Population-based Monitoring of HIV Drug Resistance in Namibia with Early Warning Indicators

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Abstract

Introduction—HIV drug resistance (HIVDR) testing is not routinely available in many resource-limited settings (RLS), therefore ART program and site factors known to be associated with HIVDR should be monitored to optimize the quality of patient care and minimize the emergence of preventable HIVDR.

Methods—In 2009, Namibia selected five World Health Organization Early Warning Indicators (EWIs) and piloted abstraction at nine antiretroviral therapy (ART) sites: *ART prescribing practices, Patients lost to follow-up (LTFU) at 12 months, Patient retention on first-line ART at 12 months, On-time antiretroviral (ARV) drug pick-up*, and *ARV drug-supply continuity*.

Results—Records supported monitoring of three of five selected EWIs. 9/9 (100%) sites met the target of 100% initiated on appropriate first-line regimens. 8/9 (89%) sites met the target of ≤20% LTFU, although 20.8% of ART starters (range 4.6%-44.6%) had a period of absence without documented ART coverage of 2.3 months (range 1.5-3.9 months). 6/9 (67%) sites met the target of 0% switched to a second-line regimen.

Conclusions—EWI monitoring directly resulted in public health action which will optimize the quality of care, specifically the strengthening of ART record systems permitting monitoring of five EWIs in future years and protocols for improved ART patient defaulter tracing.

Keywords

HIV; AIDS; Africa; anti-retroviral agents; drug resistance

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INTRODUCTION

At the end of 2008, more than 4 million (3,700,000-4,360,000) people were receiving antiretroviral therapy (ART) in low- and middle-income countries.1 This number is expected to increase in response to revised public health guidelines published by the World Health Organization (WHO) recommending the initiation of ART at CD4+ T-cell counts <350 copies/mm.2 An unintended consequence of treatment scale-up is the possible emergence of HIV drug resistance (HIVDR) in populations even when patient adherence to ART is optimally supported. HIVDR has the potential to undermine the dramatic gains which ART has had in reducing the morbidity and mortality of HIV-infected patients in resource-limited settings (RLS).3

In RLS, viral load and HIVDR testing are not routinely available primarily because of their cost and insufficient local laboratory capacity. Monitoring of ART program factors known to be associated with the emergence of HIVDR for the purpose improving programmatic functioning, may minimize the emergence of preventable HIVDR. For example: HIVDR testing is not required to predict the emergence of drug-resistant HIV in settings where inappropriate prescribing practices (mono- or dual-therapy), treatment interruptions due to suboptimal patient adherence, poor patient retention on ART, or ART supply shortages or stock-outs occur at unacceptably high levels. These factors have been shown to be associated with the development of HIVDR;[4,5,6,7,8,9,10] thus, their monitoring may alert national ART program planners to issues which may be adjusted to minimize the emergence of HIVDR.

HIVDR Early Warning Indicators

The foundation of the WHO's global HIVDR prevention and assessment strategy,11 which includes laboratory-based surveys of acquired12 and transmitted[13] HIVDR, is the monitoring of HIVDR Early Warning Indicators (EWI). EWIs assess ART site and program factors potentially associated with HIVDR.[11] Utilizing data routinely collected in patients' medical and pharmacy records, EWI monitoring is a minimum-resource strategy designed to be integrated into national monitoring and evaluation programs. When monitored annually at all ART sites or a large number of representative sites, EWIs provide countries with evidence to make programmatic adjustments at the level of an individual site or at the national level, when necessary.

HIV in Namibia

Namibia is a Southwest African country with a population of 2,108,665 individuals.[14] Based on 2008 antenatal sero-surveillance data, an estimated 17.8% of Namibians aged 15-49 years are infected with HIV-1.[15] The epidemic is predominantly spread via heterosexual contact, and prevalence estimates vary by region with up to 31% infected with HIV-1 in the most heavily-affected areas in the north.[15]

ART rollout

ART has been available in Namibia's private sector since 1997 and in the public sector since 2003. As of 2007, approximately 40,000 patients were receiving ART in the public sector and 12,000 patients in the private sector, representing 88% of patients eligible for ART, one of the highest coverage rates in Sub-Saharan Africa.[16] At present, ART is available at all 35 public hospitals and at an additional 101 satellite/outreach service points.

