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An Interrupted Time Series Analysis of the Second line Antiretroviral Policy Change from Lopinavir Boosted with Ritonavir to Atazanavir Boosted with Ritonavir Based Regimens in Namibia

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Abstract

Setting: Despite that ATV/r has a better safety profile than LPV/r, there is continued prescribing of LPV/r.

Objective: The impact of the policy change on switching from LPV/r to ATV/r was determined.

Methods: Monthly ART Patients by Regimen data from the MoHSS PMIS Dashboard was accessed for the second line LPV/r and ATV/r based regimens. Data collected were aggregated per month from January 2015 to March 2018. Results obtained were analyzed using R and Minitab. Forecasts of the data between April 2018 and January 2019 were done using Microsoft Excel spreadsheet.

Results: A downward trend of 127 patients being enrolled on LPV/r based after ATV/r introduction and an upward level of 210 patients being initiated on LPV/r based regimens every month were observed before and after the implementation of the guideline in January 2017. Though, the implementation was not rapid, the rate of switching patients from previous second line regimens was rapid from March 2017.

Conclusion: The policy change led to significant level and trend change in the number of patients switched from LPV/r based second line regimens to ATV/r based second line regimens.

Keywords: Policy change; Second line regimens; Antiretroviral therapy; Guidelines; Patients

Introduction

Over the last two decades, the treatment of people living with HIV/AIDS (PLWHA) has been evolving with different classes of drugs being introduced, often fast-tracked for approval [1,2]. The goal of therapy has been to improve the health outcomes of patients and allow them to integrate and be useful in the society in which they found themselves.

World Health Organization (WHO) introduced guidelines aimed at assisting low and middle income countries (LMIC) to adopt viable therapy regimens for PLWHA. In the 2016 WHO Guidelines on the Use of Antiretroviral drugs [3], atazanavir boosted with ritonavir was introduced as the preferred Protease Inhibitor (PI) backbone of second line regimens, while lopinavir boosted with ritonavir was the alternate PI. LMICs can adopt this recommendation when formulating or updating their guidelines. As at 2015, Clinton Health Access Initiative (CHAI) market estimated about 22% of adults on second line regimens were taking ATV/r as their PI backbone [4].

According to the WHO, 2.9% of patients on ARV were on second line regimens with LPV/r as the PI backbone, ATV/r is being used as an alternate to LPV/r [3]. Namibia has about 210 000 PLWHA; out of these, about 150 000 patients are on antiretroviral therapy (ART). Among the patients on ART in Namibia, about 5% are currently on second line regimens [5]. This percentage is higher than the 2.9% reported by the WHO (2010), however, it is believed that the number will go up over time.

First line regimens such as the Nucleoside Reverse Transcriptase Inhibitors (NRTIs) e.g. Zidovudine and Lamivudine and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) e.g. Efavirenz and Nevirapine, used as part of antiretroviral treatment (ART) regimens are known to have low genetic barriers, thus, they develop resistance to the drugs earlier compared to the second line regimens [6]. The implication of this is, patients that are being maintained on first line regimens will experience treatment failure due to development of resistance to the ARV over time [7].

The Ministry of Health and Social Services, Namibia introduced a new ART guideline in August 2014 [8]. It included the introduction of ATV/r as a preferred Protease inhibitor (PI) backbone for second line regimens in Namibia to replace LPV/r. Atazanavir is known to be safer compared to Lopinavir with regard to metabolic adverse effects such fat redistribution [9]. Thus, the introduction of the drug assumes a better compliance and treatment outcomes for patients that were previously on LPV/r based regimens.

Objective

The study sought to assess the implementation of the new ART guidelines with specific emphasis on the time to introduction of ATV/r as a PI backbone for second line regimens in Namibia. Also, to estimate the projected number of patients will remain on LPV/r based regimens by January 2019 as mentioned in Table 1 and Figure 1.

