Prevalence of HIV Drug Resistance Before and 1 Year After Treatment Initiation in 4 Sites in the Malawi Antiretroviral Treatment Program

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Since 2004, the Malawi antiretroviral treatment (ART) program has provided a public health–focused system based on World Health Organization clinical staging, standardized first-line ART regimens, limited laboratory monitoring, and no patient-level monitoring of human immunodeficiency virus drug resistance (HIVDR). The Malawi Ministry of Health conducts periodic evaluations of HIVDR development in prospective cohorts at sentinel clinics. We evaluated viral load suppression, HIVDR, and factors associated with HIVDR in 4 ART sites at 12–15 months after ART initiation. More than 70% of patients initiating ART had viral suppression at 12 months. HIVDR prevalence (6.1%) after 12 months of ART was low and largely associated with baseline HIVDR. Better follow-up, removal of barriers to on-time drug pickups, and adherence education for patients 16–24 years of age may further prevent HIVDR.

Malawi has suffered from the spread of the human immunodeficiency virus (HIV)/AIDS epidemic, with 12% of persons aged 15–49 years estimated to be living with HIV [1]. Since 2004, the Malawi antiretroviral treatment (ART) program has used a public health approach based on World Health Organization (WHO) clinical staging, limited laboratory monitoring, and standardized ART regimens for first-line ( stavudine [d4T], lamivudine [3TC], nevirapine [NVP]), alternative first-line (zidovudine [ZDV]) substituted for d4T and/or efavirenz for NVP) in case of toxicities, and second-line (ZDV, 3TC, tenofovir, and lopinavir/ritonavir) in case of ART failure. Within this program, >300 000 patients have initiated ART as of December 2010. However, clinical and immunological monitoring lack sensitivity for detection of virologic failure [2–4] and with ongoing unrecognized replication, accumulation of complex resistance mutations may occur [5]. As part of the HIV drug resistance (HIVDR) surveillance strategy recommended by the World Health Organization (WHO), the Malawi Ministry of Health conducts periodic prospective evaluations of cohorts of patients initiating ART to evaluate virologic suppression and HIVDR development at 12–15 months after initiation of ART [6].

Varying HIVDR prevalence rates among people taking ART have been reported in Africa. Surveys conducted at 6 months after ART initiation have detected...
prevalence rates of resistance of 5%–24% [7, 8]. In Mozambique, resistance mutations were identified in 5% of the samples after 12 months of ART initiation [9]. Among individuals in national ART programs with confirmed virological failure, the presence of at least 1 resistance-conferring mutation ranged from 44% to 100% [5, 7–17]. In Malawi, a retrospective survey assessing drug resistance mutation after 12–15 months of ART initiation showed resistance mutations rates ranging from 2.5% to 4.7% in 4 sites [18], but possible resistance associated with losses to follow-up was high.

We report on a prospective survey that evaluates the suppression of HIV RNA (defined as HIVDR prevention) in 4 sites at 12–15 months after ART initiation. We also describe factors that potentially influenced development of HIVDR and could be addressed by ART program changes.

**METHODS**

**Antiretroviral Treatment Site Characteristics and Patient Enrollment**

This was a prospective survey of patients initiating ART in 4 different clinics in Malawi: 3 central hospitals (Queen Elizabeth Central Hospital [QECH], Blantyre; Mzuzu Central Hospital, Mzuzu; and the Lighthouse Clinic, Lilongwe) and 1 district hospital (Thyolo District Hospital, Thyolo). These sites were chosen because they were among the first providing ART in Malawi and had the capacity to implement the survey: they were able to enroll enough patients to reach the target sample size rapidly and had capacity to collect and store samples on site.

Between 11 February and 30 June 2008 we consecutively enrolled adults (aged ≥15 years) who initiated ART following national ART guidelines. We excluded patients on ART who were transferring from other sites. Patients who had occasionally taken antiretroviral drugs from friends or relatives or used antiretroviral drugs to prevent mother-to-child transmission of HIV were included in the survey to reflect the patient population starting ART at these sites. Informed consent was obtained from each participant.

**Sample Size**

According to the WHO generic protocol [6], the sample size for each site is 96. Analysis includes defaulters, patients who stopped ART, those who switched to a second-line regimen and who were alive and on ART by 12 months. Patients who died or transferred to other clinics were excluded from the analysis. To accommodate for expected attrition due to deaths and transfers to other clinics, sample sizes were increased to 150 per site.

