully sequenced samples of individuals on INSTI-based regimens (denominator)	46	
R263K	6	13
E138K	3	7
G118R	2	4
S147G	2	4

https://dx.doi.org/10.4314/mmj.v37i1.3

^Thymidine Analogue Mutations (TAMs). HIVDR, Human Immunodeficiency Virus Drug Resistance; ART, Antiretroviral Therapy; DTG, Dolutegravir; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-NRTI; PI, Protease Inhibitor; INSTI, Integrase Strand Transfer Inhibitor

Table 4. Regimens recommended by the HIVDR committee and standardized ART outcomes after ≥6 months

Recommended regimens			
	All, n (%)	Males, n (%)	Females, n (%)
ABC/3TC+DTG	11 (13)	3 (4)	8 (9)
ABC/3TC+LPV/r	1 (1)	0	1 (1)
AZT/3TC+DTG	2 (2)	1 (1)	1 (1)
TDF/3TC+ATV/r	1 (1)	1 (1)	0
TDF/3TC/DTG	50 (59)	23 (27)	27 (32)
TDF/3TC/DTG+DRV/r	9 (12)	3 (4)	6 (7)
TDF/3TC/DTG+DTG	5 (6)	4 (5)	1 (1)
TDF/3TC/DTG+DTG+DRV/r	5 (6)	2 (2)	3 (3)
Information not available	8 (9)	2 (2)	6 (7)

Standardized ART outcomes			
	All, n (%)	Males, n (%)	Females, n (%)
Not available	2 (2)	1 (1)	1 (1)
Alive in Care	65 (71)	28 (30)	37 (40)
VL results available	60 (92)	26 (43)	34 (57)
VL <1,000 copies/mL	32 (53)	17 (65)	15 (44)
VL ≥1,000 copies/mL	28 (47)	9 (35)	19 (66)
Defaulted	3 (3)	1 (1)	2 (2)
Transferred out	9 (10)	3 (3)	6 (7)
Died	12 (13)	6 (7)	6 (7)
Stopped ART	1 (1)	1 (1)	0

HIVDR, Human Immunodeficiency Virus Drug Resistance; ART, Antiretroviral Therapy; DTG, Dolutegravir; ABC, Abacavir; 3TC, Lamivudine; ATV, Atazanavir; r, ritonavir; LPV, Lopinavir, RAL, Raltegravir; AZT, Zidovudine; EFV, Efavirenz; TDF, Tenofovir

Table 5. Viral Load results among clients with a successfully sequenced sample

Category	No VL results n (%)	Viral load results (n=68)		
		Suppressed n (%)	LLV n (%)	HVL n (%)
Successful amplifications (n=92)	24 (26)	29 (43)	6 (9)	33 (49)
0-19 years (n=42)	9 (10)	12 (36)	4 (12)	17 (52)
20+ years (n=50)	15 (16)	17 (49)	2 (6)	16 (46)
Male (n=39)	10 (11)	16 (55)	3 (10)	10 (35)
Female (n=53)	14 (16)	13 (33)	3(8)	23 (59)
No major mutations (n=27)	5 (6)	10 (46)	2 (9)	10 (46)
1 class mutations (n=16)	5 (6)	2 (18)	0	9 (82)
2 class mutations (n=18)	4 (4)	7 (50)	1 (7)	6 (43)
3 class mutations (n=22)	6 (7)	8 (50)	3 (19)	5 (31)
4 class mutations (n=5)	2 (2)	2 (67)	0	1 (33)

VL, Viral load; LLV, low level viremia (200-999 copies/mL); HVL, high VL (≥1,000 copies/mL)

