Evaluation of Namibia's antiretroviral therapy guidelines' recommendations for switching from first-line to second-line, using predictors of first-line treatment failure: An exploratory study.

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Abstract
OBJECTIVES: The objective of this study was to find out the extent to which the antiretroviral therapy (ART) switching guidelines were complied with; and to assess whether immediate switching from first- to second- line ART would have been appropriate than attempting to comply with the guidelines. ME T H O D S: A case-control study. Cases and controls were patients on second- and first- line ART, respectively. Regression analysis was used identify factors that were associated with switching to second-line ART. Confidence level was 95% and significance at a p-value <0.05. R E S U LT S: 81 cases and 102 controls were included. VLs at six and nine months were implemented for 8.2% and 2.7%, respectively. Switching predictors were poor adherence (adjusted Hazard Ratio [aHR] = 20.3 (p=0.013); a first VL >1000 copies/ml (aHR = 20.2), <0.001); opportunistic infections (aHR = 12.9, p=0.006); male gender (aHR = 5.2, p=0.003); and lack of adherence counselling (aHR = 3.8 p=0.024). C O N C LU S I O N: A VL >1000 copies/ml was a predictor of switching. New local research is underway, with a large number of patients, to assess whether this finding applies to the dolutegravir-based regimens.

Keywords: Namibia, Antiretroviral Therapy, Guidelines, Evaluation, Viral Load, Switching, Predictor, Case-Control Study

1. Introduction

In line with the World Health Organization's (WHO) antiretroviral therapy (ART) guidelines, Namibia's ART guidelines recommended that switching from first- to second- line ART was to be implemented when the following criteria were met: when the viral load (VL) at six months was >1000 copies/ml; a confirmatory VL test >1000 copies/ml three months after the first was >1000 copies/ml; and adherence has been ensured between the VL tests (1). (NB: VL is determined on blood samples by Reverse Transcriptase-Ribo-Nucleic Acid polymerase chain reaction.) Meeting these guideline requirements was ideal for switching to be implemented, and delayed switching is associated with increased morbidity and mortality (2-4). Narainsamy *et al*., identified modifiable programmatic factors that were associated with delays in switching, including defaulting appointments, unavailability of blood results, incomplete notes for follow-up, and loss of patient records (5). To avert the resultant morbidity and mortality, Shroufi *et al.,* recommended immediate switching from first- to second- line ART when the first VL was greater than 1000 copies/ml (6). In view of Narainsamy *et al's* findings and the recommendations of Shroufi *et al*, it was imperative for us to ascertain whether the Namibian public health system had experienced similar challenges. It was important to find out the extent to which the ART switching recommendations

in Namibia's ART guidelines were complied with in routine clinical care, in addition to ascertaining whether it would have been more appropriate to implement immediate switching from first- to second-line ART if the patient's first VL was >1000 copies/ml. This is important in Namibia given that Namibia has one of the highest prevalence rates for HIV in sub-Saharan Africa (7). Consequently, we conducted this study to answer these questions as well as sought to identify the predictors of first-line treatment failure. The findings will be used to improve the future management of patients with HIV in Namibia and similar settings.

2. Method

2.1 Study design, population, and sample size

This was a retrospective study – a case-control study, nested within the cohort of patients receiving antiretroviral therapy at Eenhana district hospital, Namibia. The hospital is in Northern Namibia and provides comprehensive services to patients with HIV.

In our study, a case was defined as a patient receiving second-line antiretroviral therapy and the controls were defined as patients receiving first-line antiretroviral therapy. The OpenEpi® calculator was used to calculate the required number of cases and controls to include in the study based on a confidence level of 95%; a power of 80%; a 1:1 ratio of cases to controls; a 40% hypothetical proportion of controls with exposure; and 60% hypothetical proportion of controls. The sample size calculated was 198 (99 controls and 99 cases). The controls were selected randomly from the list of patients who were receiving antiretroviral therapy (n=3,230); and the cases were conveniently selected based on available data from patients on second-line therapy (n=151).

