Quality Analysis of some First-line Antiretroviral Drugs Dispensed in Lusaka District Health Facilities of Zambia

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ABSTRACT

In the last few years governments around the world have pledged to massively scale up the delivery of antiretroviral drugs (ARVs) to achieve universal access for all. However, recent reports of generic medicine including ARVs that they contain little or no active pharmaceutical ingredients are disturbing.

In Zambia anecdotal data show that there is an increase in morbidity and mortality in people living with HIV/AIDS. For instance, a physician at the University Teaching Hospital (UTH) reported that his eight patients did not respond to any combination after developing resistance to first-line ARVs. Currently in Zambia there is insufficient publicly available data describing the ARV drug quality in terms of active pharmaceutical ingredients (API), and labeling standards according to official monographs. The purpose of this study was to determine the quality of some first-line ARVs dispensed in health facilities of Lusaka.

A Cross Section Survey was conducted in nine health facilities of Lusaka District, using convenience sampling technique. Eleven sample units containing twenty active ingredients were analyzed. Each sample unit was sealed in a tin of either 30 or 60 tablets. A protocol of the Ministry of Health, adapted from German Pharm Health Fund (GPHF-minilab) that employs Thin Layer Chromatography (TLC) techniques was used.

It was found that over 94% of the first-line ARV medicines sampled contained the active pharmaceutical ingredients in the right amounts as per label claim on the packages and that on average over 90% of these drugs were correctly labeled. It can therefore be concluded that first-line ARVs dispensed in Lusaka District of Zambia are of good quality and meet the requirements as stipulated in the official monographs.

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INTRODUCTION

Description of the HIV-epidemic status in Zambia

Zambia, a nation with a population of about 13 million[1], is one of the countries hardest hit with the HIV/AIDS epidemic in the world[2]. The prevalence rate has remained significantly higher in urban areas 19.7% in 2007) compared with rural areas (10.3% in 2007) [3,4].

Quality issues concerning antiretroviral medicines

For almost 30 years now, the World Health Organization (WHO) has been fighting drug counterfeiting since it became a major threat in the 1980s[5]. The problem was first noticed by the pharmaceutical industry[6]. They saw that their own products were being copied. An estimated 1 in 4 packets of medicine sold in street markets in developing countries could be substandard[7].

Although it is difficult to obtain precise figures of substandard drugs[8], the Food and Drug Administration in the United States of America estimates that worldwide sales of fake drugs exceed US$ 3.5 billion per year[9], according to a paper published in the journal, PLoS Medicine in April 2005. The Center for Medicines in the Public Interest in the USA predicts that counterfeit drug sales could reach US$ 75 billion globally in 2010 if action was not taken to curb the trade[10].

According to WHO, drugs commonly counterfeited include antibiotics, antimalarials, hormones and steroids. Increasingly, anticancer and antiretroviral drugs are also faked[11,12]. Counterfeit drugs are found everywhere, but sub-Saharan Africa is particularly affected[13]. In Africa, drugs are sold through the informal economy in large open-air markets alongside fruits and vegetables[14].

Counterfeiters take inert ingredients such as chalk, and even dangerous chemicals, package them convincingly and sell them to consumers[15, 16]. Such drugs may have no therapeutic effect and can be toxic[17]. Although much counterfeit drug trade occurs in the unregulated market of unofficial drug vendors, especially in developing countries, counterfeit drugs are also found extensively in licensed pharmacies[18].

A number of factors make antiretroviral drugs an attractive target for counterfeiters, especially: high unit costs and long-

term, sustained demand[19]. In addition, stigma and fear of loss of confidentiality in health care settings increase demand for ARVs delivered through often poorly regulated private sector health care providers, pharmacies or other channels.

Consequences of Substandard drugs

Substandard drugs may have little or no therapeutic value, causing illness and death from the condition supposedly being treated. A substandard drug may be a drug of poor quality or a counterfeit[20].