https://dx.doi.org/10.4314/mmj.v37i1.3

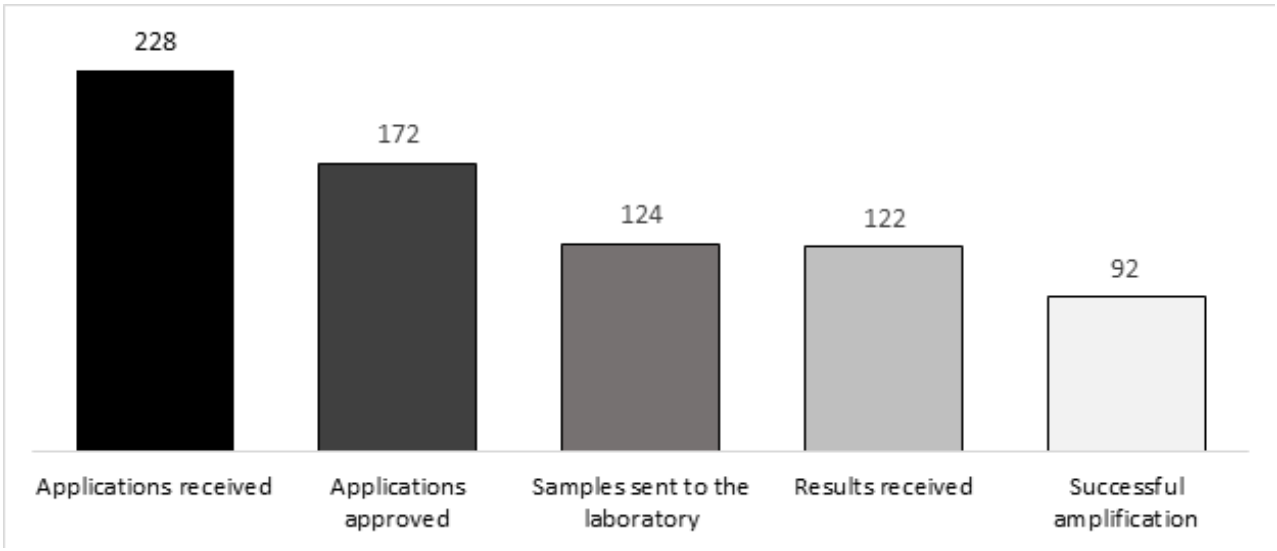

Figure 1. HIVDR testing cascade, 1 July 2020 - 31 December 2021

Standardized ART outcomes and VL results were determined at the earliest clinic visit at least 6 months after a recommendation from the HIVDR committee. VL results were categorized as in Malawi national HIV management guidelines[4]: suppressed (0-199 copies/mL), low level viremia (LLV, 200-999 copies/mL) and high VL (≥1,000 copies/mL).

Data analysis

De-identified data were cleaned and descriptive statistics were used for the outcomes of interest.

Ethical considerations

The study was reviewed by the National Health Science Research Committee, which exempted it from individual informed consent (reference number 23/02/3172), as we exclusively used routinely collected program data and risk for participants, restricted to loss of confidentiality, was minimal.

Results

Between 1 July 2020 and 31 December 2021, 4,869 follow up viral load results ≥1,000 copies/mL were reported in the national VL database and close to the same number (given a low likelihood that individuals had more than 1 result) were presumed eligible for HIVDR testing. In the same period, only 228 HIVDR testing applications were received by the national HIVDR committee. 223 of the 228 applications (98%) were from PEPFAR supported facilities, while nationally, 522 of 867 ART clinics receive PEPFAR support (60%). The mean number alive on ART at facilities from which applications were received was 2,740, while it was 1,122 at all ART clinics in Malawi (in 2020 Q1). Applications for female clients predominated, 59% (135/228) and 42% (96/228) of clients were ≤18 years old. The median age at ART initiation was 18 (inter-quartile rage [IQR] 7-34) years and the median age at HIVDR testing application was 27 years (IQR 15-41). The median duration on ART at the time of application was 7 years (IQR 4-11). Of the 228 applications, 127 (56%) were from individuals on an INSTI-based regimen at the time of the HIVDR application (43% [98/228] on tenofovir/lamivudine/dolutegravir), the rest were on PI-based regimens. (Table 1)

HIVDR testing cascade

In total, 75% (172/228) of applications were approved for testing. Of 56 applications that were not approved, in 38% (21/56) this was due to the HIVDR committee determining that poor adherence was not yet sufficiently addressed, in 29% (16/56) due to a viral load result of less than 5,000 copies/mL (related to an observed increased potential of non-sequencing between 1,000-5,000 copies/mL using DBS samples), in 14% (8/56) due to inadequate information on the HIVDR application form and in 20% (11/56) due to other factors. Among the approved applications, 72% (124/172) had HIVDR testing samples sent to the laboratory, of which 98% (122/124) results were received and communicated to the applying clinician. Of the samples sent, 75% (92/122) underwent successful sequencing. Overall, 74% (92/124) of samples sent resulted in a useable HIVDR result. In total, 71% (65/92) of the successfully amplified samples had mutations, of which two had minor mutations only. (Figure 1)

