

RESEARCH ARTICLE

Antiretroviral adverse drug reactions pharmacovigilance in Harare City, Zimbabwe, 2017

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Abstract

Introduction

Key to pharmacovigilance is spontaneously reporting all Adverse Drug Reactions (ADR) during post-market surveillance. This facilitates the identification and evaluation of previously unreported ADR's, acknowledging the trade-off between benefits and potential harm of medications. Only 41% Antiretroviral (ARV) ADR's documented in Harare city clinical records for January to December 2016 were reported to Medicines Control Authority of Zimbabwe (MCAZ). We investigated reasons contributing to underreporting of ARV ADR's in Harare city.

Methods

A descriptive cross-sectional study and the Centers for Disease Control (CDC) guided surveillance evaluation was conducted. Two hospitals were purposively included. Seventeen health facilities and 52 health workers were randomly selected. Interviewer-administered questionnaires, key informant interviews and WHO pharmacovigilance checklists were used to collect data. Likert scales were applied to draw inferences and Epi info 7 used to generate frequencies and proportions.

Results

Of the 52 participants, 32 (61.5%) distinguished the ARV ADR defining criteria. Twenty-nine (55.8%) knew system's purpose whilst 28 (53.8%) knew the reporting process. Knowledge scored average on the 5-point-Likert scale. Thirty-eight (73.1%) participants identified ARV ADR's following client complaints and nine (1.3%) enquired clients' medication response. Forty-six (88.5%) cited non-feedback from MCAZ for underreporting. Inadequate ARV ADR identification skills were cited by 21 (40.4%) participants. Reporting forms were available in five (26.3%) facilities and reports were generated from hospitals only. Forty-two (90.6%) clinicians made therapeutic decisions from ARV ADR's. Averaged usefulness score was 4, on the 5-point-Likert scale. All 642 generated signals were committed to Vigiflow by MCAZ,

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reflecting a case detection rate of 4/ 100 000. Data quality was 0.75–1.0 (WHO) and all reports were causally assessed.

Conclusion

The pharmacovigilance system was useful, simple, and acceptable despite being unstable, not representative and not sensitive. It was threatened by suboptimal health worker knowledge, weak detection strategies and referral policy preventing ARV ADR identification by person place and time. Revisiting local policy, advocacy, communication and health worker orientation might improve pharmacovigilance performance in Harare city.

Introduction

Pharmacovigilance (PV) is the practice of monitoring the effects of medical drugs after they have been licensed for use, in order to identify and evaluate previously unreported adverse drug events (ADE) and reactions (ADR) [1]. This is in recognition of the trade-off between the benefits and the potential harm of all medications [2]. Though the stewardship and procedures for reporting ADRs encompass all medications, it is of particular importance in chronic medication such as antiretroviral (ARV) treatment for HIV.

A typical framework for a pharmacovigilance system at the national level includes a primary national regulatory body and several regional centres/ national centres [3]

The countries in which most of the PV systems are well-established can be classified as “advanced” (Australia, Canada, European Union, Japan, New Zealand, United Kingdom, United States) [3]. These countries generally have very detailed regulations about the pharmaceutical industry’s obligations, for both drugs in development and marketed drugs [3]. Most developing countries, including Zimbabwe, have PV systems that are classified as “rudimentary” with only basic, not a well-established legislative framework in place [3].

Rapidly increasing antiretroviral therapy (ART) access globally, has transformed HIV infection into a chronic, manageable condition with prolonged survival times [4]. Consistent with typical chronic therapy, drug-related toxicities remain a major challenge in resource-constrained settings due to a limited formulary for mitigation and inadequately trained personnel [5]. Treatment-limiting drug toxicities add a layer of complexity in the management of HIV infection by impairing patient adherence to treatment, leading to inferior clinical outcomes and higher costs to the public health system [6].