Fake drugs may be composed of toxic substances that directly cause illness and death. Counterfeited drugs with the appropriate active ingredients in subclinical amounts can also lead to prolonged illness or death[21], but pose the further risk of encouraging the spread of drug resistant pathogens.

Counterfeit drugs pose many far-reaching threats to overall global health. They put individuals at risk of experiencing adverse events or not achieving treatment goals, and also contribute to public health problems by aiding in the spread of infectious diseases[22]. It was suggested that treatment failure and drug resistance are possible consequences of the use of sub-standard drugs[23].

In Zambia, anecdotal data show that there is an increase in morbidity and mortality in people living with HIV/AIDS due to ARV drug resistance, treatment failure and adverse drug effects.

A physician at the UTH confirmed that his eight patients did not respond to any drug combination after developing resistance to first line ARVs [24,25].

According to the reviewed literature in this study, it is evident that the issue of substandard medicines is a global one. Quality analysis of drugs is very important but it is a costly venture especially in developing countries like Zambia and this is the main reason why routine checks on the quality of medicines are rarely done. Substandard drugs pose an enormous threat to public health globally[26].

The purpose of this study was to assess drug content compared to the labeled amount among ARV obtained from health centers in Lusaka District. No research concerning quality of ARVs has been done in Zambia and yet Zambia is one of the first African countries to be subjected to the life prolonging Anti-Retroviral drugs (ARVs) trials a decade ago.

The aim of the study was to determine the quality of some First-line ARVs dispensed in health facilities in Lusaka District. This was achieved by: verifying the active ingredients, evaluating the percentage content of the active ingredients and assessing the packaging and labeling standards on the containers in samples of (1) Stavudine (d4T)/Lamivudine (3TC)/Nevirapine (NVP), (2)Lamivudine (3TC)/Zidovudine AZT), (3)Nevirapine (NVP),(4) Efavirenz (EFV) and(5) Stavudine (d4T)/Lamivudine (3TC).

MATERIALS AND METHODS

Study Design

A cross-section survey was conducted in nine health facilities of Lusaka District, using convenience sampling technique.

Study Setting

This study was conducted in Zambia's capital City Lusaka. In order to have a representative sample, the study was undertaken in Lusaka District. This is where most of the public health facilities in Lusaka province are concentrated. This setting provided the researcher with easy access to drug sample collection. Furthermore, Lusaka province has HIV prevalence level of 20%. The prevalence is much higher among residents of Urban than Rural areas (19.7% Vs 10.3%).

The drug samples were collected from public health facilities. A few were selected randomly in different clusters of the District. The quality analysis of these ARVs was carried out using Thin Layer Chromatography (TLC) at Tejay Pharmaceutical laboratories in Lusaka.

Study population

The study population comprised 4 x 60 tablets Lamivudine/Zidovudine 150/300mg, 2 x 30 tablets Efavirenz 600mg, 2 x 60 tablets Nevirapine 200mg, 2 x 60 tablets Lamivudine/Stavudine/Nevirapine 150/30/200mg, and 1 x 60 tablets Stavudine/Lamivudine 30/150mg which were randomly selected from nine public health facilities of Lusaka. This sample was drawn from health facilities of Lusaka District, using convenient sampling technique. It included nine public institutions conveniently selected from the clusters of the District. The District was divided into 4 geographical clusters, and from each cluster at least 2 public health facilities were selected. Namely cluster 1(Chelston and Mtendere), cluster 2 (kalingalinga and Bauleni), cluster 3 (Kabwata, Kamwala and Makeni), and cluster 4 (kanyama and Matero).

Inclusion Criteria

Only first-line ARVs were included in the study, as long as they were not expired, with reference to the expiry date on the label. Public health facilities where ARVs are dispensed were included.

Sampling Methods

The probability, multistage sampling method was employed in the collection of ARVs for analysis. This involved a successive random sampling of clusters that progressed from large to small and met sample eligibility criteria. The first – stage sampling unit consisted of large clusters. The second – stage sampling units consisted of smaller clusters. Third – stage sampling units were given smaller [27].

