Quality Of Selected Anti-retroviral Medicines: Tanzania Mainland Market As A Case Study

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Abstract

Background Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome (HIV/AIDS) is still health problem worldwide, particularly in sub-Saharan African countries, such as Tanzania. Anti-retroviral medicines (ARVs) have significantly reduced morbidity, mortality and improved the quality of life of people living with HIV infection. Thus, good quality ARVs is amongst the key factors which guarantee successful therapeutic outcomes and prevention of development of drug resistant strains. This study was aimed at monitoring the quality of ARVs circulating on the Tanzania Mainland market.

Methodology This was a prospective cross sectional study. ARVs samples were collected in 20 regions of Tanzania Mainland, between 2012 and 2018. All samples were subjected to screening testing using the Global Pharma Health Fund ® Mini-Lab kits. Sampled ARV's that failed screening test or yielded doubtful results and ten percent (10%) of all that complied with the screening test requirements were subjected to confirmatory testing using full pharmacopoeia monographs at the Tanzania Medicines and Medical Devices Authority (TMDA), quality control laboratory prequalified by the World Health Organisation. Samples collected from the medicine distribution outlets were also subjected to product information review.

Results A total of 2,630 samples were collected, of which 83.7% (2200/2630) were from port of entry (POEs). Out of the 430 samples which were subjected to product information review, 25.6% (110/430) failed to comply with the packaging and labelling requirements. All sampled ARV's that were screened and conformed to the specifications, except of the fixed dose combination (FDC) lopinavir/ritonavir 0.27% (7/2630) and lamivudine/zidovudine/nevirapine 0.27% (7/2630) that failed the disintegration test. In confirmatory testing using full pharmacopoeia monographs, all samples conformed to the requirements, except of FDC stavudine/lamivudine/nevirapine which failed disintegration 2% (2/100) and assay tests 1% (1/100) respectively. Samples failing the assay test had low content of stavudine (86.6%) versus specification limits (90% -110%).

Conclusion The quality of majority of ARVs circulating on the Tanzania Mainland market was good. The existence of number of ARVs circulating on Tanzania Mainland market which do not comply with product information requirements was significant. These results call for continuous monitoring of quality of medicines circulating on the Tanzania market.

Background

Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) are still major global health problem particularly in sub-Saharan Africa [1, 2]. Besides being medical problem, HIV/AIDS affects other aspects of life such as economy social and demography [1]. The joint United Nations programme on HIV/AIDS (UNAIDS) estimated that by the end of 2017, 36.9 million [31.1 million–43.9 million] people worldwide were living with HIV/ AIDS [1, 2, 3]. Sub-Saharan Africa is the world's most affected region with an estimation of 25.6 million people living with HIV/AIDS [2]. Globally, HIV/AIDS has remained one of the leading causes of morbidity in the last three decade [4, 5]. The prevalence of HIV/AIDS in Tanzania for people aged between 15–64 years is 5% [1, 4]. Recent data shows that, 1.4 million people are living with HIV/AIDS in Tanzania [1, 4].

According to UNAIDS and World Health Organization (WHO) reports, 21.7 million HIV-infected patients are currently, accessing antiretroviral therapy (ART) worldwide [1–3], with about 1.2 million of them residing in Tanzania [4]. The ART have significantly reduced morbidity and mortality, by preventing relapse and opportunistic infections. Equally, it has vastly improved the quality of life and productivity of HIV-infected patients and has lowered the risk of HIV transmission [6, 7].

ART is mainly responsible for suppressing the viral replication at therapeutic plasma drug level to undetectable levels, allowing satisfactory immune recovery [6–9]. Nonetheless, treatment outcomes in HIV infected patients depends on but not limited to genetic variations in drug metabolizing enzymes, adherence to treatment and quality of medicines, of which may affect therapeutic outcomes.

Scrutiny on the quality of medicines available in Sub Saharan African countries markets has revealed poor quality medicines that are either falsified or substandard [10–23]. This has been documented in a number of countries including Tanzania [10–23]. Poor quality ART poses a major public health threat such as treatment failure, drug toxicity, poor diseases prognosis and emergence of resistant strains, increased co-morbidity and healthcare cost to government and individual [12, 22–24].

