

Reasons for first-line highly active antiretroviral therapy modification: A retrospective survey at the Infectious Disease Care Clinic Princess Marina Hospital, Gaborone, Botswana

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Declaration

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Abstract

Background

Limited highly active antiretroviral therapy (HAART) in resource-constrained countries makes the optimisation of first-line HAART regimens critical in order to improve treatment efficacy and overall prognosis. Relevant data from resource-constrained settings is still limited. HAART has been available in Botswana since 2002, providing a unique opportunity to evaluate the rate of, the reasons for and the factors associated with first-line HAART modification.

Method

This retrospective survey was undertaken at the Princess Marina Hospital Infectious Disease Care Clinic, Botswana. The researcher examined the medical records of all patients who had been initiated on first-line HAART between 1 January 2012 and 1 January 2014. This was done to determine the rate of, the reasons for and the factors associated with first-line HAART modification.

Results

Of the 199 patients who met the inclusion criteria and had been initiated on first-line HAART, 48 patients (24% –36 female and 12 male) had undergone regimen modification over a median follow-up period of 6.9 months (interquartile range 2.1-19.7 months). Drug toxicity accounted for 52% of modifications, 16.8% of patients defaulted, 16.8% had virological failure and 14.6% had their HAART modified due to other reasons. Patients with abnormal liver function tests at initiation of HAART were more likely to have their HAART modified ($p = 0.010$). Pregnant women on triple antiretroviral prophylaxis were also more likely to have their HAART modified ($p = 0.054$).

Conclusion

There was a lower rate of HAART modification compared to previous studies, mainly attributable to drug side effects or drug toxicity. Evaluating patients with abnormal liver function tests prior to HAART initiation may reduce the modification rate. This would then improve drug tolerability while preserving future drug options.

1. INTRODUCTION

Human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) is one of the most prevalent and important chronic diseases of our time. Since the beginning of the HIV/AIDS pandemic, more than 70 million people have been infected with the HIV virus and 35 million people have died of HIV/AIDS worldwide.[1] By the end of 2015, a total of 36.7 million people were estimated to be living with HIV/AIDS globally.[1] Sub-Saharan Africa is one of the most severely affected areas, accounting for about 70% of people living with HIV/AIDS worldwide.[1]

In recent years, significant progress has been made in the treatment of HIV, at least partly due to the availability of highly active antiretroviral therapy (HAART).[2] The goal of the current treatment strategies includes hindering the viral replication as completely as possible through a combination of three or more HAART drugs.[3] HAART use has resulted in a significant reduction in mortality and morbidity associated with HIV/AIDS worldwide.[2] New global efforts have led to a tremendous increase in antiretroviral therapy access, especially in resource-constrained countries.[4] In 2016 it was estimated that 19.5 million people living with HIV/AIDS globally had access to treatment, reflecting about 53% HAART coverage.[4]

Even though the challenge of complete coverage still stands in most developing countries, it is important that we sustain the benefits of HAART. The long-term success of treatment programmes depends on establishing the rate of, the reasons for and the factors associated with modification of first-line HAART.[5] Evidence shows that globally up to 70% of patients have their HAART modified and that more than 40% of them have it modified in the first 12 months of treatment.[5, 6, 7, 8] The main reason for modification or discontinuation of HAART is drug toxicity.[9] Drug toxicity may lead to discontinuation or suboptimal therapy due to poor adherence and eventually treatment failure. Although this is a global problem, affluent countries suffer less because of the variety of treatment options available.[10]

In resource-constrained countries, treatment regimens are limited and fewer options are available for patients unable to tolerate HAART. Treatment modification may pose a challenge to treatment programmes, impacting on the overall cost of antiretroviral therapy and ultimately on patient prognosis.[11] For this reason, it is important to increase the duration of a patient's initial first-line regimen and to optimise the use of well-tolerated

drugs.[12] There is thus a need to develop new strategies to maximise drug tolerability and treatment benefits from available first-line HAART. In order to achieve this goal, it is important to understand the reasons for modifying first-line HAART. This knowledge could help to individualise drug regimens that are better tolerated whilst at the same time preserving future treatment options.

Botswana is one of the countries with the highest prevalence of HIV/AIDS in the world with 350 000 people infected with HIV in 2015.[1] Botswana was one of the first African countries to establish a national HIV/AIDS treatment programme called ‘Masa’, meaning ‘new dawn’ in the Setswana language.[13] Since the introduction of Masa in 2002, the national HAART guidelines have been adapted to align with an improved understanding of the biology of HIV, to decrease adverse events associated with HAART and to accommodate the availability of improved drugs.[13] Currently, more than 78% of people living with HIV/AIDS in Botswana have accessed HAART via various clinics and hospitals. As a result, Botswana is in a unique position to evaluate the rate of, the reasons for and the factors associated with first-line HAART modification in the context of a developing country.