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t	Year	Date	LPVr	MA/LPVr (2)	CMA/LPVr (2)	St, It	St	Deseasonalise Yt/St	Tt	Prediction
1	Y1	Jan-15	3937	-	-	-	1	3930	4550	4558
2		Feb-15	4217	4077	4084	1.03	0.99	4245	4537	4507
3		Mar-15	3964	4091	4084	0.97	1	3953	4485	4497
4		Apr-15	4189	4077	4124	1.02	1	4173	4511	4528
5		May-15	4152	4171	4195	0.99	0.99	4184	4498	4463
6		Jun-15	4286	4219	4211	1.02	1	4296	4485	4474
7		Jul-15	4119	4203	4260	0.97	1.01	4073	4472	4522
8		Aug-15	4517	4318	4393	1.03	0.99	4565	4458	4412
9		Sep-15	4417	4467	4443	0.99	1	4425	4445	4437
10		Oct-15	4419	4418	4488	0.98	1	4401	4432	4450
11		Nov-15	4695	4557	4641	1.01	1	4694	4419	4419
12		Dec-15	4756	4726	4772	1	1	4778	4406	4385
13	Y2	Jan-16	4880	4818	4863	1	0.99	4927	4393	4351
14		Feb-16	4935	4908	5000	0.99	0.99	5006	4380	4317
15		Mar-16	5248	5092	5003	1.05	0.98	5350	4366	4283
16		Apr-16	4580	4914	4849	0.94	0.98	4692	4353	4249
17		May-16	4988	4784	4883	1.02	0.97	5135	4340	4216
18		Jun-16	4975	4982	4898	1.02	0.97	5147	4327	4182
19		Jul-16	4652	4814	4614	1.01	0.96	4837	4314	4149
20		Aug-16	4178	4415	4272	0.98	0.96	4366	4301	4115
21		Sep-16	4078	4128	4080	1	0.95	4283	4288	4082
22		Oct-16	3986	4032	3921	1.02	0.95	4208	4274	4049
23		Nov-16	3632	3809	3560	1.02	0.94	3854	4261	4016
24		Dec-16	2989	3311	3337	0.9	0.94	3188	4248	3984
25	Y3	Jan-17	3739	3364	3704	1.01	0.93	4008	4235	3951
26		Feb-17	4350	4045	4158	1.05	0.93	4687	4222	3918
27		Mar-17	4192	4271	4002	1.05	0.92	4540	4209	3886
28		Apr-17	3275	3734	3566	0.92	0.92	3566	4196	3854
29		May-17	3521	3398	3516	1	0.91	3853	4182	3822
30		Jun-17	3748	3635	3668	1.02	0.91	4124	4169	3790
31		Jul-17	3653	3701	3665	1	0.9	4040	4156	3758
32		Aug-17	3605	3629	3608	1	0.9	4009	4143	3726
33		Sep-17	3568	3587	3584	1	0.89	3989	4130	3694
34		Oct-17	3595	3582	3586	1	0.89	4041	4117	3663
35		Nov-17	3586	3591	3612	0.99	0.88	4052	4104	3631
36		Dec-17	3679	3633	3632	1.01	0.88	4180	4090	3600
37	Y4	Jan-18	3585	3632	3568	1	0.88	4096	4077	3569
38		Feb-18	3422	3504	-	-	0.87	3931	4064	3538
39		Mar-18	3377	-	-	-	0.87	3901	4051	3507
40		Apr-18	-	-	-	-	0.86	-	4038	3476
41		May-18	-	-	-	-	0.86	-	4025	3446
42		Jun-18	-	-	-	-	0.85	-	4012	3415
43		Jul-18	-	-	-	-	0.85	-	3998	3385
44		Sep-18	-	-	-	-	0.84	-	3985	3355
45		Oct-18	-	-	-	-	0.84	-	3972	3324
46		Nov-18	-	-	-	-	0.83	-	3959	3294
47		Dec-18	-	-	-	-	0.83	-	3946	3265
48		Jan-19	-	-	-	-	0.82	-	3933	3235

N.B: The data used and forecast results obtained are in red.

Table 1: Table showing predicted number of patients on LPV/r based second line regimens form April 2018 to January 2019.

Methods

Study design and setting

A cross-sectional interrupted time series analysis of all the national second line ART patients by regimen data from January 2015 to March 2018 in Namibia was conducted. Interrupted time series is a good study design when the impact of a new intervention in the public healthcare sector is being monitored [10-12]. Research ethics board approvals were obtained from MoHSS (Reference No. 17/3/3) and Ethics Committee of the University of Namibia (Reference No. SOPHA/209/2017). Patient informed consent was not required because only reported data were used in the study. This report adheres to the Reporting of studies

