RESEARCH ARTICLE

Prevalence and predictors of virologic failure among HIV patients on antiretroviral therapy in Makueni County: a cross-sectional study [version 1; peer review: 1 approved with reservations]

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Abstract

Background: The growing number of people on antiretroviral therapy in Kenya has led to a decrease in HIV morbidity and mortality. However, virologic failure (VF) threatens to reverse these gains. In Makueni County, existing data indicate challenges in achieving viral load (VL) suppression among persons living with HIV (PLHIV). Few studies have been carried out investigating VF in the region despite its high incidence of HIV infections.

Methods: An analytical cross-sectional study was conducted among PLHIV in Makueni County to investigate the determinants and estimate the prevalence of VF. The prevalence of VF and its associated 95% exact binomial confidence interval was estimated, and a mixed-effects logistic regression model used to evaluate the relationship between the predictors and VF.

Results: The estimated period prevalence of VF between October 2018 and June 2019 was 13.2% (95% CI: 12.7%–13.8%). Being 15 years or older (aOR=0.53; 95% CI: 0.44 – 0.645) and having blood samples tested for reasons other than baseline VL measurement was associated with lower odds of VF: breastfeeding mothers (aOR=0.1; 95% CI: 0.01 – 0.97); clinical failure (aOR=0.08; 95% CI: 0.01 – 0.44); confirmation of VF (aOR=0.2; 95% CI: 0.07 – 0.62); no VL data (aOR=0.06; 95% CI: 0.01 – 0.31); routine VL (aOR=0.04; 95% CI: 0.01 – 0.12); drug substitution (aOR=0.03; 95% CI: 0.01 – 0.08). Taking ABC-based, AZT-based, or other non-TDF-Based regimens increased the odds of VF (aOR=1.61; 95% CI: 1.34 – 1.94), (aOR=1.75; 95% CI: 1.52 - 2.01), and (aOR=1.55; 95% CI: 0.99 - 2.44) respectively.

Conclusion: This study showed that over 13% of HIV patients on ART in Makueni County had VF between October 2018 and June 2019. The significant risk factors associated with VF were found to be age lower than 15 years, taking a non-TDF-based ART regimen, and blood

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sampling for baseline VL measurements.

Keywords
Virologic failure, prevalence, predictors, HIV patients, antiretroviral therapy, Makueni County.

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Introduction

Over the last decade, Kenya has made tremendous strides towards the control of the HIV epidemic; reporting a 68.5% reduction in HIV incidence between 2013 and 2021.[1,2] This reduction has been attributed to the dramatic increase in antiretroviral therapy (ART) coverage from 5000 in 2003 to 1,199,101 in 2021 among people living with HIV (PLHIV).[1,3,4] Emerging virologic failure could reverse these gains especially in areas where virologic monitoring has not been implemented in concert with ART scale-up.[3,5,6] Virologic failure (VF) refers to a persistently detectable viral load (VL) exceeding 1000 copies/ml after at least six months of ART based on two successive measurements done within a three-month interval (with adherence support between measurements).[7]

The prevalence of VF is an important metric for the global control of HIV.[8] In sub-Saharan Africa, the overall proportion of patients experiencing VF has been reported as 14% with a range from 0–43%.[9–12] A study in Malawi reported VF in 32% of inpatients on ART between 2015 and 2017.[13] A VF rate of 11.5% was reported in Northern Ethiopia after a median time on ART of 36 months.[14] In Tanzania 25.4% of children on ART for four years experienced VF.[15] In Kenya, 24% of adult patients on ART had VF between 2008 and 2011.[3,5] A failure rate of 34% was reported among children 18 months to 12 years on first-line combination ART followed for a median 49 months.[6]