**Survey Procedures**

Prior to commencement of the survey, each site developed survey procedures that were in line with their daily operations. Plasma specimens were collected before the start of ART and at the 12–15-month follow-up visit and stored onsite at −80°C until transportation on dry ice for storage at the HIV reference laboratory at the Community Health Sciences Unit in Lilongwe. After specimen collection completion, specimens were shipped on dry ice to the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, for analysis.

**Laboratory Tests**

Plasma specimens received by the WHO-accredited Specialized Drug Resistance Laboratory at the CDC were accessioned after specimen identifier confirmation and quality checks according to the College of American Pathologists regulations and were stored at −80°C before testing. For HIV RNA quantification, RNA from patient plasma specimens was extracted using the automated Abbott Sample Preparation System (m2000sp) and HIV RNA was then quantified by the m2000rt Real Time analyzer (the m2000rt test; Abbott, Chicago, Illinois). With 0.2 mL of input plasma volume for RNA extraction, the lower detection limit is 150 copies/mL of plasma. For specimens with detectable HIV RNA, the remnant RNA was used for HIV drug resistance genotyping using the broadly sensitive genotyping assay developed and validated at the CDC [19]. Genotyping was performed for all the baseline and endpoint specimens with detectable HIV RNA at 12–15 months’ follow-up. This procedure differs from WHO protocol that requires only specimens with a viral load (VL) ≥1000 copies/mL to be genotyped. Phylogenetic analyses were performed for sequencing quality and accuracy, confirming that specimens from baseline and 12–15 months’ follow-up were from the same patients. HIV subtyping was performed using BioEdit [20] and MEGA4 software [21] with reference sequences from the Los Alamos HIV Database [22]. Drug resistance-associated mutations in protease and reverse transcriptase gene regions from all quality-assured sequences were interpreted with the HIVaDo program employed in the Stanford HIV drug resistance database [23]. Presence of mutations listed in this database defined as high, intermediate, or low resistance to relevant antiretroviral drugs used routinely in Malawi was defined as HIVDR.

**Data Collection, Management, and Analysis**

We collected baseline variables (demographics, tuberculosis status, WHO clinical stage, CD4 count and VL at the start of ART, previous ART use), and information about drugs prescribed during the course of ART, appointment dates, dates of attendance, drug pickup dates, opportunistic infections, and adherence measures. We determined endpoint ART outcomes as follows: dead, defaulted/lost to follow-up, transferred out, stopped ART, or alive and on ART at 12–15 months. Defaulter status was defined as not having attended the ART clinic ≥3 months after a missed appointment date.
Data were analyzed with Stata/MP 11 (College Station, Texas) software. The \( \chi^2 \) test, Wilcoxon rank-sum test, and k-sample equality of medians test were used as appropriate to determine statistical differences between groups. Odds ratios (ORs) were calculated using logistic regression, but multivariate analysis could not be done due to small numbers in the outcome of interest.

**Classification of Participants at Endpoint**

Participants were classified into 1 of the 3 HIVDR categories at endpoint (12–15 months following ART initiation) as follows:

1. HIVDR prevention (virologic suppression): alive on first-line ART with a VL < 1000 copies/mL. The WHO-specified target for HIVDR prevention (virologic suppression) is \( \geq 70\% \) of participants at each site.
2. Possible resistance: alive on first-line ART with VL \( \geq 1000 \) copies/mL but with no HIVDR, or defaulted or stopped ART.
3. Detected resistance: alive on first-line ART with VL \( \geq 1000 \) copies/mL and a combination of mutations generating a high-, intermediate-, or low-level resistance classification to antiretroviral drugs routinely used in Malawi (determined using the Stanford HIV drug resistance database algorithm [23]).

To generate prevalence rates, we used a denominator that consisted of the sample including defaulters but excluding death and transfers.

**RESULTS**

**Baseline Characteristics**

We prospectively enrolled 603 participants of whom 330 (57.2\%) were female. Men were older than women at the time of ART initiation (median age, 39 vs 35 years; \( P < .001 \)) (Table 1). Eleven percent of the participants had tuberculosis. The tuberculosis disease rates varied significantly by site, from 3.8\% at Mzuzu Central Hospital to 17.5\% at Lighthouse Clinic (\( P = .003 \)). None of the patients reported previous antiretroviral drug use, except 9 women who had used single-dose NVP for prevention of mother-to-child transmission (PMTCT) purposes.