The UNAIDS report shows that, in Sub Sahara African countries about 6% of patients receiving first line ART are obliged to switch to second line regimen per year, which are more costly [9]. For this reason, continued monitoring of the quality of ART is of importance as can identify substandard and falsified medicines circulating on the market, thus, preventing them from causing harm to patients.

Therefore, this study was aimed at monitoring the quality of selected ART circulating on the Tanzania Mainland market. The primary objective of this study was to determine the proportion of poor quality ART circulating on the market and secondary was to determine the quality of information on the primary and secondary packaging and availability of patient information leaflet.

Methods

Study design

This was a prospective cross sectional study.

Study settings

This study was conducted in 20 out of 26 regions of Tanzania mainland namely; Morogoro, Tanga, Dar es Salaam, Dodoma, Coast, Simiyu, Njombe, Arusha, Shinyanga, Kagera, Singida, Rukwa, Iringa, Geita, Kilimanjaro, Mara, Mbeya, Mtwara, Mwanza and Ruvuma. The regions were selected based on the pre-defined criteria including, highly populated regions, regions bordering other countries, regions with high prevalence of HIV infection and those reported to have medicine quality problems.

Study duration

Antiretroviral drugs (ARVs) samples were collected from medicines distribution outlets in 20 regions of Tanzania Mainland, between 2012 and 2015 and port of entry between 2012 and 2018.

ARVs sample size and collection

Convenience sampling method was used in the collection of selected ARVs. Samples were collected from the port of entry (POEs) and medicines distribution outlets such as Medical Stores Department (MSD), public and private hospitals, dispensaries, health centres, retail and wholesale pharmacies and Accredited Drug Distribution Outlets (ADDO) in two distribution levels. Level I covered POEs and MSD and level II covered public and retail healthcare facilities, wholesale and retail pharmacies and ADDOs. Samples were collected by trained drug inspectors according to the prepared sampling plan and Tanzania Medicines and Medical Devices Authority (TMDA) standard operation procedures. Drug inspectors were able to collect two (2) brands per surveyed medicines at each collection site. All samples were collected in their original containers and information details were filled in the sample collection tool. Each collected sample was coded according to the prescribed coding format. Coded samples with their respective sample collection tool were kept in the labelled sampling envelope and sealed. Storage and handling of samples during collection, transportation and before analysis complied with the manufacturer's instructions and TMDA sample chain of custody procedures.

Samples collected from POEs and medicine distribution outlets were subjected to screening test at TMDA zone laboratories and respective quality assurance (QA) centres. Those from medicine distribution outlets were further subjected to product information review (PIR).

Of the sampled ARVs from medicines distribution outlet, 100% of them that did not comply with screening testing requirements or yielded doubtful results and 10% of those that complied with screening test requirements were transported to TMDA-WHO prequalified laboratory at the headquarter office for further analysis.

ARVs selection criteria

ARVs selected in this surveillance were those frequently prescribed for the management of HIV-infection with main focus on first line regimen as per National Guidelines for Management of HIV/AIDS [25] or those reported to have quality problem. These included the following active pharmaceutical ingredient (API): Efavirenz, nevirapine, lamivudine, zidovudine, abacavir sulphate, tenofovir disoproxil fumarate and fixed dose combination (FDC) containing tenofovir disoproxil fumarate /emtricitabine, lamivudine/zidovudine/nevirapine, lamivudine/stavudine/nevirapine, tenofovir/lamivudine/efavirenz, tenofovir/ emtricitabine/efavirenz and lopinavir/ritonavir.

Site sampling techniques

A purposive sampling technique was used for the selection of medicine collection sites, from regions and district levels down to the distribution channels.

Quality evaluation

Product information review

Prior to further laboratory analysis, samples collected from medicine distribution outlets were subjected to PIR. Each sample was evaluated visually on physical appearance of primary and secondary packaging. Availability and information on package information leaflets (PIL) based on the TMDA labelling requirements and approved product information was also assessed.