Even though studies have been carried out to assess the rate of, the reasons for and the factors associated with HAART modification, HAART guidelines have changed over time with the use of newer antiretroviral drugs. Most studies were carried out during a time when older antiretroviral drugs were in use. Since the introduction of newer HAART drugs with improved efficacy and tolerability profiles, there have been limited studies investigating the rate of, the reasons for and the factors associated with HAART modification. To improve tolerance of first-line HAART, it is therefore important that we continue to investigate the rate of, the reasons for and the factors associated with HAART modification with these newer improved drugs.

The author is unaware of any published study in Botswana that assessed the durability of first-line HAART. This study could provide information that could help to improve decision making concerning newer improved drugs and HAART initiation in HAART-naive patients in Botswana.

2. AIMS AND OBJECTIVES

The overall aim of the study was to determine the rate of, the reasons for and the factors associated with first-line HAART modification in HAART-naive patients at Princess Marina Hospital (PMH) in Gaborone, Botswana. The specific objectives were the following:

- To determine the rate of first-line HAART modification.
- To determine the reasons for first-line HAART modification.
- To identify the factors associated with HAART modification.

3. METHODS

3.1 Study design

This was a retrospective survey, using a standardised data collection checklist to extract data from the existing medical records. The researcher decided to adapt a validated checklist that had been used in a previous international study.[14] The checklist was modified to include patients' comorbidities and laboratory findings to identify risk factors associated with treatment modification. The checklist is available in addendum of this thesis. A pilot test was done with five patient files to test the logistics and to gather information prior to the study in order to improve the quality and efficiency of the checklist.

3.2 Study population and patient selection

All the medical records of HIV-infected patients who attended PMH from 1 January 2012 to 1 January 2014 were reviewed by the principal researcher to identify those patients who met the study inclusion criteria as stated below.

Inclusion criteria

1. HIV-positive HAART-naive adults > 15 years, including pregnant women for prevention of mother-to-child transmission, who had been initiated on first-line HAART between 1 January 2012 and 1 January 2014 with cluster of differentiation 4 (CD4) < 350 or World Health Organization (WHO) clinical stages 3 or 4.
2. At least two recorded follow-up visits post HAART initiation.
3. Initiated on first-line HAART regimens of
 - tenofovir disoproxil (TDF) + emtricitabine (FTC) + efavirenz (EFV); or
 - TDF + FTC + lopinavir/ritonavir (LPV/r)/ nevirapine (NVP); or

- zidovudine (AZT) + lamivudine (3TC) + EFV/NVP/LPV/r; or
- abacavir (ABC) + 3TC + EFV/NVP/LPV/r.

4. Reasons for and dates of treatment modifications available in the records.

3.3 Setting

This retrospective survey was carried out at PMH, which has the largest infectious disease control outpatient clinic in Botswana. This clinic is run by three medical officers, nine nurses and three health care auxiliaries from Monday to Friday. Around 90-100 patients per day and more than 13 000 patients annually are seen in this clinic. The hospital also receives complicated HIV-related cases from surrounding local clinics to be seen by an HIV specialist who runs the clinic on Wednesdays. The hospital is located in the southern part of the country. Since 2002, when the Masa HIV/AIDS programme was introduced, the hospital has been providing comprehensive HIV care at no charge to the patient as part of the national HAART programme.

In this facility, standard WHO-adapted treatment and care guidelines are followed. During the study period, the 2012 Botswana HAART guidelines, which are in accordance with the 2010 WHO recommendations, were in use. Treatment consisted of nucleotide reverse transcriptase inhibitors (NRTI) backbone of TDF or AZT or ABC with FTC or 3TC and either NVP, EFV or LPV/r.[15,16] Patients presenting with WHO stages 3 or 4 and/or CD4 < 350 cells/mm³ were eligible for the initiation of HAART.[15, 16] Clinical and laboratory findings were collected at each hospital visit.