In the public sector, ART is provided free of charge following a population-based model of care with one first-line regimen and three alternate first-line regimens consisting of two nucleoside reverse transcriptase inhibitors (NRTI) combined with a non-nucleoside reverse transcriptase inhibitor (NNRTI). Three second-line regimens are available, consisting of 2

NRTIs with a ritonavir-boosted protease inhibitor (PI). ART initiation is based on WHO clinical staging and/or CD4 cell count < 200 cells/ mm^3. Where available, viral load testing is performed six-months after ART initiation and targeted viral load testing is performed to confirm clinical or immunological failure.[17] With support from Management Sciences for Health (MSH) Namibia, a standardized pharmacy record system, the Electronic Dispensing Tool (EDT), has been introduced.

Minimizing HIVDR

Since its inception, Namibia's ART program has forged strong collaborations with national and international support partners to provide the highest possible quality ART delivery. Namibia has been proactive in minimizing preventable HIVDR by mandating the use of standardized national ART prescribing practices, WHO pre-qualified drugs, and the use of standardized medical and pharmacy record-keeping systems which facilitate population-based evaluation of ART. In 2009, the Namibia Ministry of Health and Social Services (MoHSS) finalized its national plan for the prevention and assessment of HIVDR following WHO recommendations.[11]

METHODS

Early Warning Indicators selection

Based on a review of available patient records, Namibia chose to pilot the following five EWIs: *ART Prescribing practices, Patients lost to follow-up (LTFU) at 12 month, Patient retention on first-line ART at 12 months, On-time ARV drug pick-up, and ARV drug-supply continuity.* [11,18,19] Definitions for these selected EWIs and their respective recommended targets are summarized in Table 1.

Pilot site selection and data abstraction

9 pilot sites were chosen at random from among 15 sites which had historical data in EDT available for abstraction. Teams headed by MoHSS abstracted data into an electronic tool provided by WHO. Data validation was performed by re-abstracting a minimum of 10% of the variables from different sources.

Sample size

In order to make the results generalizable to each site, the sampling strategy was based on calculating a minimum sample size for each indicator at each site, based on the number of eligible patients for each EWI. Two different cohorts of 'eligible patients' were formed: 1) Patients consecutively initiating ART for the first time on or after January 1, 2007 (ART prescribing practices, Patients LTFU at 12 month, and Patient retention on first-line ART at 12 months) and 2) Patients consecutively picking up ART on or after October 1, 2007, regardless of duration of regimen (On-time ARV drug pick-up). Sample size calculations were performed to provide a 95% CI of ±7%, assuming a true prevalence of 50% because this provided the most conservative estimate of the sample size required. The sample size for all EWIs at all sites was 180. For ARV drug-supply continuity, data were abstracted on stock-outs of each ARV drug in routine use from January 1, 2008 until December 31, 2008 using site-based pharmacy stock cards.

RESULTS

Namibia piloted abstraction of *ART prescribing practices, Patients LTFU at 12 months*, and *Patient retention on first-line ART at 12 month* at nine sites. Data from 3,240 patients were abstracted and analyzed. (Table 2) *On-time ARV drug pick-up* and *ARV drug-supply*

continuity could not be monitored because information entered into existing patient records was found to be incomplete or inaccurate.

ART prescribing practices

All patients analyzed from each of the 9 sites were prescribed an initial first-line regimen following national guidelines with100% of sites achieving the target of 100% appropriate prescribing practices.[18,19] (Table 2)

Patients lost to follow-up at 12 months

8 of 9 sites (89%) met the target of ≤20%[18,]19 of *Patients LTFU at 12 months.* (Table 2) The median LTFU was 15% (interquartile range [IQR] 12%-17%). Although not classified as LTFU at 12 months, 20.8% (range 4.6%-44.6%) of ART starters at all sites had a period of absence without documented ART coverage of a median of 2.3 months (range 1.5-3.9 months) during their first year of treatment.

Patient retention on first-line ART at 12 months

6/9 sites (67%) met the target of 0% of patients switched to a second-line regimen 12-months after initiation of therapy. At two sites, one patient had been switched to an appropriate second-line regimen after virological failure, and at one site, one patient had been changed to an inappropriate triple NRTI regimen. (Table 2)

On-time ARV drug pick-up

Data for *On-time ARV drug pick-up* was unavailable except at one site where the proportion of patients picking up pills on time was 72%, which fell significantly short of the suggested WHO target of ≥90%.[18,19]

ARV drug-supply continuity

It was not feasible to abstract usable data to assess *ARV drug-supply continuity* at any pilot site.