The predictors of VF have been largely grouped into patient and regimen-related factors.[16,17] Among the patient-related factors, age, WHO stage, CD4 count, clinician skill level, suboptimal adherence, and treatment history have been highlighted as important predictors of VF.[11,18–22] A meta-analytic study reported that about 70% of patients with VF would be virally suppressed following an adherence intervention.[23] Additional factors including rural residency, gender, treatment interruption, opportunistic infections and tuberculosis (TB) co-infection were significantly associated with VF.[24–26] Regimen-related factors including the potency and tolerability of the ART regimen have been reported as predictors of VF.[17,27,28] Poor tolerability due to unpalatable formulations, toxicity and adverse drug events, large ART pill burden, high frequency dosing and complex handling of drugs increased the odds of VF.[16,26,29–32] In Kenya, little has been published on VF. However, the few available studies identified predictors of VF among them poor drug adherence, young age, male gender, being married, low socio-economic status and clinical stage of disease.[3,5,33] With VF being strongly predictive of higher risk of advanced disease and death,[13,34] the economic burden associated with VF presents a challenge to the ART programs involved, and has potential serious public health implications for Kenya's HIV response which is heavily dependent on external resources.[1]

The objectives of this study were to estimate the prevalence of virologic failure in HIV patients in Makueni County during the period of October 2018 and June 2019, and to identify the socio-demographic and regimen-related risk factors for virologic failure among the patients in Makueni County, Kenya.

Methods

Study area and design

The study site was Makueni County, one of the 47 counties in Kenya located on the South-eastern part of the country. In 2020 the prevalence of HIV in Makueni County was 3.5%,[35] with the county displaying a mixed epidemic pattern where HIV prevalence varied between 3%-10% among the general population and 23-30% among key populations.[1] Data indicate that challenges faced with HIV epidemic control in Makueni County include moderate ART coverage with 21% unmet need, moderate testing inefficiencies, high mother to child transmission and low VL suppression among children.[36] HIV services in Makueni County include HIV testing and treatment, prevention, and care services. These services are available for high risk populations, PLHIV and their partners, families and caregivers, according to the Kenya national guidelines.[37] An analytical cross-sectional study design was employed to estimate the prevalence and identify the predictors of VF among PLHIV in Makueni County between October 2018 and June 2019, the period for which the data were available.

Data

Data from this study were abstracted from the National Viral Load/early infant diagnosis (EID) monitoring system. This system is a repository of HIV VL and EID data and is managed by the National AIDS and STI Control Programme (NASCOP). Briefly, NASCOP spearheads the Ministry of Health's interventions in tackling HIV/AIDS through policy formulation, coordination of procurement and supply chain management, training and monitoring and evaluation of the HIV response.[38] The national VL/EID system is an electronic data management system for monitoring patients. It contains patient information on medication and ART history and demographic data. Health facilities feed data into the system which is available publicly via an interactive computer interface tool that graphically represents programme indicators.[39,40]

Data collected from all PLHIV across all ages, resident in Makueni County and who had VL tests done between October 2018 and June 2019 in point of care facilities under the national VL/EID monitoring system were included in the study.

Additionally, those classified as receiving ART by either having detectable blood levels of selected ART or by reporting current ART use were also included. On the contrary, all PLHIV in Makueni County on ART for six months or less and those with missing information on key variables and/or invalid VL outcomes were excluded. An initial screening of the database showed that 23,067 entries were made between 2018 and 2019 from health facilities in Makueni County. A total of 16,340 eligible participants met the inclusion criteria and were selected for this study.

Study population, eligibility and selection of participants

A simple random sampling design was employed with a sampling frame that comprised all PLHIV with VL test results from point of care centers in Makueni County and who were enrolled in the national VL/EID monitoring framework between October 2018 and June 2019.

Outcome definition

For this study, cases were defined as those with VF identified as detectable viral load ≥1,000 copies/ml after a minimum of six months on ART, as per the Kenya national treatment guidelines.[37]

Ethical considerations

Ethical approval for this study was granted by the Kenyatta National Hospital and University of Nairobi joint Ethics and Research Committee (KNH-ERC/A/508) on 14th December 2022. To safeguard participant confidentiality, any identifying information contained in the data was removed during the abstraction process.

