

ORIGINAL ARTICLES

Results from implementing updated 2012 World Health Organization Guidance on early-warning indicators of HIV drug resistance in Zimbabwe

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ABSTRACT

Objective: This study evaluated the performance of sentinel sites in preventing the emergence of HIVDR using Early Warning Indicators (HIVDR EWI) survey.

Methods: Adult and paediatric patient data on: On time pill pick up, Retention in care, Pharmacy stock-outs, and Dispensing practices was collected. Information from pharmacy registers was verified using facility-held cards. This was a cross-sectional analysis of retrospectively collected data from 72 sites providing both adult and paediatric ART as well as two providing adult ART only. All data were entered into and analysed using a WHO EWI data abstraction electronic tool.

Results: Twenty-one percent of sites providing adult and 4.2% of sites providing paediatric ART managed to meet the target for on time pill pick up. Retention in care indicator was met by 48.7% (95% CI: 36.9-60.6) of sites. ARV stock-outs occurred in 81.1% (95% CI: 70-89.3) adult sites and 63.9% (95% CI: 50-78.6) paediatric sites. ARVs were appropriately dispensed by 86.5% (95% CI: 75.6-93.3) of adult sites and 84.7% (95% CI: 74.3-92.1) of paediatric sites.

Conclusions: Most sites had low performance in many indicators in this survey and failed to meet the recommended targets. Some policies such as the current buffer stock and storage outside Harare should be revised in order to improve site access to ARVs. The country should prioritize the provision of viral load testing services in all provinces. The electronic patient management system should be rolled out to all ART sites to improve patient tracking and monitoring by sites.

Key Words: Zimbabwe, Early warning indicators, Stock-outs, Retention

1. INTRODUCTION

An estimated 35 million people are living with Human Immunodeficiency Virus (HIV) worldwide, although the burden of the epidemic continues to vary considerably between

countries and regions.^[1] The greatest burden is in resource-limited settings such as Sub-Saharan Africa.^[2] In response, there were rapid scale-up of Antiretroviral Therapy (ART) programs throughout the world.^[3,4] This rapid scale-up be-

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came possible through the public health approach to rapidly scale up ART using standardized and simplified treatment and guidelines for initiation and monitoring of ART.^[5] Such approaches are consistent with international standards as well as being appropriate to the Zimbabwean situation characterized by limited resources.^[6] Zimbabwe is experiencing a generalized HIV epidemic with an adult prevalence rate of 14.7%, according to the 2012 National HIV/AIDS Estimates. An estimated 1,328,535 Zimbabweans were living with HIV and AIDS at the end of 2012.^[7] Among children aged 0-14 years, an estimated 186,745 were living with HIV and AIDS. In both adults and children, the estimated HIV incidence rate in 2012 was 0.96.^[7]

The Ministry of Health and Child Care (MOHCC), through the AIDS and TB Unit, implements programs aimed at HIV prevention, care treatment, support, and mitigation. The main programs include; HIV Testing and Counseling (HTC), Prevention of Mother to Child Transmission of HIV (PMTCT), Care and Treatment, Condom Programming and Workplace Prevention Programs. Counselling and testing are the entry point to all HIV prevention, care, treatment and support programs. The benefits of HTC include behaviour change, early referral for care, treatment, support and access to ART.

The National ART program in Zimbabwe that started in April 2004 is implemented as a comprehensive care and support package that addresses the medical, social, emotional, and economic needs of people living with HIV and AIDS. Patients on treatment for HIV do not pay for services related to HIV care including ART medicines. A phased out approach was used to rapidly scale up ART services nationwide. The ART program started decentralizing HIV Care & ART services to primary care clinics in 2008 as a measure to improve access to HIV care. The National ART Coverage, defined as the proportion of HIV-infected patients in need of ART who are actually taking ART at the end of that particular year, rose from 55% in 2010 to 77% in 2012 in 980 ART initiating sites across the country. The national adult ART coverage as at December 2012 was 85% for adults and for children it was 43%.^[8] These medicines are provided for free in public health facilities using a standard first line and second line ART regimens.

Despite the obvious benefits that rapid scale-up has had on Acquired Immune Deficiency Syndrome (AIDS)-related morbidity and mortality, potential and widespread emergence of transmission of HIV drug resistance may reverse those benefits. In 2004, World Health Organization (WHO) and the United States Centers for Disease Control and Prevention (CDC), in collaboration with HIVResNet, developed a comprehensive global strategy for the assessment and prevention

of HIVDR. This strategy was adopted and adapted by Zimbabwe.^[9] In line with the strategy, a technical working group was formed in Zimbabwe which oversees the implementation of the strategy. The EWI survey is conducted annually in Zimbabwe and data collected analysed.