2.2 Independent and dependent (outcome) variables

These were the independent variables, their levels presented in parenthesis:

- Gender (male and female);
- Age (years, continuous data);
- Antiretroviral therapy regimen (categories and actual regimens);
- Viral load categories (< or ≥ 1000 copies/ml);
- When the first viral load was measured (before, at, and after 6 months);
- When the second viral load was measured (before, at, and after 3 months after the first viral load);
- Adherence to ART (good, fair, and poor);
- Patient education and counseling after the first viral load (yes or no);
- Reasons for switching ART (virologic failure, virologic and immunologic failure, and clinical failure);
- Duration the patients had spent on first-line antiretroviral therapy (years, continuous data); and
- Clinical events (experienced or not experienced)

The outcome (dependent) variable, and its levels are presented below:

- The last recorded ART regimen (second-line ART, and first-line ART).

From the list above, independent variables were subsequently selected for inclusion in the regression model based on clinical reasoning and time relationships.

2.3 Definitions:

- Virologic failure was defined as a VL persistently >1000 copies/ml following two consecutive measurements separated by three months, including adherence support intervention (1).
- Switching to second-line ART represented first-line treatment failure, which was backed by high VL (>1,000 copies/ml) test results. Maintenance on first-line ART represented first-line treatment success, also backed by undetectable VL or VL <1000 copies/ml.

2.4 Data analysis

The patients' records were distributed to the two outcome groups, namely: treatment success (maintained on first-line ART) and treatment failure (switched to second-line ART). For descriptive purposes, means and standard deviations for the continuous variables, and proportions for the categorical variables were calculated. Comparisons of means (and standard deviations (SD]) and proportions between the two outcome groups were conducted using the Students t-test for continuous variables, and Pearson's chi-square for categorical variables. To identify variables that were associated with switching and their effect sizes, we conducted binary logistic regression analysis. First, we conducted a univariate analysis to describe the effects of each of the following independent variables on switching, based on the crude hazard ratio (cHR): age, the first VL results, adherence, adherence counselling, opportunistic infections, length of time spent on first-line ART, gender, the non-nucleoside reverse transcriptase inhibitor (NNRTI), and the nucleoside reverse transcriptase inhibitor (NRTI) backbones in the first-line regimen. In addition, we conducted a Pearson correlation analysis to assess how the independent variables related with one another as well as to identify variables that strongly influenced others, to eliminate such variables from the regression analysis. Secondly, we conducted a multivariate logistic regression analysis using the enter method. In the multivariate regression model, the adjusted hazard ratio (aHR) of each variable was estimated having controlled for the other variables. As such, the result was the actual effect such a variable had on switching. Finally, we evaluated the regression model's predictive capacity.

This study was approved by the University of Namibia, and by the Ethics Committee of the Ministry of Health and Social Services: Namibia. The study was approved on the basis that patient confidentiality was assured via commitment to eliminate patient identifier data, no patients were to be directly involved in the study, and the data collected would be protected on a password protected computer only accessible to the researchers.

3. Results

A total of 183 patients (patient records) were included in this study. Most were female (n=133, 72.7%). At baseline, their mean (SD) age, and mean (SD) weight were 46.3 (12.8) and 54.1 (12.9), respectively. Most received Zidovudine (AZT)- and stavudine (d4T)- based first-line regimens: 52 (28.4%) and 54 (29.5%), respectively. Many received nevirapine (NVP)-containing first-line regimens (n=132, 72.1%). Few patients had VL test results at six months (n=15, 8.2%), with most having VL results later (n=149,

81.4%). Overall, 79 patients (43.2%) had a VL greater than 1000 copies/ml. Of these, few patients received the second VL at the recommended three months (n=4, 5.1%). Follow up VL results showed that more than 40% of patients had a VL above 1000 copies/ml (n=79, 43.1%). Sub-optimal adherence was documented for 9.8% (n=18) of the patients, and 16.4% (n=30) did not receive adherence counseling following their VL tests. The patients had spent a mean (SD) period of 5.5 (3.2) years on antiretroviral therapy.