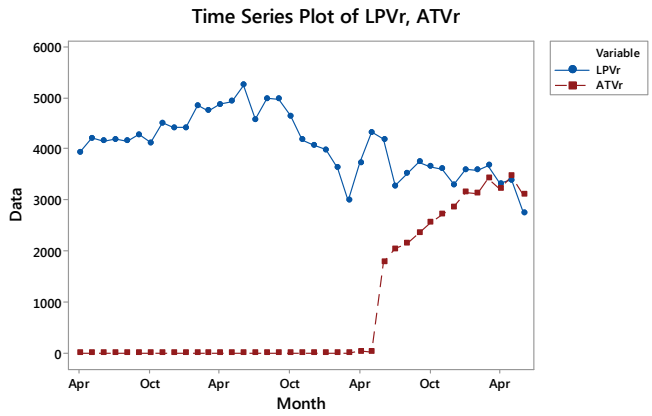

Figure 1: Time series plot of switching LPV/r to ATV/r based regimens in 6 month intervals.

Conducted by using the Observational Routinely-collected health Data statement.

Data sources

National second line ART Patients by Regimen data were retrieved from the MoHSS Pharmaceutical Management Information System Dashboard (PMIS Dashboard). ARV consumption data between the months of January 2015 to March 2018 were included in the study. The focus of the study was the adults on second line ARV regimens with LPV/r and ATV/r as the PI backbone. Adult patients' data were used in this study, considering the ethical clearance granted for the study was only for adults. The data obtained were aggregated into months and entered on a spread sheet prior to exporting into R studio® and Minitab® (Free Edition) that were used in the analysis of the data.

Study population

Aggregated monthly national ART Patients by regimen data of adult patients were included in the study. Data for LPV/r based regimens between January 2015 and March 2018 and ATV/r based regimens data between January 2017 and March 2018. Adult patients of Namibian origin currently on second line regimens in the public health sector of Namibia were included. Data were retrieved from the MoHSS Pharmaceutical Information Dashboard. Demographics of the patients were not included or required for the study.

Outcome measures

Our primary outcome was the time to implementation of the new ART guideline, with particular reference to ATV/r introduction as a preferred second line regimen. Secondary outcome included inference of the number of patients that should be on second line regimens based on ATV/r, if all the patients were switched to the drug as envisaged by the new guideline.

Population characteristics

Adult patients, from 18 years upwards, of Namibian origin currently on second line regimens in the public health sector of Namibia were included in the study Figure 2. Demographics of the patients were not included or required for the study.

Statistical analysis

The data were summarised using Microsoft Excel spreadsheet, aggregating the number of patients on LPV/r and ATV/r regimens on a monthly basis. The data were exported to R and Minitab, the software used in data analysis. ATV/r based regimens were reported first in January 2017 in the PMIS Dashboard, however, LPV/r based regimens has been used as PI backbone for second line regimens as early as 2010 [13]. Regimen characteristics were compared at 2 time points [1] peri-intervention period January 2016; and [2] post-intervention August 2017. The two predefined time points were selected a priori to identify any potential variability or nonstable health system utilization patterns of the population. Interrupted time series analysis was performed to examine the impact of the ART Guideline August 2014 on each of our primary and secondary outcomes of interest. The models quantify the time, level and trend change following the intervention, while accounting for the autocorrelation of observations. The 2014 guideline introduction was selected as the intervention, as it was the first year that ATV/r was officially introduced and promoted in the Namibian public health system. The onset date for the intervention was lagged nearly 12 months (until January 1, 2016) to account for the delay that would be required for rollout of the new guideline, the training of healthcare workers responsible for the treatment of patients on the new guideline, and the new regimen in particular and for the procurement and distribution of the regimen by the Central Medical Stores (CMS). Each year was divided into monthly intervals, spanning a total of 39 months during the study period (2015-2018) as shown in Figure 3. The outcome variables were the number of patients on LPV/r and ATV/r based regimens and the time to implementation of the 2014 ART guideline. The following segmented regression model was used:

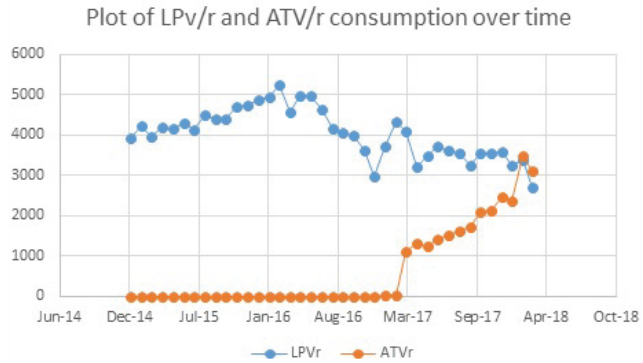

Figure 2: Scatter plot of LPV/r and ATV/r based second line regimens consumption over time.