Parameters checked during PIR included but not limited to appearance or description of the dosage forms, product's brand and generic name, dosage form and strength, name and address of the manufacturer, batch or lot number, date of manufacturing and expiration, TMDA registration

number, packaging and pack size, PIL, language and storage instruction. The information was recorded on a designed form.

Tier I laboratory screening testing

All samples were subjected to screening test using Global Pharma Health Fund® (GPHF) Mini-Lab kits manual. The performed tests were simple visual inspection, disintegration for solid dosage forms and identification test using Thin Layer Chromatography (TLC) method. Oral solutions were also tested for pH appropriateness and microbial limit as described in the United States Pharmacopoeia (USP, NF 32).3

Visual inspection

All sampled solid dosage forms were checked for uniformity of shape, physical damage, altered surface, odor, color uniformity and dirty marks. Liquid dosage forms were examined for clarity, odor and colour uniformity.

Simple disintegration test

A simple disintegration test was performed to assess the possibility of instant-release of oral solid dosage forms. This was done by using a 100mL wide neck glass bottle filled with water heated to 37°C. Tablets were shaken or stirred occasionally. Disintegration was required to occur within 30 minutes. The sample was considered failed if it did not disintegrate within 30 minutes in three (3) consecutive independent tests.

Product identification by thin layer chromatograph

TLC method was used for product identification and qualitative determination of active ingredients, related substances and impurities present in the dosage forms. This method employed the principle of comparing spots test sample and reference solutions according to GPHF Minilab. The principal spot obtained with the test sample was required to correspond with the chromatographic runs of the standard solution in terms of colour, shape, size, intensity and retardation factor (Rf) value. The test sample was considered failed if the Rf value of the test sample was different by more than 10% from that of the standard sample. Also, the sample was considered failed if the intensity of the spot was less than that of a reference containing 80% of the stated amount of the API and if failure was observed in all three independent experiments.

Tier II laboratory confirmatory testing

All samples collected from medicines distribution outlets that had failed screening test, 10% of those which had passed screening test, and those with doubtful results were subjected to confirmatory testing. Confirmatory testing was carried out at the TMDA-WHO prequalified laboratory as per USP pharmacopoeia monograph requirements [26] and/or in house specifications where no official pharmacopoeia monograph existed. Typical parameters tested were physical appearance, identification, disintegration, dissolution, assay, related substances, weight uniformity and microbial limit.

Data management and analysis

The collected data were checked for any inconsistencies. The data was double-entered into a Microsoft Access database, verified and exported to SPSS (version 20) software for analysis. Descriptive statistics were used and results for PIR, screening and conformity were expressed in percentage form.

Results

Antiretroviral samples collected

A total of 2,630 ARVs samples were collected between 2012 and 2018 from POEs and medicine distribution outlets in Tanzania Mainland. Large quantity of samples 83.7% (2,200/2,630) were collected from POEs as depicted in Figure 1.

ARVs samples from POEs were collected in large quantity in the years 2014, 2015, 2016 and 2017, 77% (1,695/2,200) compared to other years, as shown in Figure 2.

Regarding, the number of samples from different medicine distribution outlets, hospitals ranked highest amounting to 61% (262/430) as portrayed in Figure 3. Regional wise, 30% (129/430) were sampled from Dar es Salaam, Mwanza and Iringa and least quantity 1.4% (6/430) was collected from Kagera.

Thirteen generic brands (6 API and 7 fixed dose combinations) contributed to the 430 samples collected from the medicine distribution outlets. The FDC of lamivudine/zidovudine/nevirapine tablets was collected in large quantity 17% (73/430) followed by lamivudine/zidovudine tablets combination 16.3% (70/430) as compared to other ARVs. The proportions are summarized in Table 1 below:

Quality evaluation

Product information review

In this study only samples collected from medicine distribution outlets were subjected to PIR and the results are summarized in Figure 4. Of the examined samples, 25.6% (110/430) did not comply with the packaging information requirements. The highest failure rate was found in the samples collected in the year 2012, 53% (44/83). Interesting observation was found in the year 2013, whereas, all samples passed the PIR assessment. Inappropriate or lack of storage condition, lack of the name and address of the manufacturer, discrepancy of address of the manufacturer on the primary and secondary packaging and lack of package insert were the common deficiencies. On the other hand, all sampled medicines were found to be registered in Tanzania, but some of labels did not indicate the Tanzania registration numbers. The trend is comparable to recent studies conducted on antimalarial and antihypertensive drugs (10,11).