Table 1. Baseline Characteristics of Patients Enrolled in the Prospective Monitoring Survey

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lighthouse (n = 153)</th>
<th>Mzuzu (n = 150)</th>
<th>QECH (n = 150)</th>
<th>Thyolo (n = 150)</th>
<th>Total (N = 603)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>86 (58.5)</td>
<td>87 (61.7)</td>
<td>78 (54.6)</td>
<td>795 (4.1)</td>
<td>330 (57.2)</td>
</tr>
<tr>
<td>Average age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>38.7</td>
<td>39.9</td>
<td>39.0</td>
<td>39.1</td>
<td>39.0</td>
</tr>
<tr>
<td>Females</td>
<td>36.1</td>
<td>36.2</td>
<td>32.3</td>
<td>35.6</td>
<td>35.0</td>
</tr>
<tr>
<td>Current tuberculosis</td>
<td>24 (17.5)</td>
<td>5 (3.7)</td>
<td>13 (9.35)</td>
<td>19 (12.9)</td>
<td>61 (11.0)</td>
</tr>
<tr>
<td>WHO clinical staging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 or 2</td>
<td>65 (44.5)</td>
<td>55 (40.2)</td>
<td>52 (35.1)</td>
<td>70 (47.3)</td>
<td>242 (41.8)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>58 (39.1)</td>
<td>65 (47.5)</td>
<td>70 (47.3)</td>
<td>55 (37.2)</td>
<td>248 (42.8)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>23 (15.8)</td>
<td>17 (12.4)</td>
<td>26 (17.6)</td>
<td>23 (15.5)</td>
<td>89 (15.4)</td>
</tr>
<tr>
<td>Previous ARV exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMTCT prior to initiation</td>
<td>2/81 (2.5)</td>
<td>2/82 (2.4)</td>
<td>1/78 (1.3)</td>
<td>4/79 (5.1)</td>
<td>9/311 (2.8)</td>
</tr>
<tr>
<td>Median baseline CD4 count (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>167 (142)</td>
<td>136 (221)</td>
<td>137.5 (181)</td>
<td>151 (120)</td>
<td>154 (157)</td>
</tr>
<tr>
<td>Males</td>
<td>134 (144)</td>
<td>111 (172)</td>
<td>76.5 (111)</td>
<td>112 (116)</td>
<td>109 (134)</td>
</tr>
<tr>
<td>Median baseline viral loads</td>
<td>138 038</td>
<td>138 038</td>
<td>203 538</td>
<td>181 970</td>
<td>162 181</td>
</tr>
<tr>
<td>Baseline resistance results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with amplifiable baseline specimens</td>
<td>138</td>
<td>142</td>
<td>141</td>
<td>150</td>
<td>571</td>
</tr>
<tr>
<td>No resistance</td>
<td>129</td>
<td>137</td>
<td>137</td>
<td>144</td>
<td>547</td>
</tr>
<tr>
<td>NNRTI resistance only</td>
<td>8 (5.8)</td>
<td>4 (2.1)</td>
<td>3 (2.1)</td>
<td>5 (3.3)</td>
<td>19 (3.3)</td>
</tr>
<tr>
<td>NRTI resistance only</td>
<td>1 (0.7)</td>
<td>2 (0.7)</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>NRTI + NNRTI resistance</td>
<td>1 (0.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>PI resistance</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Any resistance mutation</td>
<td>9 (6.5)</td>
<td>5 (3.5)</td>
<td>4 (2.8)</td>
<td>5 (3.4)</td>
<td>23 (4.0)</td>
</tr>
</tbody>
</table>

Abbreviations: ARV, antiretroviral; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PMTCT, prevention of mother-to-child transmission; QECH, Queen Elizabeth Central Hospital; WHO, World Health Organization.
with lower CD4 counts than did females (median, 109 vs 154 cells/mm³; \(P = .003\)), as well as a lower mean body mass index (19.7 vs 21.0; \(P = .02\)) and were also more likely to start ART at WHO clinical stages III or IV (62.5% vs 54.5%; \(P = .048\)).

Of 603 enrolled patients, baseline specimens were collected from 579 (96%). HIV RNA testing was successful for 575 (99%) specimens. The median HIV RNA was 162 181 (range, 178–776 247 copies/mL). There was no significant difference between the median HIV RNA of men and women. Of the 575 specimens with HIV RNA test results, 569 (99.0%) were successfully genotyped. Phylogenetic analysis revealed that 98.0% of the viral strains were subtype C. Overall baseline HIVDR prevalence was 4.0%, ranging from 2.8% at QECH to 6.5% at Lighthouse Clinic. Baseline HIVDR prevalence was mainly determined by nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations (3.3%), most commonly K103N (in 43.5% of specimens) and Y181C (34.8%). No protease inhibitor drug resistance was identified at baseline in any participant.

