

Early warning indicators for HIV drug resistance in Malawi

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Background: Malawi started rapid scale-up of antiretroviral therapy (ART) in 2004 and by December 2006 had initiated over 85,000 patients on treatment. Early warning indicator (EWI) reports can help to minimize the risk of emerging drug resistance.

Methods: Data collected during the routine quarterly supervision of 103 public sector sites was used to compile the first EWI report for HIV drug resistance (HIVDR) in Malawi, reflecting outcomes for October to December 2006.

Results: All sites reach the World Health Organization (WHO) targets for prescribing practices and drug supply

continuity. The target for adherence was achieved by 85% of sites and 84% achieved the target for minimizing treatment defaults; however, less than half of all sites reach the WHO target for patient retention.

Conclusions: These results emphasize the importance of defaulter tracing and initiating treatment earlier in the course of HIV infection. As part of a comprehensive HIVDR monitoring programme, the Ministry of Health plans for on-going tracking of these indicators, as well as special data collection from the private sector. Plans are also underway to gather information on other recommended indicators that are not collected during routine supervision.

Introduction

On the basis of estimates from the 2005 ANC surveillance, 14% of Malawians between 15 and 49 years of age are infected with HIV. Approximately 187,000 (25% of which are children <15 years old) of the 13 million Malawians are eligible for antiretroviral therapy (ART) [1]. Malawi is one of the poorest countries in Southern Africa, with the 2003 gross national income being US\$160 per capita. In 2004/2005, ~9.3% of the national budget (12.8% of the gross domestic product) was spent on the health sector, an average of US\$20 per capita [2].

Malawi began to rapidly scale-up the provision of ART to HIV-infected eligible patients in 2004, using a national and standardized approach in all health facilities in the public sector [3,4]. In 2005, the private sector was also included, provided they used the same standardized systems that were in use in the public sector. By December 2006, >85,000 patients had initiated treatment in both public and private sectors. The national ART programme is supported through the Global Fund, with drugs procured through UNICEF, at a cost of US\$250 per patient per year.

To minimize the risk of emerging drug resistance, the Ministry of Health (MOH) provides free standardized treatment in public sector ART sites (103 as of December 2006). Urban private sector hospitals and clinics (numbering 38 in total) provide the same standardized ART regimen at a subsidized rate of less than US\$3.50 per month of treatment. The standardized regimen includes one fixed-dose combination first-line regimen: stavudine (30/40 mg) plus lamivudine (150 mg) and nevirapine (200 mg) (triomune, Cipla; Nevilast, Hetero). Clinics offer alternative first-line regimens (zidovudine plus lamivudine and nevirapine or stavudine plus lamivudine and efavirenz) for patients with adverse drug reactions, and a second-line regimen for patients who fail first-line therapy. Private sector assessments indicate that few patients in Malawi access ART outside of these public and subsidised private sector sites.

Additionally, the centralized ART programme recognizes the importance of sound data collection and reporting to support national procurement and to identify any potential problems. Sites record patient information on a national patient treatment master

card and register (see Figures 1 and 2). To monitor site performance and the overall national impact, each site is visited every 3 months and quarterly and cumulative cohort data are recorded [5]. This monitoring and evaluation system includes collecting information on programmatic factors associated with an increased risk of drug resistance, such as patient adherence, prescribing practices, continuity of drug supply and patient outcomes.

Methods

Under the guidance of the World Health Organization (WHO) initiative for HIV drug resistance (HIVDR)

early warning indicators [6], we reviewed data collected during routine quarterly supervision visits. Indicators collected in Malawi are listed in Table 1. The data presented are taken from the 103 public sector ART sites visited during routine supervision in January to March 2007, with data censored on 31 December 2006. Data from the 38 private sites providing ART treatment in Malawi are not included, owing to the unavailability of site-specific information at the time that this first report was generated.