HAART eligibility for HIV-infected pregnant women was the same as for other adults. All pregnant women not eligible for HAART were started on triple antiretroviral therapy (TAP). Initiation of TAP depended on the gestational age of the woman. If TAP was given before 14 weeks of pregnancy, it consisted of TDF + FTC and NVP or LPV/r, depending on the CD4 count.[15] When given at 14 weeks and more, it was in the form of TDF + FTC + EFV.[16] This was because before 14 weeks gestation, EFV was considered teratogenic. The duration of TAP postpartum depended on whether the woman was breastfeeding or not. During the postpartum period women were assessed for WHO stages 3 or 4, CD4 count and pregnancy and postpartum related complications before TAP could be stopped. [15] If women had developed WHO stages 3 or 4 or their CD4 count was less than 350, or clinically unstable treatment was continued.[16] Post delivery, those who were on NVP were continued on it, but those on LPV/r were switched to EFV. It is also important to note that a postpartum

woman had an option of continuing HAART even if assessed to have no WHO stages 3 or 4 disease and/or CD4 > 350, but that option had to be discussed with the medical officer.

3.4 Measurements and data collection

For the purpose of this study, modification of HAART was viewed as regimen switch or drug substitution in first-line HAART. Dose modifications were not accounted for. Time zero was the day of HAART initiation, and the cut-off date was the earliest of regimen modification. The reasons for modification were those determined by the physician or medical officer at the date of regimen change. The reasons for modification were not assigned prospectively at the time of treatment modification. These reasons were grouped retrospectively as drug toxicity, virological failure, default and other.

Laboratory findings were classified as abnormal liver function tests (LFTs), abnormal haemoglobin (Hb) and abnormal renal function tests (RFTs). Abnormal RFTs were defined as creatinine clearance < 60 cc/minute. Abnormal Hb was below 12.0 g/dL for women and below 14.0g/dL for men. Abnormal LFTs were defined as aspartate aminotransferase above 40 U/L and alanine aminotransferase above 56 U/L.

The main sources of data collection were the patient's medical records, the patient's pharmacy refill book and Meditech. Meditech is electronic patient management software used in PMH to capture patients' sociodemographic and clinical information during their hospital visits. Pharmacy refill books are used by pharmacists to record any information concerning HAART drug prescriptions during hospital visits. Information on any modification of drugs is also recorded in these books.

All the medical records of patients initiated on first-line HAART during the period of 1 January 2012 to 1 January 2014 were examined by the principal investigator to identify those meeting the inclusion criteria. A standardised validated checklist was used to capture sociodemographic information, clinical parameters and the reasons for HAART modification. From the assessed medical records, 199 patients were found to meet the inclusion criteria for the study. Sociodemographic information collected included age and gender while clinical parameters included baseline CD4 count, baseline weight, comorbidities, initial regimen, clinical stage, LFTs, RFTs and Hb levels. The medical records contained most demographic and clinical variables for each visit, hence most patient observations were extracted from this source. The reasons for modification of HAART were also extracted from the medical

records. Information missing from this source was checked by the principal investigator from Meditech and the pharmacy refill books.

Information from all the sources was de-identified, entered into a checklist and then entered into a Microsoft Excel spreadsheet on a computer. The Excel spreadsheet had variables presented in columns and patient study identity in rows. Data was transcribed after collection and verified using Excel before being transferred to a Stellenbosch University statistician for exportation into STATA version 11 for analysis.

3.5 Data analysis

Statistical analysis was done with the help of a statistician at Stellenbosch University. Patient demographics and clinical indices at the initiation of treatment were described using percentages for categorical data and median and interquartile ranges (IQRs) for continuous data. Identified reasons for modification of HAART were also described using percentages. Comparison of demographic and clinical characteristics at initiation of HAART was performed using chi-square tests, unpaired T-tests or the Kruskal Wallis test. Risk factor variables assessed included gender, age, baseline weight, CD4 counts, WHO stages, comorbidities, Hb levels, LFTs and RFTs at initiation. Variables significant at univariate analysis ($p = 0.30$) were included in the multivariate models. Person year analysis was used to determine the rate of HAART modification while time was measured from the start of HAART to the earliest regimen modification.

4. ETHICS STATEMENT

This study was approved by the ethics committees of the Botswana Ministry of Health, PMH (reference number: PMH 5/79 233-2-2016) and Stellenbosch University (reference number: S15 /07/139).

5. RESULTS

Among the 219 patients who had been initiated on first-line HAART between 1 January 2012 and 1 January 2014, 12 were excluded from the study because they had been initiated on HAART and followed once and then transferred out to local clinics. Five medical records were missing from the department while three more patients were excluded because they lacked relevant information (demographic and clinical). This left the researcher with 199 participants meeting the inclusion criteria. During this study, the researcher had access to all

medical records, including those of patients lost for follow-up, records of demised patients and records of patients who had been transferred out.