Laboratory tier I screening testing

All ARVs, sampled from POEs conformed to tier I screening test requirements. All sampled ARVs from medicine distribution outlets conformed to visual appearance and identification test requirements. However, 3.3% (14/430) of the samples from the medicines distribution outlets, failed disintegration test; these were FDC of lopinavir/ritonavir tablets (7/430) and lamivudine/zidovudine/nevirapine tablets (7/430).

Laboratory tier II confirmatory testing

Of the 430 ARVs samples collected from medicine distribution outlets and subjected to tier I screening testing, 100 of them were subjected to tier II confirmatory test. These samples included all those failed screening tests, 10% of those which passed screening test and those whose results were doubtful as depicted in Table 2.

Majority of samples 94% (94/100) complied with confirmatory test requirements. However, 3% (3/100) failed confirmatory test and 3% (3/100) samples were beyond expiry dates at the time of analysis, hence, were not analyzed. The failed samples were of FDC of stavudine/lamivudine/nevirapine 3% (3/100) which failed disintegration test 2% (2/100) and assay test 1% (1/100), having low content of stavudine (86.6%) of specified amount (limit 90% -110%). This necessitated more samples from the same manufacturer to be subjected to confirmatory test as described in the USP. The additional samples also failed assay test with results ranging between 86.4 and 87.1%. This confirmed the non conformity of stavudine against the specified requirements. These results are summarized in Figure 5.

Discussion

Quality medicines are essential to promote public health and disease management. However, various studies conducted worldwide have reported availability of poor quality medicines in the market including ARVs, mostly in developing countries such as Tanzania [10–23].

This survey assessed the quality of 2,630 ARVs samples, collected from medicine distribution outlets and POE. A total of twenty (20) regions representing more than 76% of the regions of Tanzania Mainland were selected for the purpose. The selection of the regions to be surveyed included some regions bordering other countries; frequency of inspection by the regulatory bodies; areas previously reported to have medicines quality problems and HIV prevalence patterns as indicated in HIV/AIDS and malaria indicator survey of 2011/12 and HIV impact survey of 2016/17 [24, 25]. In this survey, 30% (129/430) of samples from medicine distribution outlets were collected in three regions namely Mwanza, Dar es Salaam and Iringa matching with high prevalence of HIV infection [4, 27].

It is clear from our results that, majority 83.7% (2200/2630) of the samples were collected from POE showing the dependence of the country on imported medicines. This observation is in agreement with TFDA data of 2017 [28] and well supported with results from this study that among of the collected samples none were produced locally.

A significant increase of ARVs sampled from the POE in the year 2014, 2015, 2016 and 2017 compared to 2012/13 can be associated with the scaling up of ARVs access in low and middle income countries through the WHO and Global Fund initiatives [29]. Improved access to ARVs has accounted to the levelling off of new HIV infections cases, deaths and life longevity amongst HIV-infected patients [1–3, 9].

Despite the inclusion of ADDO and pharmacies among the medicine distribution outlets, no sample was obtained from these sources. This is an interesting finding on compliance to requirements on availability of ARVs in specialized HIV-clinics, hospitals, health centres and dispensaries [29].

Among the collected FDC samples, oral solid dosage forms were the majority (99.8%). FDCs are desirable and recommended by the WHO, as it simplify treatment, ideally resulting in improved medication concordance, clinical outcomes and quality of life of patients [7]. The FDC of lamivudine/zidovudine/nevirapine ranked highest (17%) amongst other ARVs. This was a default regimen during the survey period which is reflected by its wide collection [30].