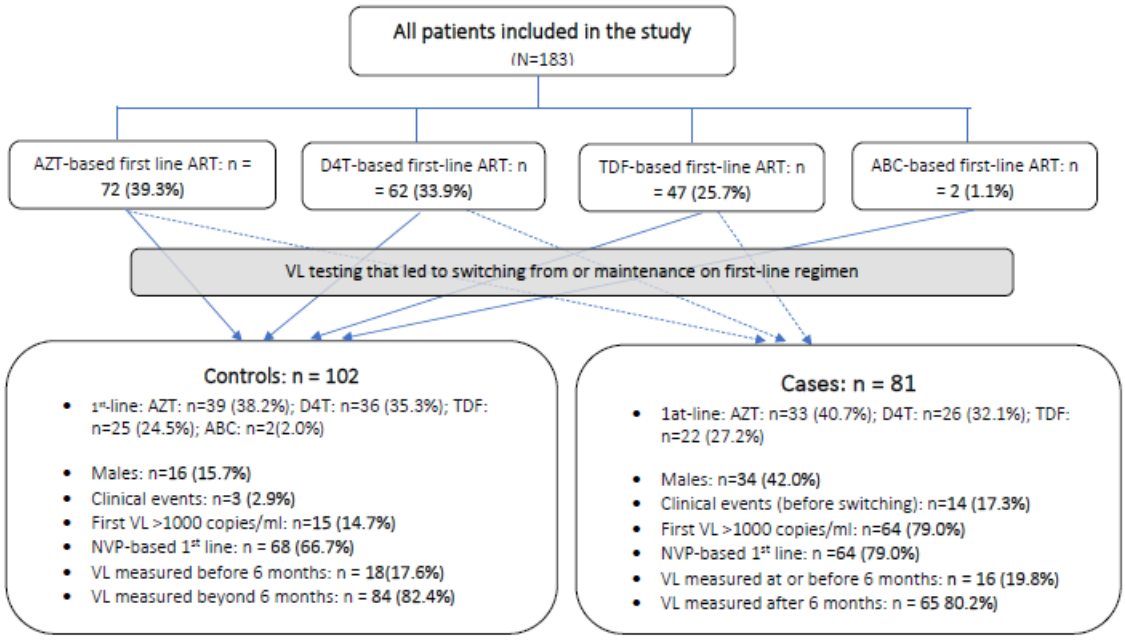
Out of the total of 183 patients, 81 and 102 patients respectively had experienced first-line treatment failure or treatment success. There was a significantly greater proportion of males than females who had experienced treatment failure (68% vs. 35.3%, p<0.001), (Table 1). The patients who experienced treatment failure weighed significantly less than the corresponding group of patients at baseline (41.8 kg vs. 49.9 kg, p<0.001), (Table 1). Between the treatment failure and treatment success groups, there was no difference in the first-line nucleoside-backbones that were prescribed (p=0.589), (Table 1). Similarly, there was no difference in the proportions who received NVP- or EFV- containing first-line ART regimens (p = 0.057). [NB: Between NVP and EFV containing first-line regimens, there was no difference in the mean (SD) time that was spent on first-line ART: 5.7 (3.2) vs. 5.0 (3.3), p = 0.201.] There was no difference in the proportions who received VL test results before six months, at six months, and after six months of ART initiation (p=0.935), (Table 1). Amongst the patients who had experienced treatment failure, the follow-up VL tests after switching to second-line therapy were implemented beyond the recommended three months mark for most of them (n=69, 82.1%) (Table 1). Fewer patients amongst those who experienced first-line ART failure had optimal adherence to their first-line ART versus those who had treatment success (38.8 vs. 61.2, p<0.001), (Table 1). Between the two groups, there was no significant difference in the receipt of adherence counseling following VL test results (58.2% vs. 41.8%, p=0.132), (Table 1). In addition, there was no difference in the period spent on first-line ART between the group maintained on first-line treatment and the corresponding group switched to second-line ART (4.8 vs. 4.9, p=0.773) (Table 1). All patients who were switched to second-line therapy had virologic failure (n=81). Amongst these, 7.4% (n=6) and another 7.4% (n=6) had experienced clinical failure and immunological failure, respectively. A significantly greater proportion of patients amongst those who had experienced first-line ART failure had experienced clinical events prior to switching versus those who were experiencing first-line treatment success (17.3% vs. 2.9%, p<0.001) (Table 1). A diagrammatic display of patient in the two groups with their similarity and differences is documented in figure 1. Amongst the patients who were switched to second-line therapy, improvement was recorded for 77.8% (n=63), 11.1% (n=9) still had a VL >1000 copies and were undergoing monitoring (Table 1), and the results were unknown for the remaining 11.1% (n=9).