Zimbabwe started implementing the EWIs in 2007 with a pilot phase after wide-scale consultations with stakeholders and feasibility assessments. The number of sites rose from 20 in 2007 to 70 in 2011. Previous definitions were used and EWI were scaled-up after piloting. With the introduction of second-generation EWIs the need to assess site performance in relation to the new EWIs became evident.^[10] The EWI survey is beneficial in places where HIVDR genotyping is not available, especially the public sector, as in Zimbabwe.^[10] By using EWIs sites are able to identify local factors that hinder the provision of quality care and are associated with the emergence of HIVDR. Sites then tailor responses to these factors based on the results of the EWI surveys. We, therefore, set out to evaluate the performance of the participating sentinel sites in minimizing the onset of HIVDR using the EWI survey.

2. METHODS

A cross-sectional analysis of retrospectively collected data from 74 sites providing ART services was conducted. Two of these were only providing ART services to adult patients while 72 provided ART to both adult and paediatric patients. From the five WHO 2012 revised HIV DR EWI, Zimbabwe MOHCC chose the first four indicators based on relevance to anticipated program interventions and availability of data, *i.e.*, On time pill pick up, Retention in care, Pharmacy stock-outs and Dispensing practices. Definitions for these selected EWIs and their respective recommended targets are summarized in Table 1. EWI definitions were based on the latest (2012) WHO EWI guidance.^[11] According to the WHO recommendations, performance was rated using a scorecard with four colours: green (excellent performance), amber (fair performance), red (poor performance) and grey (data not abstracted)^[12] (see Table 1).

For EWI3, data was abstracted on stock outs of each ARV drug in routine use for the 12 calendar months in 2012. If any ARV drug was missing from a site in any month during the year the site was deemed to have stock-out for that month. In Zimbabwe implementation of the fifth EWI on viral load is not feasible because viral load testing is not widely available in the public health sector. Thus viral load data for patients enrolled at the sites is not available for analysis. As a result it was excluded from the Zimbabwe EWI survey.

2.1 Site selection

Seventy-four ART sites (72 public and 2 private sector ART sites) from all administrative districts of Zimbabwe were purposefully selected for the 2012 EWI abstraction in 2013. Site inclusion criteria were: 1) site had been offering ART for more than 12 months, 2) site had the ability to initiate more than 30 patients on ART within a month, and 3) site had been submitting National monthly progress reports to

the MOHCC. The two private ART sites were selected given their use of the national monitoring and evaluation tools in addition to the inclusion criteria. Two extensive training sessions were held where at least two health workers from each site were trained on data abstraction process over three days. Individual site staff then conducted data abstraction in February 2013.

Table 1. Selected 2012 WHO Early Warning Indicator definitions and targets

Early Warning Indicator	Definition	Definition (Numerator/Denominator)	Targets
On time pill pick up	Percentage of patients (adults or paediatric) that pick-up ART no more than two days late at the first pick-up after the baseline	Numerator: Number of patients picking up their ART “on time”* at the first drug pick-up after baseline pick-up date Denominator: number of patients who picked up ARV drugs on or after the designated EWI start date	Red: < 80% Amber: 80%-90% Green: > 90% Paediatric targets same as adults
Retention in care	Percentage of adults and children known to be alive and on treatment 12 months after ART initiation.	Numerator: Number of adults and children who are still alive and on ART 12 months after initiating treatment Denominator: Total number of adults and children who initiated ART who were expected to achieve 12-month outcomes within the reporting period, including those who have died since starting therapy, those who have stopped therapy, and those recorded as lost to follow-up at month 12	Red: < 75% Amber: 75%-85% Green: > 85% Paediatric targets same as adults
Pharmacy stock-outs	Percentage of months in a designated year in which there were no ARV drug stock-outs	Numerator: Number of months in the designated year in which there were no stock-out days of any ARV drug routinely used at the site Denominator: 12 months	Green: 100% Red: < 100% Paediatric targets same as adults
Dispensing practices	Percentage of adults and children prescribed of picking up mono or dual ARV therapy	Numerator: Number of patients who pick-up from the pharmacy, a regimen consisting of one or two ARVs Denominator: number of patients picking up ARVs on or after the designated EWI sample start date.	Green: 0% Red: > 0% Paediatric targets same as adults

*“on-time” as it relates to pill pick-up is defined as a patient picking up their ART within 2 days of their previous prescription running out if taken according to schedule.