The Medicines Control Authority of Zimbabwe (MCAZ) which houses the National Pharmacovigilance Centre, derives its mandate from the Medicines and Allied Substances Control Act (MASCA), Chapter 15:03, enacted in 1997 [7]. This legislation provides the impetus for MCAZ’s stewardship role in regard to medicines licensure and regulation in the country. The main thrust being ensuring improved patient care and safety during medical and paramedical interventions, thereby improving public health and safety in relation to the use of medicines. In addition, the system promotes understanding, education and clinical training in pharmacovigilance and its effective communication to the public [8].

The operations of the Centre are guided by WHO guidelines for setting up and running a national pharmacovigilance Centre. In this regard, the Zimbabwe National Pharmacovigilance Policy and Guidelines serve as a handbook for pharmacovigilance activities in the country [9].

The bedrock of pharmacovigilance systems, that aim to improve medicinal products safety, is prompt, spontaneous reporting of adverse drug reactions (ADRs) as a key step to their

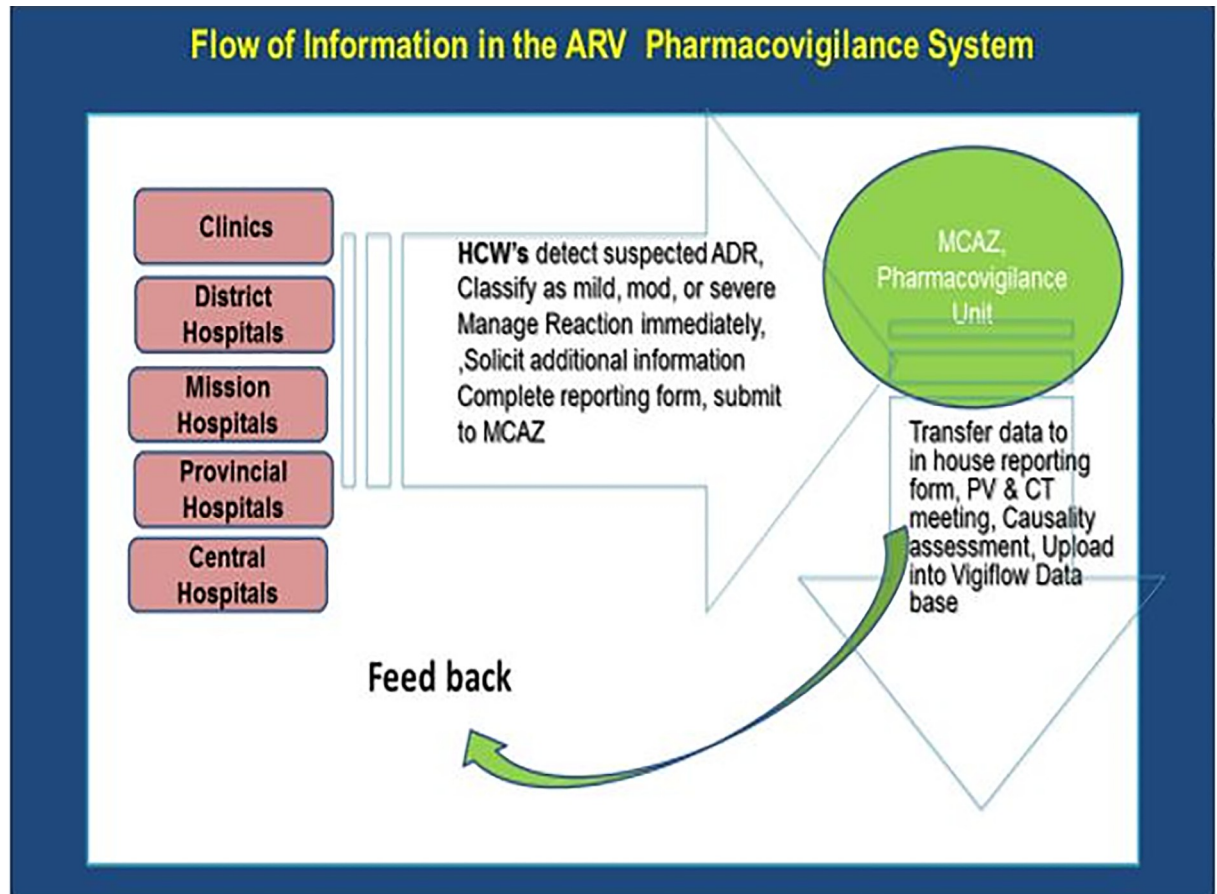


Fig 1. The ARV ADR surveillance flow diagram.