Table 1: Evaluation of differences between the patients who were maintained on first-line ART and those who were switched to second-line ART.

Variable	1st- line Treatment success	Experienced 1st-line Treatment failure	p-value
Gender, n (%)			
Female	86 (64.7)	47 (35.3)	<0.001
Male	16 (32.0)	34 (68.0)	
Age			
Age (years), Mean (SD)	49.9 (10.5)	41.8 (14.0)	<0.001
Weight			
Weight 1 (Kg), Mean (SD)	55.9 (11.5)	51.8 (14.3)	0.033
Weight 2 (Kg), Mean (SD)	59.7 (10.0)	58.1 (7.8)	0.233
First line ART, n(%)			
ABC/3TC/NVP	2 (100)	_	
AZT/3TC/EFV	10 (55.6)	8 (44.4)	
AZT/3TC/NVP	29 (55.8)	23 (44.2)	
AZT/3TC/TDF	_	1 (100)	
AZT/FTC/NVP	_	1 (100)	
D4T/3TC/EFV	7 (100)	_	<0.001
D4T/3TC/NVP	29 (53.7)	26 (46.3)	
TDF/3TC/EFV	14 (63.6)	8 (36.4)	
TDF/3TC/LPV-r	1 (100)	_	
TDF/3TC/NVP	8 (36.4)	14 (63.6)	
TDF/FTC/EFV	2 (100)	_	
AZT-based	39 (54.2)	33 (45.8)	
D4T-based	36 (58.1)	26 (41.9)	0.589
TDF-based	25 (53.2)	22 (46.8)	
ABC-based	2 (100)	_	
NVP-containing	68 (51.5)	64 (48.5)	0.057
EFV-containing	33 (67.3)	16 (32.7)	
Second line ART			
ABC/3TC/AZT/LPV-r	_	3 (100)	
AZT/3TC/LPV-r	_	3 (100)	_
TDF/AZT/3TC/LPV-r	_	75 (100)	
First Viral load			
Before 6 months	10 (52.6)	9 (47.4)	0.935
At 6 months	8 (53.3)	7 (46.7)	
After 6 months	84 (56.4)	65 (43.6)	
Average time to test	28.4 (24.1)	21.9 (18.9)	0.049
>1000 copies, n (%)	15 (19.0)	64 (81.0)	<0.001
<1000 copies, n (%)	87 (83.7)	17 (16.3)	
Follow-up VL			
Before 3 months	_	8 (100)	<0.001
At 3 months	_	4 (100)	
After 3 months	15 (17.9)	69 (82.1)	
>1000 copies, n (%)	7 (8.9)	72 (91.1)	<0.001
<1000 copies, n (%)	95 (91.3)	9 (8.7)	
Average time to switching, mean (SD)	_	4.9 (2.8)	
Adherence, n (%)			
Optimal	101 (61.2)	64 (38.8)	<0.001
Sub-optimal	1 (5.6)	17 (94.4)	
Counselling after VL test			
Yes	89 (58.2)	64 (41.8)	0.135

Variable	1st- line Treatment success	Experienced 1st-line Treatment failure	p-value
No	13 (43.3)	17 (56.7)	
Reasons for Switching			
Clinical and Virologic	_	6 (100)	
Immunologic & Virologic	_	6 (100)	
Virologic	_	69 (100)	
Period (time), mean (SD)			
Spent on 1st-line ART	4.8 (3.0)	4.9 (2.8)	0.773
Spent on ART	4.8 (3.0)	6.5 (3.3)	<0.001
Clinical events			
Yes	3 (17.6)	14 (82.4)	0.001
No	99 (59.6)	67 (40.4)	
Follow-up Records			
Continue 1st line	95 (100)	_	<0.001
Improved	6 (8.7)	63 (91.3)	
VL high, monitoring	1 (10.0)	9 (90.0)	

Figure 1: Diagram showing the control and case groups came about, the similarities in first-line ART regimens, and the differences in other variables that predicted treatment failure



A total of 17 clinical events were documented in 17 patients. A few (n=5) could have been adverse drug reactions, for example rashes and urticaria, while others were more likely manifestations of failing first-line ART e.g. Tinea coporis, tuberculosis, and herpes (Box 1).