Sampling was based on calculating a minimum sample size for each indicator per site and 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 the EWI sample start date of January 1, 2012 (patient retention in care), and 2) Patients consecutively picking up ART on or after the EWI sample start date of January 1, 2012, regardless of duration of regimen (On-time ARV drug pick-up). Eligible patients were enrolled until the required sample size for that site was reached.

2.2 Sample size calculation and data abstraction

Sample size calculations were performed to provide a 95% CI of $\pm 7\%$, assuming a true HIV prevalence of 50%. This provided the most conservative estimate of the sample size required for each site. The sample size for each site was based on the total number of patients at the site meeting the eligibility definition of patients to be represented for each EWI according to WHO guidance.^[13] For Retention in care, a census of all patients initiating ART in the 12 months of

2012 was taken (consistent with GARPR/PEPFAR).^[8] Stock cards from January 1 to December 31, 2012, were used to collect information on continued drug supply for each ARV drug in routine use at each site.

Data were abstracted for paediatric (0-14 years) and adult (≥ 15 years) patients until the sample sizes were achieved for each site. The collection was done using the WHO’s Microsoft Excel-based electronic data abstraction tool.^[12] The WHO electronic tool calculates all indicators automatically as data are entered utilizing colour coding to flag errors in analysis. The tool provides automatic calculations and provides an indicator value. This colour flagging forms the first part of the data quality assessment at the site level.

2.3 Patient eligibility criteria

Criteria for EWI 1 & 4 were any patient who picked up drugs from the pharmacy register during the reporting period. Criteria for EWI 2 were any patient who was initiated on ART in January 2012.

2.4 Calculation of performance

All analyses were performed using the WHO-recommended EWI scorecard. (see Table 1) The scorecards utilize four classifications: red (poor performance, below the desired level), amber (fair performance, not yet at the desired level), and green (excellent performance, achieving the desired level). Grey classification was used for sites that did not submit data on the indicator. The assumption for this grey colour was that indicator was not monitored at the site.

2.5 Data quality assessment

Data quality assessments were implemented throughout the EWI process. Reliability of the data was assessed by confirming the accuracy of 10% of the data that was electronically submitted by sites. Information from pharmacy register were considered the gold standard for pharmacy pick-up dates and ART regimens dispensed, while the national opportunistic infection (OI)/ART and Patient Care Booklets were considered the gold standard for information about patient status data (e.g. transfer in and transfer out, dates of death, and dates of stopping ART). Pharmacy data for patients who had incomplete pill pick-ups were validated and corrected by

comparing records in ART register and Patient Care Booklets, looking for dates of transfer out, death or ART stoppage.

2.6 Ethical considerations

Ethical review and approval of the protocol were received from the Medical Research Council of Zimbabwe (MRCZ) (Approval number: MRCZ/A/1638) for the period September 2013 to September 2014. Permission to conduct field work was obtained from Provincial Medical Directors, Directors City Health and District Medical Officers of the participating Provinces, City Health Departments, and District respectively. Only de-identified data were abstracted from the medical records used for public health surveillance purposes. Personal patient information was not collected from records.

3. RESULTS

There were a total of 74 adult ART sites in this study. Of these 74, only two did not provide paediatric ART services thus the remainder (72) provided ART services to both adult and paediatric patients. Table 2 summarizes results of the overall EWI survey.

Table 2. Early warning indicators summary

Early Warning Indicator (EWI) (time frame)	EWI target for all sites	Number adult of sites meeting EWI target (% of sites meeting target)	Number paediatric of sites meeting EWI target (% of sites meeting target)	Adult estimates % (95%CI)	Paediatric estimates % (95%CI)
On-time pill pick-up (1 Jan 2002-)	Green: > 90%	16/74 (21.6%)	3 (4.2%)		
	Amber: 80%-90%	10/74 (13.5%)	7 (9.7%)	76.2%	55.0%
	Red: < 80%	48/74 (64.9%)	58 (80.6%)	(67.6-84.8)	(44.8-65.2)
	Not collected	0 (0.0)	2 (2.8%)		
Retention in care (1 Jan-31 Dec 2012)	Green: > 85%	36/74 (48.7%)			
	Amber: 75%-85%	19/74 (25.7%)		6806/8078 (84.3%)	
	Red: < 75%	17/74 (23.0%)		(80.1-89.8)	
	Not collected	1 /74 (1.4%)			
Pharmacy stock-outs (1 Jan-31 Dec 2012)	Green: 100%	14 (18.9%)	23 (31.9%)		
	Red: 0%	60 (81.1%)	46 (63.9%)	N/A	N/A
	Not collected	0 (0.0)	3 (4.2%)		
Dispensing practices (1 Jan 2012-)	Green: 0%	64 (86.5%)	61 (84.7%)		
	Red: > 0%	10 (13.5%)	7 (9.7%)	0.1%	0%
	Not collected	0 (0.0)	4 (5.6%)	(0.0-0.2)	