Sample Size Determination

Samples of eleven ARVs were selected using the probability, multistage sampling method. The study was designed to tolerate an absolute sampling error of up to 5%, with confidence interval at 95%.

The following formula was used to calculate the sample size.
$n = Z^2P(100-P)/d^2$ where:-
Z = 1.96, the factor from the normal distribution.
P = Expected period prevalence.
d = Absolute sampling error.
n = Sample size.

Therefore $n = (1.96)^2 \times 50(100-50)/5^2$ = **384 tablets.**
Adjustment for handling loses was set at – 10%
= *422* tablets of ARV Medicines but rounded upwards to **430**
Since the total samples size was 430 tablets, 48 sample tablets were collected from each health facility under study in Lusaka District.

Data Collection Tools

The instrument of research was a drug collection sheet, with sections, relating to the general information of the institution and drug information including the date, the name of the drug indicated on the product package, identification number of the drug, active ingredient(s) contained in the product as indicated on the packaging, physical appearance of tablets, nature and material of packaging material, appearance of the label on the packaging, instructions on the label for the use of the product, manufacturing date as stated on the product label, batch number of the product as stated on the label, and manufacturer of the product and address as stated on the label.

Data collection Techniques

Samples of drugs from the public institutions were obtained with permission from the Permanent Secretary, Ministry of Health and Lusaka District Health Management Team (LDHMT). Data were collected after carrying out the analysis of the study units using the laid down procedures in a concise Quality Control Guide on Antiretrovirals of Pharmaceutical Regulatory Authority, Ministry of Health of Zambia. This protocol is adapted from German Pharm Health Fund, Frankfurt (October 2003). It is accessible on internet: www.gphf.org. The data were collected over the period of 12 weeks from the date of approval from the University of Zambia Biomedical Research Ethics Committee (UNZA BREC).

Data Quality Control Checks

The researcher worked closely with the Drug laboratory Analyst Manager at Tejay Pharmaceuticals Limited. Technical expertise regarding the use of laboratory equipment was sought accordingly. The researcher was involved in the analysis and monitored data quality immediately after each sample analysis. Tests were repeated three times where results did not show consistency. This was in order to ensure quality data of analysis.

Ethical Consideration

Even if this study does not directly deal with human participants, clearance was sought from the University of Zambia Biomedical Research Ethics Committee (UNZA BREC). Permission was also sought from MOH for collection of samples from health institutions. The different brands of some first-line HIV/AIDS medications which were analyzed were coded as 1A, 1B, 1C, 1D, 2A, 2B, 3A, 3B, 4A, 4B, and 5A. These codes denote different batch numbers of drug samples which were used in the analysis. They were used in the interpretation of the results.

Data Processing and Analysis

Data was analyzed using percentages, proportions and the SPSS version 16.0 for windows. The analysis was based on comparing the treatment group results with standard references.

RESULTS

None of the samples was found to contain excess amounts (>100%) of the active pharmaceutical ingredient (API), as shown in Tables, 1,2,3,4 and 5.

Table 1: Quantity of Nevirapine (NVP) expressed as a percentage

	Percentage Content of NVP in Samples				
	< 80%	80%	80% – 100%	100%	> 100%
*LL-RS		NVP			
3A	NVP				
3B			NVP		
4A			NVP		
4B			NVP		
*UL-RS				NVP	

***LL-RS** Lower Limit Reference Standard
***UL-RS** Upper Limit Reference Standards

Table 2: Quantity of Efavirenz (EFZ) expressed as a percentage

	Percentage Content of EFZ in Samples				
	< 80%	80%	80% – 100%	100%	>100%
*LL -RS		EFZ			
2A			EFZ		
2B			EFZ		
*UL -RS				EFZ	