Box 1: Clinical events experienced by patients during first-line ART

List (number) of clinical events:
1. Rash, unspecified (2) 2. Cough, unspecified (1) 3. Not identified (2) 4. Skin infections, unspecified (4) 5. Tinea coporis (1) 6. Kaposi`s palate (1) 7. Herpes, unspecified (1) 8. Tuberculosis, unspecified (1) 9. Urinary Tract Infection (1) 10. Urticaria (2) 11. Inguinal lesions, unspecified (1)

Non-parametric correlation analyses showed one strong correlation between a first VL >1000 copies/ml and switching to second-line ART (r = 0.645). There were several but weak correlations. These included a negative correlation between age and switching ART (r = -0.328). Age correlated negatively with high VL (r = -0.262), and poor adherence was positively correlated with a high VL and switching ART (r = 0.268, and r = 0.334). Other correlations are presented in the appendix. [NB: While poor adherence to ART correlates with a high viral load and the resultant switching, the weak correlation allowed these variables to be included in the regression model. The same applied to other variables that are expected to strongly correlate with each other]

Univariate regression analysis showed that the following variables were associated with an increased risk of first-line treatment failure: sub-optimal adherence, the first VL greater than 1000 copies/ml, clinical events, and male gender. Absence of adherence counseling, increasing age, and increasing weight were not associated with an increased risk of first-line treatment failure (Table 2). All were included in the multivariate regression model, which showed that a VL >1000 copies/ml, clinical events, male gender, and the NVP-based ART regimen were associated with switching or treatment failure (Table 2).

Table 2: **Identification of predictors of switching from first to second–line therapy**

Variable		Univariate analysis			Multivariate analysis		
		cHR	**95% CI**	**p-value**	**aHR**	**95% CI**	**p-value**
Adherence	sub-Optimal Optimal (ref)	26.8 1	3.5 – 206.5	0.002	0.14	0.01 – 1.41	0.095
VL (copies/ml)	>1000 <1000 (ref)	21.8 1	10.2 – 50.0	<0.001	39.0	11.3 – 134	**<0.001**
Clinical events	Yes No (ref)	6.9 1	2.0 – 24.9	0.003	20.3	2.6 – 160	**0.043**
Gender	Male Female (ref)	3.9 1	2.0 - 7.8	<0.001	10.0	2.8 – 35.4	**0.001**
Adherence counseling	No Yes (ref)	1.8 1	0.8 – 4.0	0.138	2.2	0.6 – 8.1	0.250
NRTI-backbone	D4T TDF AZT (ref)	0.8 1.1 1	0.4 – 1.7 0.5 – 2.3	0.651 0.832	2.1 1.9	0.6 – 7.3 0.5 – 7.7	0.272 0.349
NNRTI	NVP EFV (ref)	1.9 1	0.96 – 3.9	0.059	6.0	1.4 – 25.1	**0.015**
Age		0.95	0.92 - 0.97	<0.001	0.95	0.91 - 0.99	0.026
Weight		0.98	0.95 – 0.99	<0.001	0.95	0.91 – 1.0	0.051
Time to 1st viral load		0.99	0.97 – 1.0	0.771	1.2	0.99 – 1.43	0.072

Key: (ref) = reference

3.1 Evaluation of the model

The null model without independent variables included in the equation showed that the predictive capacity of the model was 55.8% accurate. A total of eight variables were included in the binary logistic regression analysis equation. The model summary, according to the Nagelkerke-R square value, showed that 68.3% of the variation in the dependent variable was explained by the model (Table 3). Further, the Hosmer and Lemeshow test showed that the observed results were not different from the expected (p = 0.175) (Table 4). The predictive capacity of the model, as shown in the classification table, was 84.5%; an increase by 28.7 percentage points from the null model. As such the model proved effective in identifying key predictors of switching to second-line ART to help guide decisions pertaining to (efavirenz) EFV- and NVP- based ART regimens.