Statistical analysis

All analyses were performed using R Statistical Software (v4.3.0; R Core Team 2023). Table 1 shows the predictor variables. Continuous variables were summarized using medians and ranges. For qualitative variables, frequencies and proportions were computed. The prevalence of VF and its associated 95% exact binomial confidence interval were estimated. This was followed by univariable mixed-effects logistic regression analysis to assess the effect of each predictor on VF. Code for the analysis is available as extended data.[41] The inclusion of age as continuous predictor in the univariable models yielded insignificant results, *age* was grouped into two categories <15 years and ≥15years. The variables "sub-county" and "facility" were included as random effects to account for clustering. At this stage, a liberal P<0.20, was used to evaluate the significance of each of the predictors. Significant variables from the univariable analysis were included in a multivariable model where a backward stepwise approach was used to eliminate variables at P≥0.05. Notably, to minimise confounding, exclusion of these variables from the model was only considered if their removal resulted in a less than 30% change in the effects of the remaining variables.[42] Two-way interactions were fitted between the remaining variables of the final model and assessed for significance.

Table 1. Predictor variables and their measurements.

Variables	Measurement of the predictor variables
Age (continuous)	This was captured in years
Sex (nominal)	This was captured as male or female
Residence (nominal)	The sub-county where the participant was domiciled
Health Facility (nominal)	One among the 82 facilities captured in the dataset where participant VL results were dispatched
Implementing partner (nominal)	The organizations partnering with the health facilities to provide HIV care and services. These were categorized as CHS - Naishi, CHAK-CDC HIV AIDs Program, AIDs Healthcare Foundation (AHF) and No partner
Sample type collected (nominal)	This was captured as dried blood spots (DBS), Whole blood, and Frozen plasma
ART Regimen (nominal)	This was the participant ART combination therapy. The possible combinations of ART for newborns, infants, children, adolescents, and adults included: Abacavir (ABC) Based regimens ABC+3TC+LPV/r; ABC+3TC+EFV; ABC+3TC+DTG; ABC+3TC+ATV/r; or ABC+3TC+NVP Zidovudine (AZT) Based regimens AZT+3TC+NVP; AZT+3TC+LPV/r; AZT+3TC+EFV; AZT+3TC+ATV/r; or AZT+3TC+DTG Tenofovir (TDF) Based regimens TDF+3TC+DTG; TDF+3TC+EFV TDF+3TC+NVP; TDF+3TC+ATV/r or TDF+3TC+LPV/r Other Drug resistance testing based second-line

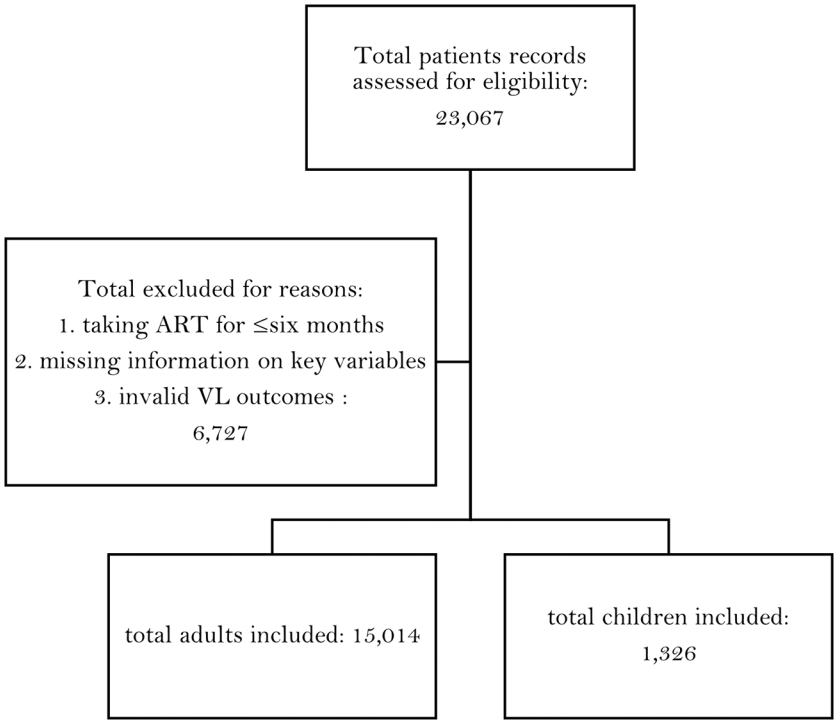

Figure 1. Flow chart of the sample size description.