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mitigation as well as updating the drug information database [10–12]. It is, therefore, a mandatory requirement for health care providers to timeously report all suspected and confirmed ADRs. This is particularly imperative in Zimbabwe, where the test-and-treat strategy for HIV infected individuals was implemented, in June 2016, resulting in the number of people on HIV treatment rapidly increasing [9].

When an ADR case is suspected or confirmed, an in-house reference number is assigned at the facility which identifies it. The data collected and entered into the standard reporting form should be checked for completeness. Additional information and clarifications should be solicited from the reporter before the report is filed. The completed form is submitted to MCAZ within 14 days. Meanwhile, corrective clinical interventions are implemented (Fig 1).

At MCAZ, received reports are transferred to the MCAZ reporting form to be tabulated for causality assessment at the next seating of the Pharmacovigilance and Clinical Trials (PVCT) meeting. The Causality Assessment process involves analysis of the reaction against a set of key aspects that include the strength of the association, consistency of the observed evidence, temporality, dose-response and identification of possible confounders [13]. The recommendations derived from this meeting are then implemented, which may be a request for further information where clarity is desired and informing healthcare facilities of findings. The data is also uploaded into Vigiflow database (WHO database of reported ADR's), including Causality Assessment outcome and case summary reports.

As part of routine monitoring [7], we compared ARV ADR data from Harare City reported through the MCAZ with the documented clinical patient records for 2016 and demonstrated a 41% discrepancy between these two reporting systems, with more cases appearing in clinical records. This indicated poor reporting practices that impede accurate quantification of the prevalence of ARV ADR'S. Failure to detect and report adverse drug reactions compromises patient safety and results in missed opportunities to update drug safety profiles. It is within this background that we evaluated the ARV ADR surveillance system in Harare City in order to identify the reasons for underreporting and recommend solutions.

Materials and methods

We conducted a mixed methods cross-sectional study and surveillance system evaluation using updated CDC guidelines for surveillance system evaluation [13].

Health Personnel involved in the ARV-ADR surveillance were eligible to participate in the evaluation. These included doctors, pharmacists, nurses and pharmacy technicians. Harare City's two hospitals were purposively selected for the study and seventeen out of 38 clinics were randomly selected. At the hospitals, all available health workers (nurses, pharmacists and doctors) working in ART clinics were recruited as study participants

From the clinics, nurses who were found on duty on the day of data collection were selected for the study. A review of patient records for ARV ADR's for the period under study (January to December 2016) was conducted for the 17 clinics and 2 hospitals with comparison with MCAZ reports for the same period.

The calculated sample size for this study, adjusted for 10% non-response rate, a sample size of 52 was reached.

A pre-tested interviewer-administered questionnaire was used to interview the health workers to determine their knowledge of the operations and usefulness of the surveillance system. The variables used to assess health worker knowledge included: the ability to accurately enumerate the key elements of an ARV ADR, (an unintended noxious response therapeutic dosage); sequentially relating the entire ADR reporting process; and, the purpose and the role of MCAZ in ADR surveillance.

The quality of the data generated was scored in relation to completeness, consistent with WHO evaluation criteria [9]. The incident detection strategies evaluated included the practised protocol to identify ADR's during health worker-patient engagement which includes the questions asked by the health worker and examinations conducted, where indicated.

A checklist, derived from the WHO assessment criteria for a PV system's stability status was applied which evaluates the availability of reporting forms, case definitions and means for communication, among other variables [9]. Records of all patients who were attended at the health facilities were reviewed to check on the number of ARV ADR cases documented and the number captured by the surveillance system and how many were missed. All notification forms from the clinics and 2 hospitals for January to December 2016 were reviewed. Simplicity, data quality, completeness, acceptability, sensitivity, timeliness and representativeness of the system were evaluated. Epi InfoTM was used to compute frequencies, means, and proportions.