The sample included 199 participants of which 68.8% were female and 31.2% were male. At HAART initiation, the median patient age was 36 years (IQR 30-41), the median CD4 count was 187 (IQR 92-300) and the median weight was 61 kg (IQR 52-75); 55.8% of the patients had started HAART at WHO stages 3 or 4. The majority of patients (90.5%) had been initiated on TDF + FTC + EFV as their first-line regimen.

Of these 199 participants, 9.6% had cancer, 15.6% had tuberculosis (TB), 27.1% had anaemia, 9.6% were on TAP because of pregnancy and 24.6% had other comorbidities at the initiation of HAART. Also, 4% had abnormal LFTs, 5% had abnormal RFTs and 27.1% had abnormal Hb levels (see Table 1 below).

Table 1: Baseline characteristics of participants

Characteristics at HAART initiation	Median (IQR)
Age (years)	36 (30-41)
Baseline CD4 count (cells/mm ³)	187 (92-300)
Baseline weight (kg)	61 (52.9-75)

Gender	N (%)
Male	62 (31.2)
Female	137 (68.8)
WHO stage	N (%)
WHO stage 1/2	88 (44.2)

WHO stage 3/4	111 (55.8)
Comorbidities and risk groups	N (%)
Cancer	19 (9.6)
Anaemia	54 (27.1)
TB	31 (15.6)
Pregnancy	19 (9.6)
Other	49 (24.6)
Laboratory findings at initiation	N (%)
Abnormal LFT	8 (4)
Abnormal RFT	10 (5)
Abnormal Hb	54 (27.1)
First-line HAART regimen	N (%)
TDF + FTC + EFV	180 (90.5)
TDF + FTC + NVP	1 (0.5)
TDF + FTC + LPV/r	1 (0.5)
AZT + 3TC + EFV	8 (4.0)
AZT + 3TC + NVP	1 (0.5)
ABC + 3TC + EFV	8 (4.0)

EFV = efavirenz, NVP = nevirapine, ABC = abacavir, 3TC = lamivudine, TDF = tenofovir disoproxil, FTC = emtricitabine, AZT = zidovudine, TB = tuberculosis, LPV/r = lopinavir/ritonavir, TAP = triple antiretroviral prophylaxis, Hb = haemoglobin, LFT = liver function test, RFT = renal function test, IQR = interquartile range, kg = kilogram

Reasons for highly active antiretroviral therapy modification

Over a median follow-up period of 6.9 months (IQR 2.1-19.7 months), 24% (n = 48) of the 199 patients had their first-line antiretroviral regimen modified. This represented an overall modification rate of 0.09 per 100 person years (confidence interval [CI]: 0.06-0.11) over a total of 47 person years follow-up. Table 2 shows the different reasons for treatment modification.

Table 2: Reasons for HAART modification among participants

Reasons for HAART modification	Frequency
1. Drug toxicity/drug side effect	N (%)
EFV-induced rash	7 (14.6)
EFV-induced neuropsychiatric toxicity	3 (6.3)
TD4-induced renal impairment	9 (18.8)
ABC-induced rash	1 (2.1)
Lipodystrophy	2 (4.2)
AZT-induced anaemia	2 (4.2)
LPV/r-induced persistent diarrhoea	1 (2.1)
2. Virological failure	8 (16.8)
3. Default	8 (16.8)
4. Other	
Post TAP	4 (8.3)
Poor compliance	2 (4.2)

Resolved renal failure	1 (2.1)
Total	48 (100)

EFV = efavirenz, ABC = abacavir, AZT = zidovudine, LPV/r = lopinavir/ritonavir, TAP = triple antiretroviral prophylaxis, TDF = tenofovir disoproxil

Table 2 shows that 52.3% of treatment modifications were due to drug side effects or drug toxicity, 16.7% of patients defaulted, 16.7% had virological failure and a further 14.6% had HAART modified due to other reasons.

The factors associated with HAART modification are shown in Table 3 below. $P < 0.1$ in univariate analysis was considered significant. Patients with abnormal LFTs at the initiation of HAART were more likely to have their treatment modified ($p = 0.01$). Pregnant women on TAP were also more likely to have their HAART modified ($p = 0.054$). Other variables did not show significant association with modification of HAART.