DISCUSSION

The monitoring of ART site and program factors potentially associated with the emergence of HIVDR is essential, especially in settings where viral load and HIVDR testing are not widely implemented.

In 2009, Namibia piloted WHO-recommended EWIs which lead to direct public health action. ART record-keeping systems were strengthened which will lead to better patient management as well as enabling the monitoring of all five nationally chosen EWIs in future years. Moreover, EWI data identified populations vulnerable to the development of HIVDR and lead to the development of operational research proposals and interventions targeted at these most-at-risk populations.

Monitoring of *ART prescribing practices* is important because inappropriate prescribing of mono- or dual-therapy or inappropriate drug combinations and/or dosing has been well substantiated to lead to the development of HIVDR in individual patients and at the population level.[4,20,21,22,23] Importantly, no inappropriate prescribing was observed at any of the nine pilot sites in Namibia, suggesting strong leadership in the public health sector.

Poor retention in treatment programs, like poor adherence to ART, is an important reason for undesirable treatment outcomes among patients receiving ART.[24,25,26] When patients

previously LTFU reinitiate ART, they may not achieve the same rates of viral suppression compared to those never LTFU due to previous selection of drug resistant virus; thus they are at increased risk of morbidity and mortality.[27] Furthermore, because patients LTFU are at risk of having acquired HIVDR due to treatment interruptions[5,6], they may transmit drug resistant HIV to others.[28]

Although the proportion of *Patients LTFU at 12 months* in Namibia was low and met the WHO target, a large number of ART starters were noted to have had a mean 2.3 month period of absence from their ART site during the first year of treatment. The MoHSS hypothesizes that many of these individuals may be "in transits", a term used to denote patients who migrate seasonally to other areas of the country for work, possibly continuing ART at a different site, only to return to the site of ART initiation at some point in the future. However, existing record-keeping systems do not permit the tracing of this mobile population at risk for the development of HIVDR. As a result of this pilot, the MoHSS has planned an intensification of existing ART defaulter tracing mechanisms through improvements in EDT, the establishment of a national patient database with unique patient identifiers, and increased mobilization and redistribution of human resources.

Namibia's results for *Patient retention on first-line ART at 12 months* suggest success in managing ARV toxicity and side-effects through in-class substitutions rather than switches to regimens using drugs from a different class. These results also highlight general success in maintaining the efficacy of available first-line regimens during the first 12 months of treatment and suggest appropriate identification and management of patients with virological failure.

With the exception of one site, data were not able to assess *On-time ARV drug pick-up*. In Namibia, routine pharmacy dispensing practice is meant to include the routine counting of remnant pills (number of pills left over from the previous prescription) and the dispensing of a specified number of days of pills. However, the number of remnant pills was not routinely recorded, thus it was not possible to calculate the actual pill run-out date, necessary to monitor this indicator. At the single site where assessment was feasible, the proportion of patients picking up pills on time fell short of the ≥90% target. Because pharmacy refill adherence has been shown to predict virological failure,[29,30] it is reasonable to hypothesize that patients not picking up pills on time may be experiencing intermittent treatment interruptions and may be predisposed developing drug resistant virus.[5,6]

ARV drug stock-outs are an important cause of treatment interruptions and HIVDR in RLS. [6,7,8,10] It was not possible to assess *ARV drug-supply continuity* because existing pharmacy records did not capture stock at the level of the site dispensary, but rather at a more central level.

EWI monitoring results were extensively discussed with individual sites during interactive feedback sessions. These sessions emphasized how sites can make use of well-maintained medical and pharmacy records to conduct their own quality of care assessments and make meaningful local adjustments in practice.

As a result of this EWI pilot, changes have been made in EDT which will not only improve the quality of patient care but will also permit abstraction of all five selected EWIs in the future. Specifically, EDT was modified to include a pill-count field into which pharmacists will record number of remnant pills at each visit. Because drug-supply continuity at the level of the dispensary was not possible to assess, EDT will be adjusted to capture this information.