***LL -RS** Lower Limit Reference Standard
***UL -RS** Upper Limit Reference Standards

Table 3: Quantity of Stavudine (D4T) expressed as a percentage

	Per centage Content of D4T in Samples				
	< 80%	80%	80% –100%	100%	>100%
*LL -RS		D4T			
4A			D4T		
4B			D4T		
5A			D4T		
*UL -RS				D4T	

***LL -RS** Lower Limit Reference Standard
***UL -RS** Upper Limit Reference Standards

Table 4: Quantity of Zidovudine (AZT) expressed as a percentage

Percentage Content of AZT in Samples					
	<80%	80%	80% –100%	100%	>100%
*LL -RS		AZT			
1A			AZT		
1B			AZT		
1C			AZT		
1D			AZT		
*UL -RS				NVP	

***LL -RS** Lower Limit Reference Standard

***UL -RS** Upper Limit Reference Standards

Table 5: Quantity of Lamivudine (3TC) expressed as a percentage

Percentage Content of 3TC in Samples					
	<80%	80%	80% – 100%	100%	>100%
*LL -RS		3TC			
1A			3TC		
1B			3TC		
1C			3TC		
1D			3TC		
4A			3TC		
4B			3TC		
5A			3TC		
*UL -RS				3TC	

***LL -RS** Lower Limit Reference Standard

***UL -RS** Upper Limit Reference Standards

The majority of the samples had their percentage content within the recommended range (80-100%). Only one sample was found to contain less amount of the API (< 80%), Table 1.

Table 6, shows the number of individual API analyzed. A total of 20 active ingredients were analyzed from 11 drug samples.

Table 6: Number of API in single and combinations of ARV drug samples

			Comment		
			Content within 80-100%	Content Below 80%	Total
Drug	AZT	Count	4	0	4
	3TC	Count	7	0	7
	EFZ	Count	2	0	2
	NVP	Count	3	1	4
	D4T	Count	3	0	3
Total		Count	19	1	20

Table 7 indicates that all the 20(100%) ARV drug Samples assayed contained Active Pharmaceutical Ingredient (API) as per labeling on the drug containers.

Table 7: Identification of API in ARV Drug Samples

			Comment		
			API Present	API Absent	Total
Drug Sample Code	1A	AZT	2	0	2
		3TC			
	1B	AZT	2	0	2
		3TC			
	1C	AZT	2	0	2
		3TC			
	1D	AZT	2	0	2
		3TC			
	2A	EFZ	1	0	1
	2B	EFZ	1	0	1
	3A	NVP	1	0	1
	3B	NVP	1	0	1
	4A	NVP	3	0	3
		D4T			
		3TC			
	4B	NVP	3	0	3
		D4T			
		3TC			
	5A	D4T	2	0	2
		3TC			
	Total		20	0	20

Table 8 shows that only 1(5 %) ARV drug Sample contained less than 80% API content, while 19(95%) of the total ARV-drug Samples contained 80-100% API content.

Table 8: Percentage Content of API in ARV Drug Samples

			Comment		
			API within 80%-100%	API below 80%	Total
Drug Sample Code	1A	AZT	2	0	2
		3TC			
	1B	AZT	2	0	2
		3TC			
	1C	AZT	2	0	2
		3TC			
	1D	AZT	2	0	2
		3TC			
	2A	EFZ	1	0	1
	2B	EFZ	1	0	1
	3A	NVP	0	1	1
	3B	NVP	1	0	1
	4A	NVP	3	0	3
		D4T			
		3TC			
	4B	NVP	3	0	3
		D4T			
		3TC			
	5A	D4T	2	0	2
		3TC			
	Total		**19**	**1**	**20**

Table 8 shows that only 1(5 %) ARV drug Sample contained less than 80% API content, while 19(95%) of the total ARV-drug Samples contained 80-100% API content.

Only 1(5%) of the total sample did not comply with the stipulated specifications as shown in Table 9.