Antiretroviral Treatment Outcomes

Overall, 436 patients (73.5%) were alive and on first-line ART at 12–15 months. The percentage of documented deaths was 8.3%. Males were more likely to be reported dead than were females (10.2% vs 5.8%; \(P = .05\)) (Table 2). Most deaths (65%) occurred in the first 8 weeks of ART initiation. Male patients (OR, 1.8; \(P = .05\)), patients who initiated ART with CD4 counts \# 50 cells/mm³ (OR, 2.4; \(P < .001\)), in WHO clinical stage IV (OR, 9.3; \(P < .001\)), and with a body mass index < 18.5 (OR, 2.8; \(P = .001\)) were more likely to die. The default rates differed considerably at the sites, from 5.3% at the Lighthouse Clinic to 18% at QECH. Most participants (60%) defaulted within the first 18 weeks of ART initiation. The mean duration of follow-up for participants who were alive on first-line ART at endpoint, those who defaulted, and those who died was 55 (range, 40–74), 20 (range, 2–66), and 11 (range, 0–50) weeks, respectively.

Appointment-keeping information was available on the 436 subjects who were alive on first-line ART at 12–15 months.
most cases clinical appointments coincided with drug pickup appointments. Patients who attended clinic >5 days after scheduled appointments were regarded as having “missed appointments” because the drug supply would be exhausted by that time. Overall, 93% of the patients kept their appointments/picked up drugs on time on at least 80% of occasions, ranging from 90% at QECH to 100% at the Lighthouse Clinic. No participant was switched to a second-line regimen, but 49 were changed to alternative first-line regimens, of whom 43 (7.1% of the participants) had d4T to ZDV substitutions.

Of the 436 patients who were alive on first-line ART at 12–15 months’ follow-up, we were able to determine HIV RNA on 395 (91%) specimens. Thirty-five specimens (8.9%) had detectable HIV RNA (range, 178–776 247 HIV RNA copies/mL), of which 29 were ≥1000 copies/mL, resulting in HIVDR prevention rates ranging from 60% at Mzuzu Central Hospital to 84% at the Lighthouse Clinic.

**HIV Drug Resistance Outcomes After 12–15 Months of Antiretroviral Treatment**

Detectable resistance ranged from 3.2% for QECH to 7.5% for the Thyolo District Hospital. NNRTI-associated resistance was higher than nucleoside reverse transcriptase inhibitor (NRTI)–associated resistance at all sites except QECH where it was the same (Table 2). In patients with detectable HIV RNA, the most common HIVDR mutation was M184V, which occurred in 19 (79.2%) patients, whereas K103N and Y181C occurred in 14 (58.3%) and 11 (45.2%) patients, respectively. Other mutations identified were K65R (11.4%) and thymidine analogue–associated mutations (TAMs) (11.4%). TAMs included D67N occurring in 3 specimens and T215Y and K219Q/E occurring together in 1 specimen. No protease inhibitor–associated resistance mutations were observed. Although few participants with baseline HIV resistance mutations suppressed HIV RNA at months 12–15, most maintained or acquired new mutations (Supplementary Table 1). All participants, except 1, with detected resistance at endpoint had HIV RNA ≥1000 copies/mL.

Possible resistance, defined by absence of relevant mutations in participants whose HIV RNA was not suppressed at endpoint, was low (2.2%), as opposed to possible resistance defined by defaulters that ranged from 7.4% at the Lighthouse Clinic to 20.1% at QECH.

Of 24 specimens with endpoint resistance, 9 had baseline mutations indicating that HIVDR mutations newly developed on ART only in 15 subjects, representing HIVDR incidence of 15 of 481 (3.1%) among the at risk group. Of the 23 subjects with baseline HIVDR mutations, 5 (21.7%) died or were lost to follow-up, 10 (43.5%) suppressed HIV RNA, and 8 developed additional HIVDR mutations. Baseline CD4 count >100 cells/μL was associated with successful suppression among those harboring baseline resistance (7 of 12 with CD4 count >100 cells/μL had suppressed compared with 2 of 8 in those with CD4 count ≤100 cells/μL). Only 1 of 8 patients with baseline presence of Y181C mutation suppressed HIV RNA and 2 died, compared with 4 suppressions out of 5 patients and 1 death in those with NRTI mutations. All these associations were not statistically significant due to lack of power.

**Bivariate Analysis of Factors Associated With Development of Resistance**

Detected resistance at 12–15 months was significantly associated with presence of NNRTI resistance at baseline, age 16–24 years at ART initiation, and missing an appointment date by 15–31 days (Supplementary Table 2).