One important limitation of this pilot is that data are derived only from patients receiving ART in the public sector. Acknowledging that over 23% of patients receive ART in the private sector, the MoHSS in collaboration with the private sector are assessing *ART prescribing practices*

and *On-time ARV drug pick-up* in the private sector using insurance company claims databases. An additional limitation of this report is that pediatric patients were not included; however, pediatric EWI monitoring assessing the use and availability of pediatric formulations and weight-based dosing will be implemented. The fact that the ART sites chosen for this pilot may not have been representative of all ART sites in Namibia does not diminish the important public health significance of these results. Over the next five years, Namibia plans to scale up monitoring of EWIs to all of its ART sites. Steps have been taken to ensure the long-term sustainability of EWI monitoring by integrating it into the existing national monitoring and evaluation system and by securing funds from the Global Fund to fight AIDS, TB, and Malaria.

In conclusion, this EWI pilot has given Namibia data which allowed it to identify areas within its national ART program which could be strengthened to minimize the emergence of preventable HIVDR. As Namibia's HIVDR evidence base grows and is augmented by data generated from WHO-recommended population-based surveys to assess transmitted and acquired HIVDR,[12,13] the quality of care for HIV-infected patients in Namibia will be further maximized and the emergence of preventable HIVDR minimized.

Acknowledgments

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TABLE 1

Selected WHO Early Warning Indicator Definitions and Targets

Indicator	Definition
ART Prescribing Practices[*]	Percentage of patients initiating ART at the site who are initially prescribed, or who initially pick up from the pharmacy, an appropriate first-line ART regimen.
	Target: 100%
Patients lost to follow-up at 12 months[§#]	Percentage of patients initiating ART at the site who are lost to follow-up during the 12 months after starting ART.
	Target: ≤20%
Patient retention on first-line ART at 12 months[#∞]	Percentage of patients initiating ART at the site who are still on ART after 12 months, and whose initial ART regimen was changed during the first 12 months to a regimen with a different drug class.
	Target: 0%
On-time ARV drug pick-up[#]	Percentage of patients picking up all prescribed ARV drugs on time, before the previous prescription would run out if taken according to schedule.
	Target: ≥90%
ARV drug-supply continuity	Percentage of months in a designated year in which there were no ARV drug stock-outs (determined at the level of site dispensary).
	Target: 100%

[*] Appropriate first-line ART regimen: An ART regimen that meets one or both of the following definitions:

- Standard regimen listed in national ART guidelines and used according to those guidelines

- Regimen recommended in the WHO treatment guidelines

[§] Patients who had not returned to the pharmacy or clinic ≤90 days after the last ART run-out date during the 12-months after the date of ART initiation and who were not known to have transferred their care to another site, stopped therapy without restarting, or died, were classified as LTFU.

[#] For EWIs: *Patients LTFU at 12 month, Patient retention on first-line ART at 12 months*, and *On-time ARV drug pick-up*, if no ARV pick-up date, regimen, and number of pills dispensed was not recorded in the records, it was assumed that no pick-up had occurred, resulting in the most conservative estimate of each indicator.

Table adapted from WHO HIV Drug Resistance EWI guidance document [19]

TABLE 2

Site-specific EWI results

ART Site	Appropriate initial ART prescribing[*] Target = 100%	LTFU at 12 months[*][#] Target ≤ 20%	Retention on first-line ART at 12-months[*] (proportion of patients switching to second line ART at 12 months) Target = 0%
Site 1	180/180 (100%)	11/180 (6%)	0/140 (0%)
Site 2	180/180 (100%)	29/180 (16%)	0/125 (0%)
Site 3	180/180 (100%)	34/180 (19%)	1/125 (0.8%)
Site 4	180/180 (100%)	35/180 (19%)	1/119 (0.8%)
Site 5	180/180 (100%)	22/180 (12%)	0/108 (0%)
Site 6	180/180 (100%)	19/180 (10%)	0/156 (0%)
Site 7	180/180 (100%)	27/180 (15%)	1/108 (0.9%)
Site 8	180/180 (100%)	30/180 (17%)	0/77 (0%)
Site 9	180/180 (100%)	76/180 (42%)	0/59 (0%)
Number of sites meeting EWI target	9/9 (100%)	8/9 (89%)	6/9 (67%)

ART - Antiretroviral therapy
LTFU - Lost to follow-up

[*] Cohort of patients initiating ART at the site on or after the sample start date (January 1, 2007)

[#] Deaths were classified as not lost to follow-up, transfers out were censored from the analyses