The checklist for PV indicators was evaluated according to WHO score values. These include core indicators (CP) which are a prerequisite to meet minimum standards of a functional PV system; Outcome indicators (CO) that assess results obtained from Causality Assessments; and Complimentary indicators (P) additional elements that indicate higher level compliance. These are abbreviated as follows CP: WHO Core Pharmacovigilance Indicator; CO: Core Outcome Indicator; P1: Complementary Process Indicators, ICSR: Individual Case

Table 1. ADR surveillance sensitivity, Harare City, 2017.

Pharmacovigilance Indicator	Key attribute Assessed	Response and Value
CP1	Total number of ADR reports received in 2015	ICSRs (AEFIs, TSR, SAEs) received by the MCAZ = 642
CP1a	Total number of ADR reports received in the previous year per 100 000 people in the population	5/1000000
CP2	Number of reports (total @31/12/16 in the national database	AEFIs = 331, TSR = 1563, SAEs = 361
CP3	Percentage of total annual reports acknowledged/issued feedback?	100%
CP4	Percentage of total reports subjected to causality assessment in the past year?	100%
CP5	Percentage of above committed to the WHO database?	86% of TSR reports received since Sept 2012 committed to VigiFlow
C01	Signals generated in the past 5 years by the pharmacovigilance centre?	+1900 ADR's (Gynecomastia, Drug-induced liver injury, Steven johnson syndrome, Lipodystrophy and Renal toxicity)
CO2	Regulatory actions were taken in the preceding year	7 products were recalled
P1	Percentage of health-care facilities that had a functional pharmacovigilance unit (i.e. submits \geq 10 reports annually to the pharmacovigilance centre)?	Sept 2012 to Dec 2016 = 119 health facilities (8.2%) 2015 = 32 health facilities submitted ADR reports (2.2%).

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Safety Report, AEFI: Adverse Event Following Immunization, TSR: Targeted Spontaneous Reporting System for Adverse Reactions, SAE: Serious Adverse Events (**Table 1**). Permission to carry out the study was obtained from the Institutional Ethical clearance boards for the Medicines Control Authority of Zimbabwe (MCAZ), Harare city and Ministry of Health and Child Care. Written informed consent was obtained from key informants.

Results

Demographic characteristics

The study successfully recruited 52 Health workers as study participants, yielding 100% response rate. Of the 52 participants recruited, 73% (n = 38) were females. The majority (75%) of the participants were Registered General Nurses (RGNs). The median years of service of all participants were 9 years (Q₁ = 7, Q₃ = 12). (**Table 2**).

Health worker knowledge of ARV ADR surveillance

Varied proportions of respondents gave accurate responses to each variable assessed on health worker knowledge. The total score was then rated using a 5-point Likert scale which ranged from very poor, poor, fair, and good to very good. Overall, knowledge was rated as fair (data not shown).

Table 2. Demographic characteristics of study participants, Harare City, Zimbabwe, 2017.

Characteristics	Frequency n = 52	Percent (%)
Gender		
Male	38	73
Female	14	27
Designation		
Medical Doctors	4	7
Registered General Nurses (RGN)	39	75
Primary Technicians	3	6
Primary Counsellors (PC)	6	12
Median (IQR) years in Service	9 (Q ₁ = 7, Q ₃ = 12)	

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System attributes

Data quality. Data quality obtained a score range of .75–1.0, according to WHO derived from country records that were committed to WHO Vigiflow. Observed completeness of available forms from the sites was consistent with the national score.

Simplicity. Out of the 52 participants, only 12 (29.4%) had ever completed an ADR form. Reported average time taken to complete AR forms, by those who had done so before was 14 minutes. However whilst being timed, participants took an average of 7–9 minutes 7/12 (19.6%) participants reported that the forms were easy to complete, and 10 out of 12 accurately outlined the entire reporting process for ADR's. Forty-three (82.7%) stated that they needed formal training to be able to fill the notification forms (excluding Medical Doctors). All ARV ADR cases were referred to Wilkins and Beatrice road hospitals where reports are generated and submitted.