Site-level information on prescribing practices, patient loss to follow-up and retention, adherence and drug supply continuity are available through the quarterly supervision visits. The first indicator for

Figure 1. National patient mastercard

NEW Patient MASTER CARD FOR ARV (front): ARV Number _____ Year _____

Name _____ Age _____ Sex _____ Initial Wt (Kg) _____ Initial Ht (cm) _____ Transfer-In (Y/N) _____

Address (physical address and phone) _____ Follow-up agreement (Y/N) _____

Name of identifiable guardian _____ Date and place of positive HIV test _____

Date of starting 1st line ARV regimen _____ Reason for ARV: Stage _____ PTB _____ EPTB _____ KS _____ PMTCT _____

Date of starting alternative 1st line ARV regimen (specify) _____ Date of starting 2nd line ARV regimen (specify) _____

Month	Date	Wt, Kg	Ht, cm	Outcome status					Of those alive			Ambulatory		Work/school		Side effects		No. pills in bottle	ARV given		CPT	Other
				A	D	DF	Stop	TO	Start	Sbs	Switch	Amb	Bed	Yes	No	Y	N		P	G		
Jan																						
Feb																						
Mar																						
Apr																						
May																						
Jun																						
Jul																						
Aug																						
Sep																						
Oct																						
Nov																						
Dec																						

Specify reason for ARV therapy (Stage III, Stage IV, CD4 <200, PTB, EPTB, Transfer-in)

Outcome status: A=alive; D=dead; DF=defaulted and not seen for 3 months; Stop=stopped medication; TO=transferred out to another unit
Of those alive: Start=alive and on first line regimen; Sbs=alive and substituted to alternative first line regimen;
 Switch=alive and switched to a second line regimen because of failure of first line regimen

Ambulatory: Amb=able to walk to/at treatment unit and walks home unaided; Bed=most of time in bed at home
Work/school: Yes=engaged in previous work / employment or at school; No=not engaged in previous work / employment or not at school
Side effects: If Yes, specify - PN=peripheral neuropathy; HP=hepatitis; SK=skin rash; LA=lactic acidosis; LD=lipodystrophy; AN=anaemia
No. Pills in bottle: If patient comes at 4 weeks count number of pills in bottle (8 pills or less = 95% adherent)
ARV given P = patient; G = guardian. Indicate the number of tins of ART given to patient or guardian
CPT: Indicate if patient on cotrimoxazole preventative therapy: **Blank column for remarks**

to an alternative first-line regimen or switching to a second-line regimen are recorded on the front of the patient mastercard and collected in aggregate from each site during the quarterly supervision visit. To date, all sites included here only offer the standard first-line, first-line alternative and second-line regimens.

The loss to follow-up indicator includes all patients who started ART in Q4 2005 in the denominator and any patients from this cohort that have defaulted by the end of 2006 in the numerator. In Malawi, a patient is considered a defaulter if three months have passed since the last clinic visit and drug pick-up. This information is recorded under outcome status at the bottom of the patient mastercard. Only the 61 sites that offered treatment in Q4 2005 are included in the calculation of this indicator.

Using the current system, sites report whether patients are on ART at 12 months but do not specify the regimen in this report. Therefore, the WHO indicator for retention on first-line ART was collected in the subset of 57 sites that offered treatment in Q4 2005 where second-line ART is not yet offered. This indicator reports the percentage of individuals that started ART at these 57 sites in Q4 2005 that are alive and on treatment (did not default, stop, transfer out or die) by 31 December 2006. As it is currently not possible to track patients that formally transfer out of a site, these

individuals are not included in the numerator or denominator of this indicator.

For the pill count adherence indicator, we include in the denominator the 38,286 patients alive and on treatment with a pill count recorded at the last patient visit in Q4 2006 and the number of these individuals with eight or less pills remaining at the last pill count in the numerator. At each visit, a patient receives either a 30-day (60 pills) or 60-day (120 pills) supply of antiretrovirals, depending on their length of time on treatment and stability. Nurses or clinicians count and record remaining pills at the bottom of the patient mastercard. The goal for individual adherence is 95% in Malawi (compared with the WHO recommended 90% adherence level); during site supervision the number of patients that had eight or fewer pills at the last visit is documented (reflecting an individual's adherence of 95% or more assuming a 30 day supply given at the previously scheduled visit). This is expected to be an undercount of the true adherence rate, as some patients are given two months supply, and 16 or fewer pills would reflect 95% adherence in these patients. Ten sites had no information on this indicator recorded during the last quarterly supervision visit.

Finally, for the WHO indicator on drug supply continuity, we report the percentage of quarters in 2006 during which there are no drug stock outages.