HIVDR associated mutations

Among samples with successful amplification, 41% (48/92) had at least one NRTI mutation, 64% (58/92) had at least one NNRTI mutation, 34% (31/92) had at least one major PI mutation, and 9% (8/92) had at least one major dolutegravir mutation. Of 127 applications for individuals on a dolutegravir-based regimen, 46 samples were successfully amplified, and 8 (17%) had dolutegravir resistance. Of samples that were successfully sequenced, 32% (29/92) had no mutations, 20% (18/92) had single-class mutations, 20% (18/92) had mutations in two classes, 24% (22/92) had mutations in three classes, and 5% (5/92) had mutations in four classes. (Tables 2 and 3)

Clinical outcomes after recommendations based on HIVDR results

Data about whether recommendations were received and were adhered to by clinicians are incomplete. Of 92 individuals with an HIVDR result, we have documentation that 84 received a recommendation from the HIVDR committee. 43/84 (51.2%) had documentation of correct implementation and of the remaining 41, documentation for 13 (15.5% of 84) was available of at least one suppressed VL after a recommendation was sent. Of the 84 available

recommendations, 55 (65%) were for a change in regimen. The 84 available recommended regimens included 2 regimens with 2NRTI + PI, 66 with 2 NRTI + dolutegravir and 14 with 2 NRTI + dolutegravir + boosted darunavir. Ten recommendations featured a twice daily dolutegravir dose. Of clients whose samples were successfully sequenced, standardized ART outcome results were extracted. The outcomes were determined with a median duration of 9 months (inter-quartile range 4-12 months) after the recommendation based on HIVDR results. Standardized ART outcomes were as follows: 71% (65/92) were alive in care, 3% (3/92) were lost to follow-up, 13% (12/92) had died, 9% (9/92) had transferred out from the facilities where HIVDR application was made and had no further outcome, 1% (1/92) had stopped ART and 2 (2%) had no outcome available. Excluding transfers, attrition from care was 20% (n=16). (Table 4)

Results of VL samples, drawn at least 6 months after the HIVDR committee's recommendation were received, were available for 74% (68/92) of individuals with sequencing results. Of these, 43% (29/68) were <200 copies/ml, 9% (6/68) were 200-999 copies/mL and 49% (33/68) were ≥1,000 copies/mL. Among individuals who were alive on ART, 47% had a VL ≥1,000 copies/mL. Among under 19-year-olds, 52% (17/33) of VL results were ≥1,000 copies/mL; among 20+ year olds this was 46% (176/35). Among men, 35% of VL results were ≥1,000 copies/mL and among women 59% (23/39). (Table 5)

Discussion

In this audit of Malawi's national HIVDR testing program, that covers a period during which the transition to dolutegravir-based ART took place, we present a retrospective evaluation of genotypic resistance testing results and outcomes after recommendations for ART regimens based on those HIVDR test results. There was considerable attrition along steps of the HIVDR testing cascade and suboptimal treatment responses among those who completed the cascade. We also highlight the emergence of dolutegravir resistance within the national program.

In comparison with the national ART cohort, which contains around 8% under 19-year-olds[1], a relatively large percentage of children and teens was observed among the HIVDR applications, which may reflect high prevalence of virological failure, a consequence of common adherence challenges in this age category[8]. The female preponderance among the applications is in line with the prevalence of female sex in the national ART cohort[1].

We observed a large gap between the number of HIVDR applications received (n=228) and the number of clients eligible for HIVDR testing based on VL results in the database from the same period (i.e. close to 5,000 individuals). This gap may reflect factors associated with clinicians, such as lack of knowledge and/or motivation to complete the necessary steps to generate an HIVDR application, as well as health system factors, including long VL result turn-around times and sample transport challenges. From 2023 onwards, after orientations for clinicians, we are noting a steady increase in the number of applications, suggesting that the HIVDR testing gap may be narrowing gradually. However, this increase of HIVDR testing poses challenges to the number of available HIVDR experts needed to approve applications, interpret HIVDR test results and provide clinical recommendations; the laboratory testing capacity (only recently, after the audit period, has HIVDR testing capacity for service delivery become available in-country) and the budget for HIVDR testing, given the high cost of genotyping. For the same reasons, routine HIVDR testing for individual switching decisions has found limited implementation in the region and we are not aware of similar HIVDR cascade overviews from other countries in the literature.