4. Discussion

We believe this is the first study in Namibia to assess whether the recommendations on switching from first- to second- line ART in Namibia's ART guidelines are being applied in practice. This is important as guideline adherence generally is seen as a key predictor of the quality of care across disease areas, and especially in this case to reduce morbidity and mortality (7-9). In addition, ascertaining potential predictors of first-line treatment failure to improve future management of these high-risk patients. We believe our findings provide evidence to determine whether an immediate switch to second-line ART would have been a better option for the patients to improve their care than an attempt to comply with

current ART guidelines on switching, amidst possible implementation challenges. Regarding programmatic issues, we found that VL tests were rarely conducted at the times recommended by the ART guidelines. Nonetheless, adherence counseling was typically provided in a timely manner following VL test results. We identified the following as predictors of first-line ART failure: unsuppressed VL at the first measurement; presence of clinical events during first-line ART; male gender; and nevirapine-containing first-line ART.

The finding that the first VL tests for most patients were conducted a considerable time after the recommended time exposes a shortfall in compliance to the ART guidelines in Namibia with respect to monitoring virologic response. A similar finding was documented by Fox *et al.,* (2020) and Thu Ya *et al.,* (2020), in South Africa and Myanmar, respectively. Fox *et al*. said that patients may well not have returned on time for testing. Alternatively, failure to conduct the test during clinic time could have been programme-related and not patient related (10, 11). However, in our study, the failure to comply with the recommended time for virologic monitoring was not associated with an increased risk of experiencing treatment failure. Whilst the delay did not increase the risk of experiencing first-line ART failure, compliance to the guidelines is expected to protect patients against clinical events that would have occurred due to further decline in the patients' immune system secondary to elevation in the VL (4). Nonetheless, we did not see any correlation between the time-to-measurement of first viral loads and the occurrence of clinical events. Consequently, this needs further investigation. In addition, our study was not designed to expose the causes of none compliance with the ART monitoring recommendations, the importance of which makes this a subject of future studies building on previous studies by our department investigating key issues associated with guideline compliance (8, 9). However, we noted that VL test results were typically accompanied by adherence counseling in a timely manner, which is encouraging. Interestingly, the absence of post VL test counseling did not increase the risk of patients experiencing first-line treatment failure since many patients had good adherence prior to this, which is also a key consideration going forward. The delay in conducting VL tests was also observed when the second VL was needed – that is, for patients who had a VL >1000 copies/ml at the first-test. Since VL tests are associated with improved treatment outcomes, such delays will likely increase the risk of experiencing serious clinical events associated with treatment failure, and needs to be addressed going forward (12, 13).

The finding that a high VL at first measurement was associated with an increased risk of occurrence of treatment failure would have been a natural expectation if poor adherence was prevalent. This is because poor adherence to ART would result in the emergence of resistant strains of the virus (14, 15). However, most of the patients had good adherence, even amongst those who experienced first-line ART failure (n=64, 79%). Consequently, we believe the discordance between good adherence and unsuppressed VLs may be associated with several possibilities. Firstly, the patients could have had pre-ART NNRTI resistance associated with single dose NVP for prevention of mother to child transmission (16, 17). Although there is cross-resistance between NVP and EFV, high level resistance to the latter requires mutations at multiple codons in comparison with NVP (16, 18, 19). Secondly, poor adherence to NVP-containing first-line ART regimens, induced by NVP related adverse drug reactions,

could have led to treatment failure (20). We are aware that NVP is associated with higher incidences and grades of skin- and liver- related adverse reactions than EFV. Perhaps, NVP-related adverse reactions could have been associated with the high risk of treatment failure associated with NVP, leading to treatment interruptions. Thirdly, there is a possibility that patients who received NVP-containing ART may have experienced drug interactions that led to sub-optimal concentrations of NVP in plasma. This would happen if NVP and rifampicin were co-administered since rifampicin is an inducer while NVP is a substrate of CYP 3A4 (21). As said above, NVP-containing ART regimens were more predisposed to treatment failure than EFV ones. This may be the subject of future research projects as we were unable to explore potential possibilities further with the data, we had available to us.

Our finding that male patients were more predisposed to first-line ART treatment failure could be associated with their sub-optimal adherence to ART. However, sub-optimal adherence was not a predictor of treatment failure in this study. Possibly, the poor health seeking behavior by the male patients is a plausible cause (22). Some studies, though, have shown less adherence to ART amongst females, while some found no gender differences on adherence (23, 24). This again will be explored further in view of the implications for future management to improve adherence to prescribed medicines.