Table 1. Performance against WHO targets

Indicator	WHO target, %	Public ART sites that meet the target (<i>n</i> =103), %	Patients in the public sector, %
Prescribing practices			
Percentage of individuals starting ART who are prescribed a standard first-line regimen (Q4 2006)*	100	100	100
Percentage of individuals on ART currently taking a standard ART regimen (first-line, second line or salvage) (Q4 2006)*	100	100	100
Loss to follow-up			
Percentage lost to follow-up during the 12 months after starting ART (cohort started Q4 2005)†	<20	84	14
Patient retention			
Percentage of persons starting first-line ART who are still alive and on ART 12 months later, excluding transfer-out patients (cohort started Q4 2005)†	>70	38	68
Pill count/adherence			
Percentage of individuals who demonstrate >95% adherence by pill count over a specified time period (adherent ≤8 pills at last visit) (Q4 2006)‡	80	85	93
Drug supply continuity			
Percentage of quarters in which there were no drug stock outages, 2006	100	100	100

*In the fourth quarter (Q4) of 2006, 12,253 patients initiated treatment and 57,356 patients were alive and on treatment. †In Q4 2005, 61 sites provided treatment; 7,803 patients are included in this cohort. ‡In Q4 2005, 56 sites provided treatment and do not currently offer second-line treatment; 5,078 patients are included in this cohort. §Pill count/adherence information was available on 38,286 patients at 93 sites at the end of Q4 2006. ART, antiretroviral therapy; WHO, World Health Organization.

This information is routinely collected by inspecting pharmacy records during supervision visits.

This report used data routinely collected from sites for the purpose of programme monitoring and evaluation and, as such, includes no personal identifiers. The Malawi National Health Science Research Committee provides general oversight and approval for the collection and use of routine programmatic data for monitoring and evaluation. This review was considered programme evaluation by the US Centres for Disease Control and Prevention, which is not classified as human subjects research.

Results

Table 1 shows the WHO recommended target for each indicator as well as the percentage of sites and total patients achieving the target. All sites successfully achieved the targets of prescribing standard first-line regimens to 100% of new patients and having all patients on a standard (first-line or second-line) therapy. Note that the 12,253 patients included in the first indicator, 'percentage of individuals starting ART who are prescribed a standard first-line regimen', includes new ART patients and transfer-in patients at each site; however, to date, all the sites in this report only start patients on a standard first-line regimen. Also, 100% of sites had no drug stock outages in 2006.

At the national level, only 14% of patients that initiated treatment in Q4 of 2005 had defaulted 1 year later, and 84% of sites offering treatment in Q4 2005 had a default rate of 20% or lower [5]. Nationally, 68% of the 5,078 patients that started ART in Q4 2005 at the 56 sites included are alive and on treatment. Excluding transfer-outs from analysis, only 38% of these 56 sites in the patient retention indicator are achieving the WHO target (>70%) for patient retention, with an interquartile range for patient retention of 61–75%. As the Malawi ART programme is in a rapid scale-up phase, there are a significant number (10% of those started in Q4 2005) of patients that have transferred to new clinics closer to their homes. As many of these patients continue on treatment at another site, the number of patients alive and on treatment might be higher than indicated here.

Of the 93 sites that had information about pill counts recorded from the last supervision visit, 79 sites (85%) had achieved the target of at least 80% of patients with 95% adherence.

Conclusions

Due to centralized support, the Malawi ART programme performs very well on drug supply and prescribing practices at the national and site level.

These results are largely attributed to the centralized provision of standardized treatment, on-going supervision of drug stocks and an established standardized system of national drug forecasting. In country, individual clinic prescribing practices and drug stocks are monitored on a quarterly basis. Additionally, the targets for initiating new patients in a month at a site are set nationally. Thus, the HIV unit can accurately estimate the number of drugs needed for procurement and reallocate drug supplies in a timely manner if required. Additionally, despite struggles to maintain the drug supply for the essential health package, the anti-retroviral programme has engaged a parallel procurement system to successfully ensure a steady supply for patients [7].