Table 3: Factors associated with modification of HAART – univariate analysis

Characteristic		Switched, N = 48	Not switched, N = 151	P-value
Age, median (IQR)	Years	36.5 (32.5-40)	36 (30-41)	0.9209
CD4, median (IQR)	Cells/uL	252 (121-388)	180 (101-291)	0.952
Weight, median (IQR)	Kg	60 (50.7-76)	61 (53-73)	0.922
Gender, n (%)	Male	12 (19.4)	50 (80.7)	0.290
	Female	36 (26.3)	101 (73.7)	
Lab findings, n (%)	Abnormal LFT	4 (8.3)	6 (39.7)	0.010
	Abnormal RFT	5 (10.4)	3 (1.99)	0.228
	Abnormal Hb	12 (25)	42 (27.8)	0.702
Comorbidities, n (%)	TB	8 (16.7)	23 (15.2)	0.811

	Cancer	3 (6.3)	16 (10.6)	0.372
	Anaemia	12 (25)	42 (27.8)	0.702
	Pregnancy	8 (16.7)	11 (7.3)	0.054
	Other	13 (27.1)	36 (23.8)	0.650
WHO stage, n (%)	1/2	21 (43.8)	67 (44.4)	0.873
	3/4	27 (56.3)	84 (55.6)	

IQR = interquartile range, LFT = liver function test, RFT = renal function test, Hb = haemoglobin, TB= tuberculosis

Factors with p-values less than 0.3 in the univariate analysis were entered into a multivariate logistic regression with switching (yes/no) as a binary outcome. After multivariate regression, only abnormal LFTs (odds ratio [OR] 11.86, 95% CI 1.18-119.20, $p = 0.036$) were associated with risk of switching. Pregnancy was also likely to be a risk factor although its OR did not reach statistical significance (OR 2.72, 95% CI 0.90-8.16, $p = 0.075$) (see Table 4 below).

Table 4: Factors associated with modification of HAART – multivariate analysis

Factor		AOR	95% CI of AOR	P-value
Lab findings	Abnormal LFT	11.86	1.18-119.2	0.036
	TAP for pregnancy	2.72	0.90-8.16	0.075

CI = confidence interval, AOR = adjusted odds ratio, LFT = liver function test, TAP = triple antiretroviral prophylaxis

6. DISCUSSION

The researcher observed a lower treatment modification rate of 0.09 per 100 person years within a median follow-up period of 6.9 months in this cohort. The reasons for modification were related to drug toxicity, virological failure, default and other. Having an abnormal LFT

at the initiation of HAART and being on TAP for pregnancy were significantly associated with increased risk of treatment modification.

This rate of HAART modification was relatively lower compared to the rates found in studies done previously when the 2006 WHO guidelines were in use.[17, 18, 19] Studies with similar settings to compare to are limited. This lower rate of modification could be due to the high efficacy of the drugs used in this setting, facilitated by the improved 2010 WHO guidelines. Another contributing factor could be the use of TDF in the first-line regimen, which has been shown to cause a significant reduction in the risk of HAART modification.[11, 15, 20, 21] Because the PMH Infectious Disease Care Clinic (IDCC) is a referral unit with specialists, they may be assisting junior medical officers with decision making on HAART initiation.

This rate is, however, still lower than that reported in some observational cohorts, mainly in North America and Europe where treatment modification rates are higher.[8, 22, 23, 24] There are several reasons that could have further attributed to the lower rates reported in this study. One of the reasons might be the lack of alternative treatment options in resource-limited settings such as Botswana. This shortcoming may inadvertently influence medical practitioners to be more hesitant to modify regimens.[14] Another reason could be that the current policies for treatment in resource-limited settings support the use of rigid predetermined cost-effective regimens.[15] Patients in resource-rich settings are more likely to be better informed about their care and would therefore foresee any unusual effects that could be attributed to their treatment. Better informed patients would be more likely to report any intolerance and have their drugs modified.

Drug side effects or drug toxicities were the commonest reason for HAART modification, similar to what has been reported in other studies.[7, 14, 17, 25, 26] EFV and DT4 accounted for most drug toxicities – 20.9% and 18.8% respectively. A higher probability of treatment modification for adverse events has been observed with EFV.[25] Despite the fact that EFV has demonstrated high virological efficacy, neuropsychiatric and neurocognitive toxicity associated with this drug is not negligible.[27, 28] Both EFV- and NVP-toxicity-related modifications are higher in the first year post HAART initiation.[11] These observations should be taken into account when prescribing first-line HAART. Close clinical monitoring is warranted in EFV-treated patients. These findings also support the 2016 Botswana guidelines that recommend that EFV should be phased out and that DTG, which has a better tolerability, should be adopted.

Virological failure accounted for 16.7% of modifications, which may suggest drug resistance or low efficacy of first-line HAART in this region. This level of virological failure may also mean that there is an adequate and a proper mechanism in place to identify virological failure in this setting.