3.1 On-time pill pick-up

“Excellent” performance (> 90% pill pick-up on time) was achieved in 21.6% of sites for adults, while 13.5% of sites had “fair” performance (80%-90% pill pick-up on time), and 64.9% of sites had “poor” performance (< 80% pill pick-up on time). The performance for all adult sites ranged from 29.2% to 100.0%. Among sites attending to children, 4.2%

achieved “excellent” performance while 80.6% had “poor” performance. The performance of sites providing paediatric ART ranged from 0% to 94% (see Table 2).

3.2 Retention in care

Less than half (48.7%) of all sites achieved “excellent” performance by retaining more than 85% of patients in care

after 12 months. Another quarter (25.7%) had “fair” performance by retaining between 75% and 85% of their patients in care. “Poor” performance (< 75% retention in care) was noted among 23% of participating sites (see Table 2).

3.3 Pharmacy stock-outs

There were no ARV drug stock-outs of adult formulations in 18.9% of sites. Data for paediatric formulation drug stock status were available for 95.2% of sites. Among these, 31.9% of sites did not experience stock-outs (see Table 2).

3.4 Dispensing practices

Among adult ART sites, 13.5% dispensed mono- or dual therapy to at least one patient. In sites providing paediatric ART, 9.7% dispensed mono- or dual therapy to children on ART. An estimated 0.1% (95% CI: 0.0 - 0.2) for adults and 0.0% for children were dispensed mono- or dual- therapy in all (see Table 2).

Data validation showed that some sites were not documenting the full OI/ART numbers of patients, and thus it was difficult to trace patients using the pharmacy registers. Data quality assessment showed that 12 sites offering adult ART and 12 Paediatric ART sites had data that varied by more than 10% of the province and the site.

4. DISCUSSION

The site performance was generally low with less than 50% of sites reaching the recommended WHO targets for on time pill pick-up, retention in care and pharmacy stock-outs. The poor performance noted may be an indication of challenges that could potential lead to the emergence of HIV drug resistance in Zimbabwe.

“On time pill pick up”, is a patient adherence measures (PAM) associated with HIVDR and eventually mortality. Low pill pick-up rate may mean missed doses thus treatment interruption among patients who miss their review dates. This low pick up may be real or perceived as it was noted that there was a lack of proper record keeping (registers) among the selected sites in Zimbabwe. This may explain the better performance by Namibia, which used electronic data. Despite this, Zimbabwe had better on time pill pick up than other African countries (Cameroon, Namibia, and South Africa) as noted by a review of the literature.^[14–16] Thus, this indicator is vital in measuring patient adherence associated with the development of HIVDR and virologic failure.^[17–19]

During data validation, it was discovered that when a patient is dispensed ARVs they may have left-over medicines. Review dates given to patients did not take into account these left-over medicines. Thus as these medicines accumulate

they may reach enough quantities to last a month. As a result, patients would come at a date later than the review date. Thus, despite missing their review dates patients may not have necessarily missed doses. Thus, pharmacy personnel and nursing staff need to consider patient pills possession during subsequent dispensing. Subsequent data quality reviews should also take this into account.

In addition, some of these facility-held patient files could not be identified for verification during the study. For example, pharmacy staff was only recording the serial part of the patient OI/ART number (e.g. 00001 instead of 0104A-2011A00001), and thus a single number represented more than one patient. These challenges in data resulted in the confidence intervals falling outside of the stipulated +/-7%.

Failure to reach the minimum standards of patient retention in care by the majority of sites is consistent with EWI reports previously published by WHO.^[20] Available data in Zimbabwe suggest that significant proportions of participants were erroneously misclassified as not retained due to lack of proper documentation of decentralized patients’ records. Studies in Malawi found the loss to follow-up to be the major factor affecting retention in care.^[21] In Ethiopia community-based organizations have provided the vital link in improving patient retention in care within HIV care settings from 77% in 2004 to 92% in 2012 with minimum resources.^[22] This may also assist in improving the performance of this indicator in Zimbabwe. Being part of a support group enables a patient to have a treatment supporting partner who would then help enhance adherence to treatment.