Samples collected from the POEs were not subjected to PIR. This is because, they were being collected on daily basis within the framework of medicines quality assurance system in which the first step is laboratory screening. On the other hand, 25.6% (110/430) of the sampled ARVs from medicines distribution outlets, subjected to PIR failed to comply with requirements. The failure rate was highest in 2012, but decreased significantly in subsequent years, as shown in Fig. 3. Adherence to regulatory requirements of individual countries as well as harmonization efforts on technical requirements across the regions could explain the continuing improvement. Compared with PIR results for other medicine categories in the implementation of PMS programs, these results are far much better [10, 11, 31].

All pharmaceutical products must be stored under conditions provided by manufacturers to ensure that their potency and qualities are not compromised during the distribution process and storage. In this study it was observed that some of the manufacturers did not indicate proper storage conditions while some provided conditions that are not achievable in tropical set up, such as “store below 25°C”. In country like Tanzania which fall under ICH zone IVb climatic condition it is not easy to achieve/maintain the aforementioned storage condition [32]. Improper storage of pharmaceutical products could negatively impact on their potency, quality, efficacy, safety and subsequently compromising the quality of life of the end users [33, 34].

Information on package inserts is necessary since it is associated with drug safety, adherence to treatment, rational drug use and reporting adverse drug reactions [35]. Our findings revealed absence of package inserts from majority of the collected samples.

This situation poses potential risk to patients on poisoning, adverse drug reactions, development of window for drug resistant strains, as well as treatment failure due to lack of important information [35].

All ARVs sampled in this study were registered in Tanzania but the registration number which is a prerequisite was not indicated on the labels to some packages. The Tanzania registration number enables easy identification of pharmaceutical products authorized by TMDA to be in the market and prevents availability of falsified products on the market. These results are consistent with PIR results from previous survey study conducted in Tanzania for other categories of medicines [10, 11].

The FDC of lamivudine/zidovudine/nevirapine and lopinavir/ritonavir tablets were the only ARVs that failed in the Tier I screening test accounting to 0.53% (14/ 2630) of the failure rate. Passing Tier II confirmatory test for these samples provided evidence that were of good quality. The situation which stresses on the need for confirmatory tests before conclusion can be made on quality of medicines. The cause of failure in the screening tests for only products sampled from medicine distribution outlets may be due to poor storage conditions. Improper storage of ARVs is known to decrease the potency and quality of pharmaceutical product [33, 34, 36].

Poor quality ARVs is associated with therapeutic or prophylactic failure and the emergence of resistant strains of HIV [37, 38]. In confirmatory testing by full monograph, all samples tested met the specifications except two (2) samples of FDC of stavudine/lamivudine/nevirapine which failed disintegration test and one (1) sample of the same which failed assay test. A sample which failed the assay specifications had stavudine content below the acceptance criteria. This was confirmed by the consistency of results obtained from repeated analysis done in triplicate. As a point of information, the stavudine concentration is no longer an issue of discussion since ARVs regimen containing stavudine has been phased out in the country due to its severe toxicity [39–41].

Disintegration of tablets within 30 minutes predicts dissolution within the required time in vivo [42], and is a precondition to drug absorption process. Poor absorption of the medicine is associated with poor therapeutic outcomes and development of resistant strains. In spite of the fact that the failure rate was only 2%, it cannot be ignored because presence of substandard drugs in the market at any percentage poses threats to society. These threats are as follows but not limited to drug toxicity, poor treatment outcomes and disease prognosis, drug resistance and death but also in terms of economic implications and effects on global pandemics [43].

Results for assay and disintegration tests in this study are consistent with reports from various studies worldwide, which have shown that failure rates for ARVs, is very low [14, 22, 44]. This can be explained by the fact that most of ARVs in the market are procured by government agencies with donor funding. The funding agencies impose stringent procurement condition such as requirements for the WHO pre-qualification for all suppliers and so, low failure rates [43]. Of importance is that for all sampled medicines that were deemed to have deficiencies during PIR, the TMDA directed manufacturers to bring requests for amendments for all deficiencies observed. Also, the manufacturers and local agents were informed to recall all batches that failed the confirmatory test from the market. The manufacturers were further directed to halt importation of such products and to conduct thorough investigations to identify possible causes of the failure.