Acceptability. Ninety per cent of the participants felt that it was their duty to complete the ADR forms and 92.3% participants were willing to continue participating in the ADR surveillance. Thus based on the subjective assessment gathered from the interview, on average, ADR surveillance is 91.4% acceptable to health workers in Harare City.

Stability. Twenty-one (40.4%) of the participants reported that they had ARV ADR case definitions in their Health facilities. However only two out of 19 (10.5%) health facilities had the ADR case definition displayed. Five (26.3%) health facilities had ADR forms available in their workstations. Thirteen (25%) of the participants knew about the 2016 invented online reporting facility, but none had ever used it due to computer, Internet and knowledge challenges. One health facility (Wilkins hospital) had accessible, facility-level ARV ADR record. All facilities had a working phone for communication.

Usefulness- perceptions of ADR surveillance system, Harare City, 2017. Overall 69.2% of the participants used ARV ADR data in patient management whilst 13.5% said they held review meetings for ADR's. There was no evidence of minutes to the referred meetings. Clinicians made therapeutic decisions using ARV ADR data, such as switching to next line regimen. Applying the 5 points Likert scale on the resultant usefulness score, ARV ADR pharmacovigilance was somewhat useful with an average score of 64.5%. (Table 3).

Representativeness. The system was not representative. The City Council imposed protocol of referring ARV ADR's to their two hospitals results in an overestimation of reports generated by the hospitals, at the same time underestimating the prevalence of ARV ADR's within the community health facilities by person place and time. Many ARV ADR's are not being reported for fear of writing reports as required by the City health department.

Timeliness of the ARV ADR surveillance system in Harare City, 2017. Severe and Moderate reactions were all (100%) reported to the authority on time (within 48 hours), entirely from the two hospitals. Mild and Incidental reactions were all (100%) treated according to facility protocol before completion and submission of the forms within 14 days.

Table 3. Usefulness of the ARV pharmacovigilance system, Harare, 2017.

Variable	Doctors (%)	Nurses (%)	Pharmacy Technicians (%)	Primary Counsellors (%)
Data used in patient management (yes)	4 (100)	28 (71.8)	1 (33.3)	3 (50)
ADR meetings held (yes)	0	5 (12.8)	0	2 (33.3)
Decisions based on ADR(yes)	4 (100)	38 (97.4)	3 (100)	4 (66.7)
Thought ADR is Useful	4 (100)	39 (100)	3 (100)	4 (66.7)
Overall Usefulness	75%	70.5%	58.3%	54.2%

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Reasons for underreporting of ARV ADR's, Harare City, 2017. Whereas MCAZ is mandated to feedback on outcomes of all reported ADR's, 46(88.5%) of the participants stated that they had received no response to their submissions and cited this as a reason for under-reporting of ARV ADR's. Unavailability of reporting forms was cited, 44, (84.6%), whilst 33 (63.5%) thought weak incident detection strategies was the reason for under-reporting ([Table 4](#)).

ARV ADR detection strategies in place, Harare City, 2017. Thirty-eight (73.1%) participants indicated that they detected ARV ADR's following client complaints, whilst 21(40.4%) identified ARV ADR's during clients routine review visits and examinations. Nine (17.3%) enquired clients how they were responding to treatment, whereas 34(65.1%) only identified ARV ADR's following clients' failure to tolerate treatment and have defaulted.

The sensitivity of the ARV ADR surveillance system in Harare City, 2017. Individual Case Safety Reports (ICSRs) received by MCAZ amounted to 642, reflecting a case detection rate of 5/ 100 000, calculated using the national population of 14 million in 2015. All received reports were tabled at PV and clinical trials committee meetings and feedback submitted to the city health authorities. We observed that 86% of the Targeted Spontaneous Reports (TSR) received since 2012 and authenticated by MCAZ were committed to the WHO Vigibase, termed Vigiflow as at 31 December 2016.