Treatment default also accounted for 16.7% of modifications. These included patients who discontinued their treatment for their own reasons but who were restarted on treatment. A systematic review of patients who initiated HAART across sub-Saharan Africa found that approximately 25% had defaulted at 1 year after initiation, a figure rising to 40% after 2 years.[29] Various studies have identified transport costs, time needed for treatment, and logistical challenges as main barriers to treatment, whereas stigma and side effects to HAART were less influential.[30, 31, 32, 33] In order to preserve the first-line HAART regimen at PMH, we need to reduce the financial and time burden of HAART and to reduce logistical barriers, such as simplifying the referral and transfer process, employing patient advocates, and adopting extended and weekend clinic hours.

An abnormal LFT at the initiation of HAART was found to be a risk factor for treatment modification in this study. Various studies have reported a high prevalence of abnormal liver enzymes in HAART-naïve patients.[34, 35, 36] This abnormality could be due to direct inflammation of hepatocytes by HIV through apoptosis or mitochondrial dysfunction and many more.[34] The underlying cause should always be investigated and properly managed prior to initiation of HAART since HAART has also been associated with drug-induced liver enzyme abnormalities.[34] In this study, LFTs had not been recorded at the time of HAART modification, making it difficult to know whether these liver enzyme abnormalities directly caused modification of HAART. This could mean that even though liver enzymes were elevated at the beginning, the underlying pathology was identified and treated accordingly through the help of specialists in the hospital. However, just as the 2010 WHO guidelines recommend, monitoring and management of elevated liver enzymes prior to treatment should be reinforced in this setting.

TAP during pregnancy was also found to be a risk factor for modification of HAART in univariate analysis ($p = 0.054$), but in multivariate analysis, the OR did not reach statistical significance. This is because the guidelines recommend cessation of HAART if the mother is stable postpartum without pregnancy complications or has not developed WHO stages 3 or 4 or $CD4 < 350$.

Even though age, gender, CD4 count, WHO stage, baseline weight and comorbidities have been identified as predictive factors for HAART modification in other studies, it was not the case in this study.[7, 14, 17, 25, 26] The reason could be that when the 2010 WHO guidelines were drawn up, these factors were taken into consideration and better recommendations were made. It could also be that high-potency drugs were used at the time of this study or that the small sample size did not allow for them to be identified.

The findings of this study should be interpreted in the light of its limitations. The analysis of a single treatment site, even though it is the largest in the country, may only reflect treatment practices at that centre, which limits generalisation to other sites. The fact that HIV specialists help to run the IDCC may also mean HAART modification is different from that at other centres in the country. The reasons for modification of HAART were not classified prospectively but were assessed from the retrospective review of patients' medical records. In some cases, this could have led to imprecise classification. To strengthen the study, the researcher combined reasons for modification that were unlikely to be independent from each other. The other weakness is that the PMH IDCC is part of a big hospital with a significant number of people initiated on HAART as inpatients and then discharged to be followed up at local clinics. Such patients had no medical records opened for them in the IDCC even though they were initiated there, which could account for the small sample size of this study. The other important limitation of this study is that it reflects prescribing practices relating to a two-year period (2012-2014), which is no longer common practice. However, contributing to the strength of this data and analysis is the fact that every episode of modification of HAART and the reason for modification were captured by one researcher, which minimised errors in collecting data from the medical records.

The findings of this study have implications for the management of patients on antiretroviral treatment. The identification of drug toxicity as the main reason for HAART modification calls for timely and proactive management of toxicity in order to prevent poor treatment outcomes, including treatment failure and default. The identification of abnormal LFTs as an important risk factor for HAART modification indicates that intensive assessment of patients for underlying liver pathology must be done prior to initiation. The common practice in the study setting is for all baseline bloods to be done prior to initiation and then for abnormal ones to be

acted upon before initiation of HAART. However, this needs to be reinforced to avoid initiation of HAART in patients with an uninvestigated cause of abnormal liver function.

Further follow-up of large cohorts of patients is required to determine the long-term adherence to and toxicities of HAART and, ultimately, the long-term clinical outcome of patients on HAART.

7. CONCLUSION

This study found lower rates of HAART modification at the PMH IDCC compared to most studies in which previous HAART guidelines were in use. There are however, limited comparable studies to determine whether indeed patients in this cohort performed differently. Drug toxicity was identified as the most common reason for HAART modification while abnormal LFTs at HAART initiation and being on TAP for pregnancy were identified as predictive factors for treatment modification. Proactive management of drug toxicity to prevent poor treatment outcomes and careful investigation of abnormal LFT's prior to HAART initiation is likely to be beneficial in the prevention of HAART modification.