The last predictor of treatment failure, namely the occurrence of clinical events, was rather challenging to evaluate. This is because clinical events such as opportunistic infections manifesting during first-line ART may be associated with sub-optimal adherence and unsuppressed/ high viral loads (25). In this regard, these clinical events are more of an outcome rather than potential facilitators of treatment failure. On the other hand, some clinical events were adverse drug reactions, which could compromise adherence and result in unsuppressed VL. However, the correlations between the clinical events and other variables were either weak or very weak. In addition, clinical events were typically treatable and did not always represent treatment failure because some patients who were maintained on first-line therapy had experienced some clinical events.

We are aware of a number of limitations with our study. The main limitation was the small number of patients included in the study. This was because of the 151 patients who had failed first-line ART, only 81 had the necessary data that was required for this study. The inclusion of fewer patients resulted in large effect sizes and very wide confidence intervals (26). Perhaps using a smaller ratio of cases to controls would have reduced these. Nonetheless, the statistical significance of the associations between the predictor variables and the dependent variable are documented in the literature and are backed with clinical reasoning. As such, our findings are valid regarding the direction of the associations, but not on the magnitudes of the effect sizes. We did not find a strong correlation between the delay in switching to second-line ART and the occurrence of clinical events, especially opportunistic infections. This was probably due to the lack of documentation of such events for many patients who were switched to second-line ART. Despite these limitations, our study highlights the importance of conducting operational research to identify challenges and their causes to use the findings to devise interventions to improve treatment success.

5. Conclusion

We have shown that the recommendations on timely virologic monitoring, as documented in the ART guidelines, were generally not complied with, but we were not able to assess whether this was a health system- or patient- related problem. However, the recommendation to provide adherence counseling at the receipt of VL results was adhered to. The delay in conducting virologic monitoring was not associated with first-line treatment failure. We conclude that un-suppressed VL at the first measurement was an indicator of treatment failure. Other factors, namely, male gender, clinical events, and NVP-containing first-line ART regimens were predictors of treatment failure (or switching to second- line ART). Since for most patients the VL was measured long after the recommended time, it is possible that a number of resistance mutations could have developed, rendering the need for adherence and the requisite counselling ineffective. For such patients, immediate switching to second-line ART would have been the most appropriate clinical decision.

References

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2. ***Maya L, Petersen LT, Geng EH, Reynold SJ, Andrew Kambugu, Robin Wood et al.** *Delayed switch of antiretroviral therapy after virologic failure associated with elevated mortality among HIV-infected adults in Africa*, AIDS, pp. 28(14): 2097 – 107. (2014)

The study indicates the importance of monitoring antiretroviral therapy outcomes by viral load tests. It emphasizes that when there is evidence of virologic failure, switching to an effective regimen should be implemented timeously to avoid severe clinical outcomes. This was an important reference for our study since we were looking into factors associated with switching from first- to second-line antiretroviral therapy.

3. ******Helen Bell-Gorrod, Matthew P Fox, Andrew Boulle, Hans Prozesky, Robin Wood, Frank Tanser et al.***The impact of delayed switch to second-line antiretroviral therapy on mortality, depending on failure time definition and CD4 count at failure.* 8, s.l. : American Journal of Epidemiology, Vol. 189, pp. 811 – 9. (2020)

This study assessed the impact of delayed switching on clinical outcomes. The authors concluded that early / immediate switching was associated with a decrease in mortality amongst the patients who had evidence of treatment failure during first-line antiretroviral therapy. This was relevant to our study since we assessed factors that were associated with switching, and also looked at whether it was appropriate to conduct immediate switching at the first indication of failing antiretroviral therapy.

4. **Victor Ssempijja, Gertrude Nakigozi, Larry Chang, Ron Gray, Maria Wawer, Anthony Ndyanabo et al.** *Rates of switching to second-line antiretroviral therapy and impact of delayed switching on immunologic, virologic, and mortality outcomes among HIV-infected adults with virologic failure in Rakai, Uganda.* BMC Infectious Diseases, pp. https://doi.org/10.1186/s12879-017-2680-6. (2017)

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This study identified programmatic challenges that prohibited appropriate monitoring of antiretroviral therapy outcomes. As a result, there was a delay in switching was associated with increases in morbidity and mortality. Their study was prompted us to conduct and exploratory study to find out if their suggestion was applicable to Namibia.

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