Notably, 10 cases of product defects were reported in 2016, seven of which were subsequently recalled by the authority. More than 1900 adverse drug reaction cases were spontaneously reported and the most common ones included gynecomastia, drug-induced liver injury, Steven Johnson syndrome, lipodystrophy and renal toxicity. The number reported (+1900) indicate the frequency of reports from the listed types of ADR's

We further observed that 119 health facilities, countrywide, actively reported ADR's (Sept 2012 to Dec 2015), yet only 32 of these facilities submitted ADR reports in 2016. This indicator is qualified by the submission of ≥ 10 reports annually to the pharmacovigilance centre. The pharmacovigilance unit met the minimum requirements of a regulatory authority, according to WHO standards. ([Table 1](#)).

Discussion

The data generated from the few reporting sites was of good quality in regard to completeness. A score of 0.75–1.0 for a country with a pharmacovigilance system that is still under development is remarkable. This is contrary to findings by Nderitu et al (2011) in Kenya who found incomplete records as a major hindrance to causality assessments in a developing pharmacovigilance system [4].

Health workers are supposed to be knowledgeable about the surveillance system so that they are able to identify and investigate suspected cases during their routine conduct of duty. Knowledge of ARV pharmacovigilance surveillance in regard to qualifying ADR's, the

Table 4. Reason for the Low ARV ADR case detection, Harare, 2017.

Reasons for under reporting	Frequency	Percent (%)
Lack of Knowledge by health workers	21	40
Weak incident detection strategies	33	63.5
Unavailability of forms	44	84.6
Health workers overwhelmed by other responsibilities	27	51.9
Lack of appreciation of the importance of reporting ADRs	30	57.7
Non response by MCAZ to reported ADRs	46	88.5

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reporting process and the role of MCAZ was low in Harare City. This was despite their recognition that reporting ADR's is within their scope of practice and accepting the responsibility.

It was noted that the majority of the health workers were not trained (formally or on-the-job) on ARV, ADR surveillance although pharmacovigilance is a component of ART management, for which all health workers are oriented on. Poor knowledge contributed to the poor performance of the system.

The City Council imposed protocol of referring all suspected ADR's to the hospitals instead of reporting directly to MCAZ resulted in it being impossible to assess the incidence and prevalence of ARV ADR's by person place and time. All reports were being generated from Wilkins and Beatrice road hospitals.

The ARV ADR's surveillance system in Harare city is simple. The few who filled the forms encountered no challenges. When MCAZ received suspected ADR reports, a pharmacovigilance and clinical trials committee sat to discuss and recommend causality assessment, particularly for peculiar reactions. All reports were responded to through the city health directorate for communication to reporting sites. However, health workers from reporting sites reported not receiving feedback, which demotivated them from continuous reporting. This was consistent with the findings of a study by Hall et al in Mpumalanga, South Africa, 2009 where feedback motivated continuous reporting of ADR's [14]. If health workers lack motivation, no active detection mechanisms may be implemented to ensure identification of all ADR's and their subsequent reporting.

Timeliness of a surveillance system is a key performance measure. However, in pharmacovigilance, reporting ADR's is preceded by immediate mitigation of the effects. Targeted spontaneous reporting (TSR) is the surveillance approach that has prescribed timelines unlike the voluntary spontaneous reporting (SR) that was being evaluated which is supposed to be part of routine practice. MCAZ acknowledged reception of ARV ADR forms within the recommended 14-day window to facilitate causality assessments. This is contrary to findings by Patidar et al in Mumbai, India 2013, who identified challenges with data transmission as an impediment to the timely reception of reports in resource-constrained environments [15].

All the participants stated that it was their duty to fill the notification forms and were willing to continue participating, hence the system was acceptable. However, the majority of the health workers stated that they needed training on case detection and on how to fill the notification forms. Similar findings were reported by Pirmohamed et al in Malawi, where none of the study participants was trained on ARV pharmacovigilance and this was attributed to the high staff turnover between 2007 and 2009 [6].