References

1. UNAIDS. UNAIDS facts sheet: latest statistics on the status of the AIDS epidemic [Internet]. New York UNAIDS. 2015 [cited 5 December 2017]. Available from:<http://www.unaids.org/en/resources/fact-sheet>.
2. Quinn TC. HIV epidemiology and the effects of antiviral therapy on long-term consequences. *AIDS* 2008;22:S7-S12.
3. Arts EJ, Hazuda DJ. HIV-1 antiretroviral drug therapy. *Cold Spring Harbour Perspectives in Medicine* 2012;2(4):a007161.
4. UNAIDS. Global AIDS update 2016. Geneva: UNAIDS; 2016.
5. Cardoso SW, Grinsztejn B, Velasque L, Veloso VG, Luz PM, Friedman RK, et al. Incidence of modifying first HAART regimen and its determinants in a cohort of HIV-infected patients from Rio de Janeiro, Brazil. *AIDS Research and Human Retroviruses* 2010;26(8):865-874.
6. Cesar C, Shepherd B, Krolewiecki A, Fink V, Schechter M, Cahn P, et al. Rates and reasons for early change of first HAART in HIV-1-infected patients in 7 sites throughout the Caribbean and Latin America. *Plos One* 2010;5(6):1-10.
7. Cicconi P, Cozzi-Lepri A, Castagna A, Trecarichi EM, Antinori A, Gatti F, et al. Insights into reasons for discontinuation according to year of starting first regimen of highly active antiretroviral therapy in a cohort of antiretroviral-naïve patients. *HIV Medicine* 2010;11:104-113.
8. D'Arminio Monforte A, Lepri AC, Rezza G, Pezzotti P, Antinori A, Phillips AN, et al. Insights into the reasons for discontinuation of the first highly active antiretroviral (HAART) regimen in a cohort of antiretroviral naïve patients. I.C.O.N.A. Study Group. *Italian Cohort of Antiretroviral-Naïve Patients. AIDS* 2000;14:49 mm 9-507.
9. Mocroft A, Youle M, Moore A, Sabin CA, Madge S, Lepri IC, et al. Reasons for modification and discontinuation of antiretrovirals: results from single treatment centre. *AIDS* 2001;15:185-194.

10. Hammer SM, Eron JJ, Reiss P, Schooley RT, Thompson MA, Walmsley S, et al. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society – USA panel. *Journal of the American Medical Association* 2008;300:555-570.
11. Inzaule S, Otieno J, Kalyango J, Nafisa L, Kabugo C, Nalusiba J, et al. Incidence and predictors of first line antiretroviral regimen modification in Western Kenya. *Plos One*. 2014;9(4):e93106.
12. World Health Organization. Towards Universal Access Progress Report. Scaling up Priority. HIV/AIDS interventions in the health sector. Available: <http://www.who.int/hiv/pub/2008progressreport/en> (Accessed 2009, September 18).
13. Farahani M, Vable A, Lebelonyane R, Seipone K, Anderson M, Avalos A, et al. Outcomes of the Botswana national HIV/AIDS treatment programme from 2002 to 2010: a longitudinal analysis. *Lancet Global Health* 2014;2:e44-50.
14. Takuva S, Louwagie G, Zuma K, Okello V. Durability of first line antiretroviral therapy: reasons and predictive factors for modification in Swaziland cohort. *Journal of Antivirals and Antiretrovirals* 2012;4(1):14-20.
15. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach. Geneva: World Health Organization; 2010 revision.
16. Botswana Ministry of Health. Botswana national HIV & AIDS treatment guidelines. Gaborone: Botswana Ministry of Health; 2012.
17. Kiguba R, Byakika-Tusiime J, Karamagi C, Ssali F, Mugenyi P, Katabira E, et al. Discontinuation and modification of highly active antiretroviral therapy in HIV-infected Ugandans: prevalence and associated factors. *Journal of Acquired Immune Deficiency Syndrome* 2007;45:218-223.
18. Braitstein P, Ayuo P, Mwangi A, Wools-Kaloustian K, Musick B, Siika A, et al. Sustainability of first-line antiretroviral regimens: findings from a large HIV treatment program in western Kenya. *Journal of Acquired Immune Deficiency Syndrome* 2010;53:254-259.