Table 9: Proportion of compliance of ARVs in the total sample population

		Comment		
		Complied	Did not comply	Total
Generic Drug	AZT	4	0	4
	3TC	7	0	7
	EFZ	2	0	2
	NVP	3	1	4
	D4T	3	0	3
	Total	**19**	**1**	**20**

Table 10 shows that the drug sample that did not comply had shelf life of 24 months, expiring in October, 2011, which is not a short expiration date.

Table 10: Expiration date and Compliance of ARV drug samples

		Outcome		
		Complied	Content Below 80%	Total
Expiry Date	2011– 06	2	0	2
	2011 – 09	5	0	5
	2011 – 10	4	1	5
	2011 – 11	2	0	2
	2012 – 04	6	0	6
	Total	**19**	**1**	**20**

For the eleven sampled ARV-drugs analyzed for labeling requirements on the package according to Statutory Instrument No. 47 of 1993, two products had 90% compliance while nine had 100% compliance.

All the eleven samples scored 100% compliance to labeling information on the inserts. This implies that all the sampled ARV-drugs had the manufacturer's inserts present in packages which were adequately labeled according to PRA standards as required by law.

DISCUSSION

A cross-section study was carried out to determine the quality of selected first-line ARVs dispensed in public health facilities in Lusaka Urban District of Zambia. The drugs evaluated include (1) Stavudine (d4T)/Lamivudine (3TC)/Nevirapine (NVP), (2)Lamivudine (3TC)/Zidovudine AZT), (3)Nevirapine (NVP),(4) Efavirenz (EFV) and(5) Stavudine (d4T)/Lamivudine (3TC) using GPHF-Minilab techniques and the Statutory Instrument No. 47 of 1993.

Zidovudine (AZT)

Upon analysis of zidovudine (AZT) in the samples, the outcome was that all the four samples namely; 1A, 1B, 1C and 1D contained AZT in the right quantities as per label claim on the packaging. These samples were from four different pharmaceutical Indian manufacturing companies. They were of different batch numbers and were all manufactured in 2009 with an expiry date of 2012. It is important to note that usually ARVs have on average an expiration date of 24 months. It is also interesting to observe that these samples were obtained from different health facilities in Lusaka District; these are Kalingalinga, Bauleni, Kamwala and Kanyama.

Lamivudine (3TC)

The determination of 3TC in the seven samples of 1A, 1B, 1C, 1D, 4A, 4B and 5A resulted in the right identification and quantification of 3TC in all of them. 4A and 4B drug samples were also from different Indian pharmaceutical companies, with different batch numbers and were manufactured in 2009, expiring in 2011. These were sampled from Kabwata and Chelston respectively.

Efavirenz (EFZ)

The two samples of EFZ (2A and 2B) analyzed were from the same Indian pharmaceutical company but had different batch numbers. They were also manufactured in 2009 and were expiring in 2011. Kalingalinga and Kabwata are the health facilities from which the samples were obtained. Upon analysis, EFZ was identified and in right amounts. However, it is important to note that unlike the other ARVs, analysis of EFZ requires acetonitrile as one of the reagents for the mobile phase. This made its analysis a bit more expensive than others.

Stavudine (D4T)

D4T was identified and quantified in right amounts as per label claim in three samples; 4A, 4B and 5A. 5A was obtained from Mtendere Health Center. Its manufacture date and expiry were in 2009 and 2011 respectively. The three different batches were employed in the analysis of D4T and all of them passed the test.

Nevirapine (NVP)

Four samples; 3A, 3B, 4A and 4B were analyzed for NVP. NVP was correctly identified in all the samples but when it came to quantification of the API only three samples passed the test.

Sample 3A was found to contain less than 80% of NVP content. 3A and 3B were samples from the same Indian pharmaceutical company whose batch numbers were different. The sample in question (3A) was collected from Matero Main Clinic. This sample had good expiry date as shown in figure 6.3. This implies that its inadequate percentage content had nothing to do with its expiration date.