Zimbabwe is compliant with the WHO minimum requirements of a functional pharmacovigilance system as stipulated by the core and complementary structural pharmacovigilance indicators (2015). The MCAZ, whose mandate is to ensure medicine safety through the institution of regulatory frameworks is compliant to WHO minimum pharmacovigilance indicators for a functional PV centre [14]. A total number of 642 reports were received by 31 December 2016, translating to 4/100 000 people, having considered a population size of 15.6 million for 2015 which is a core pharmacovigilance indicator (CP1). This is remarkable for a developing PV centre. Exercising its regulatory mandate (PV indicator C02), the authority recalled 7 out of the 10 products when defects were reported. This was commendable as it fosters compliance to set regulations.

For a reporting facility to be a functional pharmacovigilance unit, it should submit submits ≥ 10 reports annually to the pharmacovigilance centre according to WHO PV indicator P1. Only 2 centres, Wilkins and Beatrice road Hospitals fit this category in Harare city and there were a total of 119 centres countrywide as at 31 December 2015 since the programme was implemented in 2012. However, in 2016 alone, only 32 health facilities submitted ADR

reports countrywide. This reveals that there are facilities which were initially reported but have backtracked which is a cause for concern. There is, therefore, need to investigate what might have demotivated them from maintaining the set standards as this lowers the national performance.

Active ARV ADR detections entail enquiring from the client how they are responding to the treatment. This was found to be lacking among healthcare staff in Harare city, instead, most participants revealed that they were detecting ADR's from client complaints. Poor ARV ADR's detection in a city results in inaccurate quantification of the prevalence of ADR's in the post-market surveillance period. Reasons highlighted for poor ARV ADR detection were a lack of knowledge and training among health workers, MCAZ introduced an online reporting on 1 September 2016 but the facility remained unutilised due to lack of knowledge of its existence.

The ARV ADR surveillance system was reported to be useful although the majority lack knowledge on the surveillance system. Only one facility, Wilkins hospital had an available local database of all reported ADR'S which provided an opportunity for local utilisation of this data in programming.

The participants cited non-response by MCAZ to submitted reports as a major reason for under-reporting of ARV ADR's. On the other hand, MCAZ indicated 100% response to all submitted reports. Further analysis revealed that although MCAZ responded to all submitted reports, the communication was conveyed through the City health directorate. Unfortunately, this communication was not being disseminated to report generating facilities. Unavailability of reporting forms, lack of appreciation of the importance of reporting ARV ADR's and health workers being overwhelmed with other responsibilities were other reasons attributed to under-reporting. This is contrary to the scope of accepting ADR detection as part of routine clinical practice as indicated by the same participants which also consistent with findings by Nderuti et al, 2013 in Kenya who identified lack of appreciation of the value of ADR reporting in the post-market surveillance period as a hindrance to reporting [4].

Conclusions

We concluded that the ARV ADR pharmacovigilance system was useful, simple, acceptable, sensitive, unstable and not representative. The quality of data generated and committed to Vigiflow was good. The reasons for under-reporting ARV ADR's were a lack of knowledge of health workers, weak incident detection strategies, local protocol and poor information dissemination within the council. Though MCAZ responded to ARV ADR reports from the few reporting health facilities, this feedback was not received by the report generating facilities. MCAZ was fulfilling its mandate of ensuring pharmacologic safety as envisaged by the minimum PV indicator compliance as well as exercising its regulatory authority by licensing and recalling defective medicines

We, therefore, recommended training of all untrained health workers involved in ADR pharmacovigilance. ARV ADR case definitions and notification forms were distributed to health facilities in the city which did not have these. The local authority was engaged, in liaison with MCAZ, for a possible review of the local policy and facilitate reporting of ADR's from detecting health facilities. MCAZ and Harare city directorate pledged to explore effective feedback dissemination mechanisms that will ensure all facilities receive feedback for reported ARV ADR's

Supporting information

S1 File. Pharmacovigilance dataset for Harare City, Zimbabwe, 2018.
(XLSX)

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