Results

Descriptive statistics

All PLHIV in Makueni County and enrolled in the national VL/EID database were assessed for eligibility. An initial screening of the database showed that 23,067 entries were made between 2018 and 2019 from health facilities in Makueni County. A total of 16,340 eligible participants met the inclusion criteria and were selected for this study. Among those included, 15,014 were adolescents and adults aged ≥15 years, and 1,326 were children aged 0-14 years (Figure 1).

Table 2 shows the descriptive statistics of the study. During the study period, the median age of the participants was 43 years (range: 0-93 years). Of the participants, 69.6% (n=11365) were female with 83.3% enrolled on a TDF-based

Table 2. Descriptive statistics of HIV patients on ART in Makueni county for the period between October 2018 and June 2019.

Variable	Values	Median	Range	Frequency n (%)
Sex	Male	-		4975 (30.4)
	Female	-		11365 (69.6)
Age	0.0-93	43	33; 52	
Subcounty	Kaiti	-		1639 (10.0)
	Kibwezi East	-		3073 (18.8)
	Kibwezi West	-		4217 (25.8)
	Kilome	-		1119 (6.8)
	Makueni	-		3860 (23.6)
	Mbooni	-		2432 (14.9)
Partner	AHF	-		1311 (8.0)
	CHAK-CDC	-		945 (5.8)
	CHS-Naishi	-		13343 (81.7)
	No partner	-		741 (4.5)

Table 2. *Continued*

Variable	Values	Median	Range	Frequency n (%)
Sample type	DBS	-		16059 (98.3)
	Frozen plasma	-		239 (1.5)
	Whole blood	-		42 (0.3)
Justification for VL testing	Baseline	-		18 (0.1)
	BF mothers	-		8 (0.05)
	Clinical failure	-		13 (0.08)
	Confirmation of VF	-		867 (5.3)
	No data	-		17 (0.1
	Other	-		4 (0.02)
	Routine VL	-		13811 (84.5)
	Single drug substitution	-		1602 (9.8)
ART- Regimen	ABC	-		1016 (6.2)
	AZT	-		1575 (9.6)
	Other	-		136 (0.8)
	TDF	-		13613 (83.3)

ART regimen (n=13613) The estimated period prevalence of VF between October 2018 and June 2019 was 13.2% (95% CI: 12.7%-13.8%).

Analytic statistics

From the results of the univariable analysis (Table 3), sex, age, partner, sample type, ART-regimen, and justification were found to be significantly associated with VF at a 20% significance level and were subsequently offered to the multivariable model.

In the multivariable analysis, only *age, justification* and *ART-regimen* were found to be significant predictors of VF at the 5% significance level (Table 4).

Being 15 years or older reduced the odds of VF by a factor of 0.53 (aOR=0.53; 95% CI: 0.44-0.645) controlling for the ART regimen and the justification for VL testing. Compared to patients taking a TDF-based ART-regimens, those taking

Table 3. Univariable analysis of the determinants of virologic failure among HIV patients on ART in Makueni County during the period between October 2018 and June 2019.