Compliance to the labeling requirements of Statutory Instrument No. 47 of 1993

Drug labeling refers to all printed information that accompanies a drug, including the label, the wrapping and the package insert. In Zambia drug labeling is regulated by Pharmaceutical Regulatory Authority (PRA) through the

Statutory Instrument No. 47 of 1993. The regulations apply to prescription only drugs, pharmacy medicines and general sale medicines. PRA requires that drug labeling be balanced and not misleading. The label must be scientifically accurate and provide clear instructions to health care practitioners and to consumers.

Package (labeling on the container)

The evaluation of compliance was based on the following information; Brand name, Name and strength of active ingredient, Quantity of medicine, Date of manufacture, Expiry date, Batch/lot number, Manufacture licence number, Medicine category, Storage conditions and Name and address of manufacturer. It was observed that sample 1B and 1C both containing AZT/3TC did not reflect medicine category on the package. This means that 18% of the drug samples under study did not meet the requirements of the Statutory Standard on labeling for Zambia. Medicine category refers to prescription only drugs (POMs), pharmacy medicines (P) and general sale medicines (GS). Like other essential medicines 1B and 1C are required by law to show POM on the package. This is because the omission of POM on the package is misleading both to the health practitioners and consumers.

Package Inserts (manufacturer's literature)

Inserts contain necessary supplementary information that cannot be accommodated on the outer package of the drug. The manufacturer's literature usually includes information on; Name of medicine, Pharmacological properties, Direction of use, Side effects, Contraindications, Warnings and Precautions. The law also requires that this information is depicted on the insert. On this score all samples obtained 100%.

STUDY LIMITATIONS

Some limitations in this study are that not all the first-line ARV medicines were sampled and analyzed in Lusaka District partly due to: (i) Non-availability of reference standards at PRA as well as the manufacturers of ARVs (ii) High cost of some reference standards from manufacturers and (iii) Limited number of ARVs that can be analyzed by using the GPHF Mini Lab protocols.

High Performance Liquid Chromatography was not done to allow for further verification and possible reasons as to why some drugs were of poor quality. This is because this demands for extra financial resources and more time than is possible for masters program.

This study did not consider the factors affecting the quality of the ARV-drugs such as manufacturing errors, transit conditions, and storage conditions and Good Manufacturing Practice (GMP) to mention but a few. The researcher is cognizant of the fact that any of these stated factors could have contributed to or be the reason for the less percentage content of NVP in sample 3A.

CONCLUSIONS

Finally, the results discussed and presented above indicate that 100% ARV-drug samples were correctly identified for API and over 94% of the total drug samples contained API in right amounts and that over 90% of these samples were correctly labeled according to the Statutory Instrument No. 47 of 1993 of the Pharmaceutical Regulatory Authority, Ministry of Health in Zambia. Therefore, it can be concluded that first-line ARVs dispensed in Lusaka District of Zambia are of good quality and meet the requirements as stipulated in the official monographs such as the BP and USP.

Lastly but not the least, substandard and spurious ARV-drugs are a big challenge to health care systems especially in the developing countries. However, it is interesting to note that this study in particular has provided objective evidence contrary to frequent insinuations and anecdotal contentions that substandard first-line ARVs are highly rampant in Lusaka District.

RECOMMENDATIONS

- Pharmaceutical Regulatory Authority, Ministry of Health should decentralize its laboratory operations items of GPHF Mini Lab services because this will be an effective way of complimenting the services of a newly established medium size laboratory which is centrally based in Lusaka. GPHF Mini Lab remains an indispensable tool for analysis of drugs in resource limited settings like ours.
- Pharmaceutical Regulatory Authority, Ministry of Health should recruit skilled laboratory analysts in all the nine provinces of Zambia, so that the portable GPHF Mini Lab can be utilized for routine check-ups on the quality of ARV-drugs in Zambia.
- Future research studies should be done on a larger scale to include all ARV-drugs with the help of all stakeholders, so as to have a more representative and conclusive picture on the quality of all the ARVs that are available in Zambia.

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