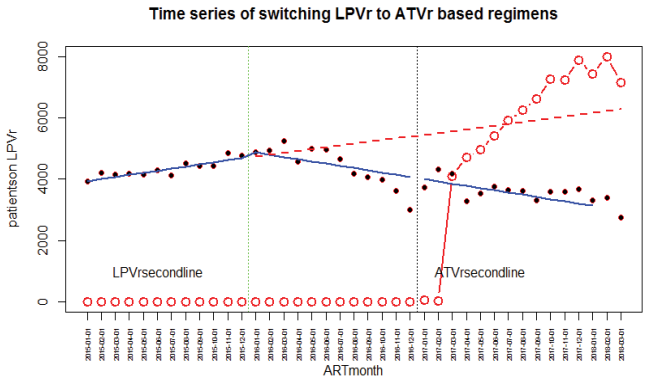

Figure 3: Time series analysis of switching LPV/r to ATV/r based regimens.

$$Y_t = \beta_0 + \beta_1 * T + \beta_2 * X_t + \beta_3 * T * X_t + e_t$$

Where, Y_t is the outcome, i.e. the number of patients that are switched from LPV/r based regimens to ATV/r based regimens at time t, T is the time (in months) that elapsed since the start of the study, X_t is a dummy variable indicating the pre-intervention period (coded 0), or the post-intervention period (coded 1); β_0 estimates the baseline outcome at T=0; β_1 is an estimate of the peri-intervention outcome trend (i.e. the change in outcome with time); β_2 is an estimate of the change in outcome immediately after the peri-intervention period, i.e. compared to the outcome at the pre-intervention period; β_3 the change in the post-intervention outcome trend compared to the pre-intervention outcome trend; e_t represents the random variability not explained by the model. For all statistical tests, a p-value of ≤ 0.05 was considered to be significant.

MS Excel 2007 was used to forecast the number of patients that will be on either LPV/r or ATV/r based regimens per month.

Results

In Table 2, an average of 4336 patients were on LPV/r based second line regimens between January 2015 and December 2016, this varies considerably from month to month (range: 2989–5248), prior to the introduction and consumption report of ATV/r. This number decreased to an average of 3533 (range: 2708–4329) between January 2017 and March 2018. The number of patients switched to ATV/r based second line regimens increased over time with an average of 1704 (range: 14 – 3471) patients between January 2017 and March 2018. Table 2 displays a reduction in the number of patients on LPV/r based regimens over time, however, a projected total number of patients on second line regimens is depicted in Figure 4 at approximately 7000, if every patient were switched to ATV/r based second line regimens at the end of March 2018.

Table 3 shows an increased level in the number of patients that were being switched to LPV/r based second line regimens before the implementation of the guideline with approximately 210 patients being initiated LPV/r based second line regimen every month (210.29; CI: -234.86, 655.45) however, the downward trend of the number of patients on the same regimen continued after the introduction of ATV/r based second line regimens, as can be seen on the graph. There was a downward trend in the number of patients enrolled on LPV/r based second line regimens (-127.22; CI -184.98, -69.46) monthly; this was observed by the spike in the number of patients switched to ATV/r based regimens monthly as shown in Figure 5.

The number of patients on LPV/r based second line regimens was predicted from April 2018 to January 2019. There was a decline over time, with the highest number of patients in April 2018 (3476) and lowest in January 2019 (3235).

Discussion

There was a slight increase in the number of patients before the implementation being initiated on LPV/r based second line regimens. There was an increase in the number of patients on LPV/r by about 210 patients immediately after the implementation, however, the trend went down by about 127 patients per month indicating that patients are being switched to ATV/r based second line regimens.