A large percentage (25%) of HIVDR applications was rejected. Inappropriate and incomplete applications resulted from insufficient knowledge about the HIVDR testing indications among applying clinicians, as observed on application forms. As the audit period progressed, HIVDR experts became stricter with the VL threshold after observing a high prevalence of non-sequencing. With DBS samples, the probability of non-sequencing with VL results in the range of 1,000-5,000 is increased[9] and given the high costs of HIVDR testing (especially when taking place abroad), a threshold of 5,000 copies/mL became more commonly used instead of the 1,000 copies/ml, which is recommended in national and international guidelines[4,10]. We observed a 28% drop off between approval of HIVDR test applications and samples sent for HIVDR testing. This may be due to gaps in communication between the HIVDR secretariat, experts, clinicians and clients, which is needed to make clients return to health facilities for providing an HIVDR test sample. Given such observations, more efficient approaches for application, approval and sample collection need to be considered. This may include sending samples for HIVDR testing together with the application, automatic processing of HIVDR testing in the laboratory if a follow-up or targeted viral load result is above an agreed VL result threshold or utilizing a urine tenofovir assay (an objective measure of recent ART adherence) in HIVDR testing algorithms[11]. Since the introduction of in-country HIVDR testing, the percentage of non-sequencing has dropped strongly from 25% to below 10%, most likely due to prevention of sample quality decay during transport and because part of the samples is now taken as plasma instead of DBS.

Sixty-five percent of samples sequenced had HIVDR mutations, but this may not reflect the true prevalence of mutations in the Malawi HIV program, as this audit is not a representative survey. Multi-class resistance was considerable, as more than a quarter of the sequenced results had 3- and 4-class mutations. We found that 9% of all samples and 17% of samples from individuals on dolutegravir-based regimens, had major dolutegravir resistance mutations, indicative of a significant development of dolutegravir resistance in the Malawi ART program. Since the audit period reflects HIVDR testing during a period with fairly short-term exposure to dolutegravir-based regimens, these percentages are likely to rise, as literature suggests that it may take >1 year of exposure to dolutegravir for resistance to develop[12]. We emphasize that because the sample of this audit is not nationally representative, the percentage of dolutegravir resistance observed in this audit should not be regarded as the prevalence in Malawi. The observed types of resistance-associated mutations were as expected for clients exposed to current and previous ART regimens in Malawi.

Clinical outcomes after HIV management recommendations based on HIVDR testing were generally disappointing. While standardized ART outcomes were available for 98% of persons with HIVDR test results, only 80% were retained

in care, 74% had a VL test result and of those, only half had VL suppression <1,000 copies/mL. Differences in clinical outcomes between age categories and sexes and HIVDR resistance categories were unremarkable. The clinical and virological outcomes are worse compared to observations of similar cohorts in Zambia, Mozambique and Zimbabwe around the time of our audit[13-16]. The high attrition from care and poor VL suppression observed in our audit suggest that factors such as the vulnerability of the client population, the protracted nature of the HIVDR test procedures and the challenging communication between secretariat, experts, applying clinicians and clients had considerable impact on eventual client outcomes, including deaths.

We recognize limitations of this audit. Since a very small percentage of eligible clients had a sample submitted and sample submission was likely biased (more applications came from larger health facilities and from health facilities supported by PEPFAR-funded organizations), this audit did not evaluate a representative sample of clients with virological failure in the Malawi HIV program. Further, VL outcomes may have been affected by disruptions in supplies due to the COVID-19 pandemic, including for drugs and VL commodities. The audit period 2020-2021 was chosen despite the COVID-19 interference, because we wanted to have sufficient follow up time to enable review of ART and VL outcomes after recommendations following HIVDR testing.

Conclusions

Programmatic HIVDR testing in Malawi has increased awareness of issues related to HIVDR in the national HIV program, including the emergence of dolutegravir resistance, and a team of local experts has been built to support HIVDR testing and HIVDR surveillance. However, this audit of HIVDR testing in Malawi between 2020-2021, demonstrated large gaps in the HIVDR testing cascade and suboptimal clinical outcomes after recommendations following HIVDR testing. These results indicate that more effective and efficient HIVDR test procedures, from applications through follow up after treatment modifications, in the Malawi HIV program are required, as well as interventions to improve clinical outcomes.

Conflicts of Interest

The authors declare no conflict of interest

Funding

HIVDR testing in the Malawi national HIV program is funded by PEPFAR, through USAID and CDC. Research reported in this publication was supported by the Fogarty International Center of the National Institutes of Health under Award Number D43TW010060. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Acknowledgments

We thank clients whose samples were included, their clinicians and health care providers, the secretariat of HIVDR testing of the Malawi HIV program based at the Lighthouse Trust, and the Partners in Hope molecular laboratory for making this work possible.

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