Pharmacy stock status similarly affects adherence to medication where stock-outs result in patients missing doses. In most sites, there was clear stock out of medicines. This was attributed to the absence of provincial stores for ARVs. The presence of provincial stock cushions district sites from stock-outs as the ordering and supply turnaround time is reduced. Because the supply of ARVs is currently centralised and making use of a central delivery team turnaround time of deliveries is very long. In Malawi, this centralised distribution system has been shown to perform poorly.^[23]

On the other hand, the definition of stock-outs in Zimbabwe is strictly limited to the absence of drugs in the storerooms. A few sites still had remaining drugs in the dispensary but, by definition, an absence of medicines in the storeroom and documented stock-out on the stock card was classified as having stock-out. So patients may still be receiving their medication regardless of the site being classified as having ARV medicine stock-outs. Another problem in Zimbabwe is the lack of proper pharmacy inventory management. This makes monitoring of this indicator difficult. For example,

more than one patient may have the same OI/ART number recorded as pharmacy staff may not have recorded the full OI/ART number. Namibia also had inaccurate stock records in their 2010 EWI survey, resulting in poor performance on this indicator.^[18]

Some patients from a few sites were dispensed mono- or dual-therapy in Zimbabwe in 2012. According to patient care booklets, these patients were prescribed the correct ARVs drugs but pharmacy personnel did not provide all prescribed ARV drugs. Reasons for this were not documented in the registers. Namibia performed better than Zimbabwe on this indicator with more than 90% of sites achieving zero percent mono- or dual therapy dispensed for both adult and paediatric formulations.^[18] African countries reporting the percentage of sites meeting the WHO target ranged from 74% (Bennett *et al.*) to 100% (Fokam *et al.*).^[19,24]

Study limitations include the purposive nature of site selection. Thus, these results may not be representative of Zimbabwe due to site selection bias with larger ART sites being over-represented. In addition, some facilities did not have properly maintained pharmacy registers where the unique patient OI/ART numbers were incomplete. Thus, data verification from OI clinics proved difficult in these sites. As a result, it is difficult to determine if the sites selected for this study were in fact not performing well on the indicators affected by poor data capturing. Although this data shows the performance of health facilities towards preventing the development of HIV drug resistance, they do not necessarily link this to patient behaviours. It would be prudent to compare patient level data to the performance of facilities on EWIs.

EWI monitoring has helped to highlight deficiencies in the ART program patient tracking system. Reported weaknesses in current data systems include incomplete records, missing data, use of non-standardized records, and intra- and inter-clinic variability in data documentation. Zimbabwe may be at a high risk of developing HIVDR due to the low pill pick up rate, low patient retention in care and drug stock-outs. This indicates the continued need for tracking resistance patterns among patients on ART. These results are important in countries employing the public health approach to HIV management with standardized ART regimens in sub-Saharan Africa such as South Africa, Malawi, and Zambia. Learning from weaknesses noted in the implementation of these EWIs in Zimbabwe will enable these countries to improve their own HIV management systems and avoid similar errors. Comparison of the implementation of EWIs in Zimbabwe, which has a paper based system, to Namibia, which used an electronic system, shows the benefits of moving with technol-

ogy. The fact that health care workers correctly prescribed ARV medicines needs to be emulated in other countries as this works towards preventing HIV drug resistance.

Recommendation

There is need by pharmacy and nursing staff to consider patient pills possession during subsequent dispensing. Subsequent data quality reviews should also take this into account. The full unique OI/ART number should also be recorded in pharmacy registers to enable tracking of these patients within pharmacies.

Patients should be linked to community support group in an effort to improve patient tracking and retention in care. Once a patient is retained in care, the chances of taking tablets improve. Being part of a support groups enables the patient to have a treatment supporting partner thus enhancing their adherence to treatment. At the same time, record keeping should be improved to account for patients in care, *e.g.*, using patient appointment registers.

Site buffer stocks for ARVs should be increased as the current 2 months buffer is not enough to cover sites while waiting for the next supply. Decentralized ARV storage to provincial store rooms would improve district access. Sites without adequate storage space need support through the erection of new storerooms to enable proper inventory management. Training pharmacy staff on the need to properly document patient mono- or dual therapy could drastically improve data in the registers. The availability of these medicines on site also ensures that a patient gets their resupply each time they come for their reviews.

The introduction of the electronic patient monitoring system will go a long way in alleviating some of the challenges noted in documentation in both pharmacy and clinics which were characterized by missing data. Using this system it would also benefit the HIV program to assess patient level data to assess the relationship between patient characteristics with performance on the EWIs.

In spite of the challenges being faced in accessing viral load testing, Zimbabwe needs to prioritize purchase of these machines. This will enable sites to monitor and identify patients with possible HIV drug resistance earlier.

DISCLAIMER

The findings and conclusions in this report are those of the author(s) and do not necessarily represent Guidance on Disclaimers for CDC Scientific Publications the official position of (the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry).

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