19. Messou E, Anglaret X, Duvignac J, Konan-N'dri E, Komena E, Gnokoro J, et al. Antiretroviral treatment changes in adults from Cote d'Ivoire: the roles of tuberculosis and pregnancy. *AIDS* 2010;24:93-99.
20. Chi BH, Mwango A, Giganti M, Mulenga LB, Tambatamba-Chapula B, Reid SE, et al. Early clinical and programmatic outcomes with tenofovir-based antiretroviral therapy in Zambia. *Journal of Acquired Immune Deficiency Syndrome* 2003;54:63-70.
21. Kumarasamy N, Vallabhaneni S, Cecelia AJ, Yepthomi T, Balakrishnan P, Saghayam S, et al. Reasons for modification of generic highly active antiretroviral therapeutic regimens among patients in southern India. *Journal of Acquired Immune Deficiency Syndrome* 2006; 4:53-58.
22. Van Roon EN, Verzijl JM, Juttman JR, Lenderink AW, Blans MJ, Egberts AC, et al. Incidence of discontinuation of highly active antiretroviral therapy (HAART) and its determinants. *Journal of Acquired Immune Deficiency Syndrome Human Retroviral* 1999;20:290-294.
23. Fellay J, Boubaker K, Ledergerber B, Bernasconi E, Furrer H, Battegay M, et al. Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study. *Lancet* 2001;358:1322-1327.
24. Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeters or less. *New England Journal of Medicine* 1997;337:725-733.
25. Davidson I, Beardsell H, Smith B, Mandalia S, Bower M, Gazzard B, et al. The frequency and reasons for antiretroviral switching with specific antiretroviral associations: the SWITCH study. *Antiviral Research* 2010;86:227-229.
26. Prosperi MC, Fabbiani M, Fanti I, Zaccarelli M, Colafigli M, Mondi A, et al. Predictors of first-line antiretroviral therapy discontinuation due to drug-related adverse events in HIV-infected patients: a retrospective cohort study. *BMC Infectious Disease* 2012;12:296.
27. Gazzard B, Balkin A, Hill A: Analysis of neuropsychiatric adverse events during clinical trials of efavirenz in antiretroviral-naive patients: a systematic review. *AIDS Review* 2010; 12:67-75.

28. Ciccarelli N, Fabbiani M, Di Giambenedetto S, Fanti I, Baldonero E, Bracciale L, et al. Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. *Neurology* 2011;76:1403-1409.
29. Rosen S, Fox M, Gill CG. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. *PLoS Medicine* 2007;4:e298
30. Aidi M. Patient Retention in Treatment – Contributing Factors and Challenges in Tanzanian Patients on Antiretroviral Therapy. 2009 2009 HIV Implementers Meeting, Windhoek, Namibia 2009(Abstract 1259).
31. Roura M, Busza J, Wringe A, Mbata D, Urassa M, Zaba B. Barriers to sustaining antiretroviral treatment in Kisesa, Tanzania: a follow-up study to understand attrition from the antiretroviral program. *AIDS Patient Care and STDs* 2009;23:203–210.
32. Murray LK, Semrau K, McCurley E, Thea DM, Scott N, Mwiya M, et al. Barriers to acceptance and adherence of antiretroviral therapy in urban Zambian women: a qualitative study. *AIDS Care-Psychological and Socio-Medical Aspects of AIDS/HIV* 2009;21:78–86
33. Miller CM, Ketlhapile M, Rybasack-Smith H, Rosen S. Why are antiretroviral treatment patients lost to follow-up? A qualitative study from South Africa. *Tropical Medicine & International Health* 2010;15(s1):48-54.
34. Gil ACM, Lorenzetti R, Mendes GB, Morcillo AM, Toro AADC, Silva MTN, et al. Hepatotoxicity in HIV-infected children and adolescents on antiretroviral therapy. *Sao Paulo Medical Journal* 2007;125(4):205-209.
35. Hoffmann CJ, Charalambous S, Thio CL, Martin DJ, Pemba L, Fielding L, et al. Hepatotoxicity in an African antiretroviral therapy cohort: the effect of tuberculosis and hepatitis B. *AIDS* 2007;21(10):1301-1308.
36. Lucent K, Clement A, Fon N, Weldeji P, Ndikvu C. The effects of antiretroviral treatment on liver function enzymes among HIV-infected outpatients attending the central hospital of Yaound'e Cameroon. *African Journal of Clinical and Experimental Microbiology* 2010;10(3):174-178.

APPENDIX

Data extraction checklist

Patient demographics

Age:

Gender:

Baseline weight:

Comorbidities: Tuberculosis Epilepsy Arthritis COPD/lung disease

Diabetes Psychiatric illnesses Cardiac disease Liver disease Cancer

Other

If other, specify _____

Clinical stage:

Date commenced on initial HAART regimen:

Initial HAART regimen:

Clinical parameters

Baseline CD4:

Baseline LFTs:

Baseline RFTs:

Baseline Hb:

Reasons for modification:

Date of HAART modification:

Adapted