Most sites successfully reach the adherence and loss to follow-up targets, which is good from the perspective of minimizing the potential for drug resistance. In other sites, the quarterly monitoring visits (during which this data is collected) allow the MOH supervisors to discuss the issue with the ART clinic staff and attempt to find solutions. For example, a solution may mean the whole team discussing the issue of high loss to follow-up with the district health officer to find resources to undertake tracing of patients who have not attended the clinic at their due date. Currently, not all sites automatically trace defaulters because of limited resources. However, the MOH is aware of the need for defaulter tracing and several efforts are underway either as operations research or best practice assessment.

Many ART sites fail to achieve the targets for patient retention, although the interquartile range of 61–75% indicates that most sites are close to the 70% retention target. Failure to achieve the 70% retention target at ART sites is largely attributed to the fact that many patients start treatment severely ill (WHO clinical stage III and stage IV) and die in the initial months of treatment – nearly 8% of patients started on ART died within 3 months of treatment initiation [8,9]. However, an individual in stage I or stage II can initiate treatment if the CD4⁺ T-cell count is <250 cells/mm³, and as the number of laboratories with capacity and supplies to test CD4⁺ T-cell counts expand, an increased number of patients may initiate treatment sooner. We expect earlier initiations to lead to a decline in this early mortality rate. Also, improved diagnosis and appropriate treatment of opportunistic infections at initiation would also improve rates of early mortality. As one response, Malawi is currently revisiting the tuberculosis (TB)/HIV strategy, in the hopes of encouraging HIV testing in TB populations and improving TB diagnoses and follow-up in HIV-infected populations. Finally, tracking the outcomes of patients that transfer out would allow Malawi to report on these patients in

this indicator. Indeed, if a significant proportion of these patients remain alive and on treatment at another site as believed, then inclusion of transfer-out patients would improve site performance on the patient retention indicator.

Because of the complexity of extracting the data required for some WHO recommended indicators, not all indicators can be reported using data collected during the routine quarterly supervision visit, especially information on drug pick-up and appointment keeping that look at the percentage of patients who do not miss appointments. However, information for any of the recommended indicators is captured at each ART site and could be extracted through special data collection, including intensive chart reviews at sentinel sites or electronic extraction from select sites supported by an electronic patient data system (see Box 1). Also, only one site currently routinely tests patients for viral load, but this data could be made available from their electronic data system. The HIV Drug Resistance Task Force is formulating the best approach to collect and report this information in Malawi.

An additional limitation of this preliminary early warning indicator (EWI) report is that the data only include the public sector sites in Malawi, although again the same systems are used in the private health facilities and similar information could be collected from this sector. At preparation of this initial EWI report, data collected from private sites was not readily available to the MOH; however, the HIV unit is working with the private sector to provide the anti-retroviral monitoring data on a quarterly basis, in the same data format, so that it can be included in all upcoming programme evaluations. In the future it will be important to investigate programmatic factors that could contribute to resistance at these private sector sites, in order to comprehensively understand the risk of emerging HIVDR at all sites in Malawi.

Through the WHO recommended EWIs, managers of the Malawi antiretroviral program can monitor and respond to programmatic factors that have been associated with the development of HIVDR. However, these indicators do not allow for antiretroviral supervisors to track drug resistance in individual patients or monitor actual levels of drug resistance at clinics. This limitation emphasizes the importance of complementing results from EWI reports with HIVDR monitoring surveys, which link these programmatic indicators with patient viral suppression and drug resistance mutations after 12 months of treatment.

The MOH and its partners recognize the importance of on-going monitoring for HIVDR. The first HIVDR Threshold Survey was completed in 2006 and results indicate that the level of transmitted drug resistance is

Box 1. Data availability for early warning indicators in Malawi

Data available through routine quarterly supervision

- Prescribing practices.
- Loss to follow-up.
- Patient retention.
- Pill count/adherence.
- Drug supply continuity.

Data available through special data extraction

- Antiretroviral drug pick-up.
- Antiretroviral therapy appointment keeping.
- Viral load suppression (at select sites).

<5% [10]. Malawi is also in the process of collecting information on the development of resistance under treatment pressure through a retrospective HIVDR monitoring survey, with a follow-up prospective survey in July. The results from routine implementation of these surveys, combined with regular EWI reports will support national decision-making on ART programme planning and other HIVDR prevention measures. It is hoped that these will lead to the continued success of HIV treatment scale-up in Malawi.

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Disclosure statement

The authors declare that they have no competing interests.

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