**DISCUSSION**

This survey demonstrates that in 4 sites of the Malawi ART program, ≥70% of patients suppressed HIV RNA at 12–15 months after ART initiation, meeting the WHO target of HIVDR prevention. Detected resistance was low at 12–15 months, and HIVDR profiles were as expected for NNRTI-based therapy and highly associated with the presence of baseline resistance. Possible resistance was considerable, mainly determined by high defaulter rates.

Although it is reassuring that HIVDR targets were met, we observed several issues of concern. There was considerable intersite variation of HIVDR prevention and possible HIVDR resistance. The Mzuzu Clinic reported lower viral suppression partly because a number of participants who were alive on first-line ART (and thus included in the denominator) were missed for HIV RNA specimen collection at 12–15 months. A high number of defaulters in QECH and Mzuzu caused relatively low virologic suppression and high possible resistance rates in those sites. The Lighthouse Clinic [24] and the Thyolo District Hospital have active community tracing programs of patients who miss scheduled ART visits, which prevents defaulting and allows correct categorization of participants as deaths rather than defaulters, thereby resulting in higher viral suppression rates. This and other efforts to retain patients in care are important to improve ART outcomes and to reduce possible HIVDR rates. Men started ART with more advanced HIV disease than women and had a higher mortality rate as a consequence. Although our data did not demonstrate this, it is possible that men also have a higher chance of virologic failure and HIVDR development, as advanced disease at baseline was a risk factor for ART failure in other studies [25].

The prevalence of resistance at 12–15 months observed in this survey is comparable to a report from neighboring Mozambique [9]. The low level of detected resistance in both cohorts may be related to optimal adherence, reflected by a high degree of
appointment keeping for drug collection among patients who were alive on first-line ART. The resistance rates in this survey were also similar to those from our retrospective study in 2007 at the same sites [18], which does not suggest a progressive increase in HIVDR as the ART program matures. However, it will be important to maintain HIVDR vigilance by continuing regular surveys. The predominance of the M184V and K103N mutations was expected given the standard first-line regimens used and was consistent with other studies from Malawi and the region [9, 11, 13, 18]. The relatively low rate of TAMs we identified at the 12–15-month follow-up point confirms other studies suggesting that TAMs develop relatively slowly compared with M184V- and NNRTI-associated mutations. However, ZDV substitution for d4T toxicity was uncommon (7.1%) in this cohort and TAMs are more likely to develop with ZDV-containing regimens than with d4T-containing regimens [26]. Similar to other studies on treatment failure of d4T-based regimens, we observed K65R mutations although at lower frequency than when ART failure is detected using clinical or immunological monitoring [4, 5]. Baseline resistance to NNRTIs was relatively high in this cohort. One explanation could be the widespread use of single-dose NVP in the Malawi PMTCT program, although few women reported its use. However, the mutations occurred in both men and women, suggesting that transmitted resistance or unidentified ART exposure (such as antiretroviral drug sharing) may have occurred.

The 16–24-year age range at ART initiation was a predictor for HIVDR. Adolescents typically struggle with management of chronic diseases and HIV [27]. Programs addressing the challenges of drug adherence among adolescents may minimize the emergence of drug resistance. The risk of developing HIVDR was also higher in those who missed antiretroviral drugs for a period of 14–31 days compared with those missing drugs for >31 days and those missing <14 days. Wild-type HIV may become the predominant quasi-species when antiretroviral drugs are missed for a longer duration, and therefore drug mutations may have not been detected in those who missed ART for >31 days [28]. Missing drug pickup by a small number of days may not have been associated with missed doses if patients accumulated tablets at home during ongoing therapy, as clinic visits were scheduled every 28 days, whereas 30-day supplies were dispensed. As expected, NNRTI resistance at baseline was strongly associated with resistance at 12–15 months, although some were able to suppress HIV replication despite the presence of baseline mutations. Baseline NRTI mutations did not prevent viral suppression of 4 patients alive on first-line ART at 12–15 months; however, NRTI resistance at baseline was too infrequent to enable drawing conclusions on its consequences for HIVDR and virologic suppression at 12–15 months.

CONCLUSIONS

Monitoring in 4 sites of the Malawi ART program revealed that HIVDR before the start of ART was low (4.0%), that HIV RNA was suppressed in >70% of participants 12–15 months after ART initiation, and that HIVDR prevalence was low (6%) at the same point. ART defaulting remains a concern and led to a considerable level of possible resistance. Strategies to reduce ART defaulting, to facilitate timely drug collection, and to improve adherence among young adults may further reduce possible and detected HIVDR.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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