Conclusion

The quality of the majority of ARVs surveyed was good. This results indicates that the efforts made by the WHO and other organizations on prequalification and purchase policies on ARVs have a positive effect. The study also evidenced the existence of a significant number of ARVs circulating on the Tanzania Mainland market which do not meet packaging information requirements. Product information is crucial for proper handling and use of medicinal products. Thus, lack of and/or inadequate information on the package of the products could have negative

impact on the lives of the intended users. These results call for continuous monitoring of quality of medicines circulating on the Tanzanian market with much emphasis on the adequate information on packages leaflets.

Abbreviations

ADDO: Accredited Drug Dispensing Outlet; MSD: Medical Stores Department;

TMDA : Tanzania Medicines and Medical Devices Authority; TLC: Thin Layer Chromatography; ARVs: Antiretroviral drugs; WHO: World Health Organization; POEs: Port of entries.

Declarations

Ethics and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All relevant data generated and analyzed during this study are available from the Director General of TMDA on reasonable request.

Competing interests

The Authors declared that no competing interest.

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Authors' contributions

SM and KM contributed in study conception and design, data collection, analysis and manuscript writing, SK contributed in data collection, analysis and manuscript writing. BAM contributed in data analysis and manuscript writing and proof reading. GS, YHM and DHS contributed in laboratory and data analysis and manuscript writing, whereas AB and EA contributed in data collection and manuscript writing. Lastly, AF, AK and EK contributed in writing and proof reading the manuscript. All authors participated in reading and approving the final manuscript.

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Tables

Table 1: Proportions of anti-retroviral medicines sampled from medicine distribution outlets between 2012 and 2015

S/N	Name of active (s) ingredient(s)	Number of samples	Percentage
1	Efavirenz tablets	66	15.3
2	Nevirapine tablets	23	5.4
3	Nevirapine oral suspension	11	2.6
4	Lamivudine tablets	10	2.3
5	Zidovudine tablets	2	0.5
6	Tenofovir Disoproxil Fumarate tablets	5	1.2
7	Lamivudine/Zidovudine tablets	70	16.3
8	Abacavir Sulphate tablets	16	3.7
9	Lopinavir/Ritonavir tablets	18	4.2
10	Tenofovir Disoproxil Fumarate /Emtricitabine tablets	14	3.2
11	Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz tablets	29	6.7
12	Lamivudine/Zidovudine/Nevirapine tablets	73	17
13	Lamivudine/Stavudine/Nevirapine tablets	66	15.3
14	Tenofovir Disoproxil Fumarate /Efavirenz/Emtricitabine tablets	27	6.3
TOTAL		430	100

Table 2: Number of samples selected and tested for confirmatory testing

Figures

Product name	Samples collected and screened			Confirmatory test	
	Samples collected	Samples screened and passed	Samples Failed	Samples eligible for confirmatory	Samples selected and tested
Efavirenz	66	66	0	7	14
Nevirapine tablets	34	34	0	4	7
Lamivudine tablets	10	10	0	1	10
Zidovudine tablets	2	2	0	1	2
Tenofovir Disoproxil Fumarate tablets	5	5	0	1	5
Lamivudine/Zidovudine tablets	70	70	0	7	7
Abacavir Sulphate tablets	16	16	0	2	4
Lopinavir/Ritonavir tablets	18	12	7	9	9
Tenofovir Disoproxil Fumarate / Emtricitabine tablets	14	14	0	2	4
Tenofovir Disoproxil Fumarate / Lamivudine/Efavirenz tablets	29	29	0	3	6
Lamivudine/Zidovudine/Nevirapine tablets	73	73	7	14	14
Lamivudine/Stavudine/Nevirapine tablets	66	59	0	10	10
Tenofovir Disoproxil Fumarate / Efavirenz/Emtricitabine tablets	27	27	0	3	8
Total	430	416	14	61	100

Figure 1

Proportion of antiretroviral drug samples collected from port of entry and medicine distribution outlets

Figure 2

Number of antiretroviral drug samples collected at the port of entry annually (2012 - 2018)

Figure 3

Samples of antiretroviral drugs collected from different medicine distribution outlets

Figure 4

Results of product information review per year

Figure 5

Proportion of samples passed laboratory tier II confirmatory testing

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