The Namibian ART guideline [8] does not describe the eligibility criteria to be used when switching patients to ATV/r based second line regimens. Prescribers assessed patients' eligibility to be switched to the new regimen, ATV/r based on some criteria such as viral load

Date	LPVr	ATVr	Time	Level	Trend
Jan-15	3937	0	1	0	0
Feb-15	4217	0	2	0	0
Mar-15	3964	0	3	0	0
Apr-15	4189	0	4	0	0
May-15	4152	0	5	0	0
Jun-15	4286	0	6	0	0
Jul-15	4119	0	7	0	0
Aug-15	4517	0	8	0	0
Sep-15	4417	0	9	0	0
Oct-15	4419	0	10	0	0
Nov-15	4695	0	11	0	0
Dec-15	4756	0	12	0	0
Jan-16	4880	0	13	1	1
Feb-16	4935	0	14	1	2
Mar-16	5248	0	15	1	3
Apr-16	4580	0	16	1	4
May-16	4988	0	17	1	5
Jun-16	4975	0	18	1	6
Jul-16	4652	0	19	1	7
Aug-16	4178	0	20	1	8
Sep-16	4078	0	21	1	9
Oct-16	3986	0	22	1	10
Nov-16	3632	0	23	1	11
Dec-16	2989	0	24	1	12
Jan-17	3739	31	25	1	13
Feb-17	4350	19	26	1	14
Mar-17	4192	1778	27	1	15
Apr-17	3275	2046	28	1	16
May-17	3521	2150	29	1	17
Jun-17	3748	1601	30	1	18
Jul-17	3653	2561	31	1	19
Aug-17	3605	2714	32	1	20
Sep-17	3568	2866	33	1	21
Oct-17	3595	3149	34	1	22
Nov-17	3586	3133	35	1	23
Dec-17	3679	3421	36	1	24
Jan-18	3585	3561	37	1	25
Feb-18	3422	3492	38	1	26
Mar-18	3377	3598	39	1	27

Table 2: ARV consumption by regimen showing the number of patients reported to be on each regimen by month.

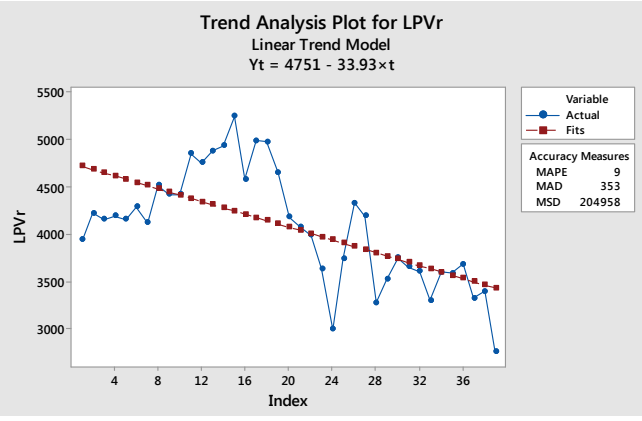

Figure 4: Trend analysis plot for LPV/r showing a downward trend in the number of patients over time.

Variable	Parameter Estimate (95% CI)	Standard Error	t Value	p-value
β0 (pre-intervention level)	3883.76 (3476.05, 4291.46)	200.83	19.339	<0.0001
β1 (pre-intervention trend)	64.91 (9.51,120.30)	27.29	2.379	0.023
β2 (pre-intervention level)	210.29 (-234.86, 655.45)	219.27	0.939	0.344
β3 (pre-intervention trend change)	-127.22 (-184.98, --69.46)	28.45	-4.471	<0.0001

p=0.05, f statistic=27.25

Table 3: Estimated coefficients for the interrupted time series analysis of the introduction of ATV/r based second line regimens.

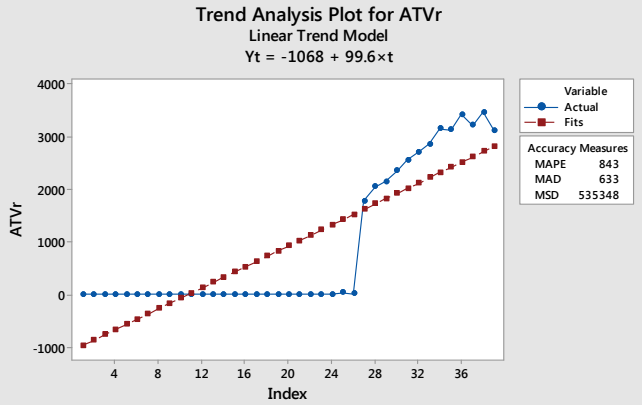

Figure 5: Trend analysis plot ATV/r showing an upward trend in the number of patients of patients over time.

suppression and being "stable" on their current regimens. The uptake of the new regimen was not rapid, as the first reported consumption was in January 2017 which was 16 months after the introduction of the new guideline. This has implications on the treatment outcomes of patients maintained on LPV/r based regimens or other second line regimens, due to the fact that ATV/r is known to be more tolerable and has less adverse reactions compared to LPV/r and NVP based second line regimens that were used prior to the introduction of ATV/r [13]. There were no competing interventions at or around the time of the introduction of the new guideline.

Considering the clinical work up necessary to switch a patient from one regimen to the other, the projected start date for ATV/r was not met, until January 2017 when the first reported usage of the regimen was documented. This has an impact on the adherence of patients who has been informed about a regimen that is much better than their current regimens. Patients tend to lose confidence in the system and invariably their healthcare providers who promised a "better life" for them.

It took about 28 months (August 2014 to December 2016) for the implementation of the ART guideline [8] with regard to the introduction of ATV/r as preferred PI back bone for second line regimens in Namibia. The delay in the introduction of ATV/r may be due to the communications within the MoHSS and with its partners; training of personnel such as medical doctors, pharmacists and nurses who are responsible for the treatment or switching of eligible patients; availability of the new drug at the Central Medical Stores prior to or immediately after the introduction of the new regimen. From the predicted number of patients over the next 12 months, it is evident that switching of all patients from LPV/r based second line regimens to the preferred ATV/r based second line regimens will take a long time, thus, the impact of such delay in policy implementation on patients' health outcomes has to be determined after at least one year of policy implementation. Quantitative or qualitative research into prescribers' ability to implement the policy or hindrances to implementation of the policy may be an area to be explored in the future.

Limitations

Underreporting by facilities is common, as seen in the fluctuating number of patients every month. Though, this may be expected due to the current manual reporting system that is used by the MoHSS.

Non-availability of updated reporting parameters for ATV/r on EDT/EPMS, prior to, during or after the introduction of ATV/r, thus, possibly hampers the reporting of the regimen consumption.

Reporting rates by the facilities that are required to submit monthly reports to the national level contributes to accuracy or completeness of reports available on the PMIS Dashboard.

Policy makers and implementers should work together in ensuring the success of policies that has far reaching impact on the healthcare system and welfare of patients and the nation as a whole.

A population level design was used in the study based on a national database. The impact of time varying covariates such as programmatic and economic impacts could not be accessed. Also, we could not assess patient-level and provider-level variables.

Also, having used secondary data from the national database, we could not validate its accuracy despite the quality control measures being put in place by the MoHSS.

Nonetheless, this study provides a true reflection of the current situation in Namibia and possibly, other LMICs.

Conclusion

The implementation of the August 2014 ART guideline incorporating the use of ATV/r as PI backbone did not take off immediately, but it took about 28 months before the first consumption reports were made. With the increasing number of patients that are failing first line regimens due to varying reasons, implementation of such guidelines should be given priority so as to minimize the morbidity or mortality that may occur due to late initiation/switching of patients that are failing the regimens they are on [14]. One observation that was made in the 2014 guideline was the absence of the eligibility criteria for patients to be switched to ATV/r. also, ATV/r based second line regimens were not categorically asserted as the preferred option of patients on second line ART, and however, this was addressed in the 5th edition of the ART guideline released in 2016 [15].

Recommendations

A formal system for implementation of guidelines in specified time frame, guided by the activities necessary to accomplish the goals of the guidelines needs to be set up.

Integrating the healthcare delivery reporting systems electronically will minimize underreporting and provide full picture of the ARV regimens used by patients and number patients on various regimen

will be known. If reports are being generated simultaneously as patients are seen, it will minimize underreporting or non-reporting of activities performed or consumption data of ARVs.Having a program for the facilities for every service provided that feeds into the national EPMS program will enhance the actual quantification of the number of patients on different regimens at a particular time.

Ensuring that every stakeholder are carried along during implementation of guidelines is important, considering the rising number of patients that are failing first line regimens and those that are yet to be transitioned to the preferred ATV/r regimen [16].

Declarations

- Ethical approval was obtained from the Ethics Committee of the Ministry of Health and Social Services and Ethics Committee of the University of Namibia.Consent for publication - Not applicable
- The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
- There was no competing interest in the conduct of this study.

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- BAA did the write up and final data analyses. KD did the initial data analysis and review of the manuscript. TWR did the review and gave new insights to the write up. BKDS reviewed part of the manuscript.
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