Variable	Values	VF frequency (n=2162)	OR	95% CI Lower Upper	P-value
Sex	Male	716 (14.4)	1.16	1.05-1.28	<0.001
	Female	1446 (12.7)	Ref		
Age	≥15 years <15 years	372 (28.1) 1790 (11.9)	0.98 Ref	0.97-0.98	<0.001
Partner	AHF	192 (14.6)	0.71	0.43-1.17	0.068
	CHAK-CDC	130 (13.8)	0.66	0.45-0.98	
	CHS-Naishi	1722 (12.9)	0.66	0.49-0.90	
	No partner	118 (15.9)	Ref		
Sample type	Whole blood	8 (19)	2.01	0.92-4.38	0.072
	Frozen plasma	34 (14.2)	1.42	0.96-2.09	
	DBS	2120 (13.2)	Ref		

Table 3. *Continued*

Variable	Values	VF frequency (n=2162)	OR	95% CI Lower Upper	P-value
Justification for VL testing	BF mothers	2 (25)	0.1	0.01-0.97	<0.001
	Clinical failure	3 (23.1)	0.08	0.01-0.44	
	Confirmation of VF	349 (40.3)	0.20	0.07-0.62	
	No data	3 (17.6)	0.06	0.01-0.31	
	Routine VL	1671 (12.1)	0.04	0.01-0.12	
	Drug substitution	120 (7.5)	0.03	0.01-0.08	
	Baseline	14 (77.8)	Ref		
ART- Regimen	ABC based	271 (26.7)	2.95	2.54-3.42	<0.001
	AZT based	348 (22.1)	2.29	2.01-2.61	
	Other	27 (19.9)	2.13	1.39-3.26	
	TDF based	1516 (11.1)	Ref		

Table 4. Multivariable analysis of determinants of virologic failure among HIV patients on ART in Makueni County during the period between October 2018 and June 2019.

Variable	Values	aOR	95% CI Lower Upper	P-value
Age	≥15 years	0.53	0.44-0.645	<0.001
	<15 years	Ref		
ART- Regimen	ABC based	1.61	1.34-1.94	<0.001
	AZT based	1.75	1.52-2.01	
	Other	1.55	0.99-2.44	
	TDF based	Ref		
Justification for VL testing	BF mothers	0.16	0.02-1.19	<0.001
	Clinical failure	0.12	0.02-0.69	
	Confirmation of VF	0.34	0.11-1.07	
	No data	0.11	0.02-0.61	
	Routine VL	0.08	0.02-0.24	
	Drug substitution	0.05	0.02-0.17	
	Baseline	Ref		

ABC-based, AZT-based, or other regimens had about two times higher odds of VF (aOR=1.61; 95% CI: 1.34-1.94), (aOR=1.75; 95% CI: 1.52-2.01), and (aOR=1.55; 95% CI: 0.99-2.44) respectively, controlling for age and the justification for VL testing. Compared to patients whose blood samples were taken for baseline viral load measurement, those who gave samples for other reasons had lower odds of VF: breastfeeding mothers (aOR=0.1; 95% CI: 0.01-0.97); clinical failure (aOR=0.08; 95% CI: 0.01-0.44); confirmation of VF (aOR=0.2; 95% CI: 0.07-0.62); no VL data (aOR=0.06; 95% CI: 0.01-0.31); routine VL (aOR=0.04; 95% CI: 0.01-0.12); drug substitution (aOR=0.03; 95% CI: 0.01-0.08), controlling for their age and ART regimen.

Discussion

Prevalence of VF

In this study the VF rate was estimated at 13.2% among HIV patients in Makueni County. This is an improvement in the VF rate compared to the national reports in 2015 when more than 60% of adults receiving ART in Makueni County had VF.[43] This prevalence of VF is comparable with the findings from a national cross-sectional survey in Uganda that found a VF rate of 11%.[10] A similar burden has been observed elsewhere in Sub-Saharan Africa.[5,11,44–47] Nonetheless, the VF frequency was higher in Zimbabwe (30.6%)[48] and Togo (51.6%),[49] likely attributable to poor ART adherence.

Risk factors for VF

This study revealed that younger age was associated with higher odds of VF. This is similar to the findings of a national-based household survey in Kenya where decreasing age was associated with higher risk of VF.[2] A possible explanation for this finding could be that the youth face a myriad of challenges encompassing behavioral and psychosocial such as peer-related stigma, anxiety, lack of disclosure, sexual, reproductive and gender health concerns that may undermine adherence.[47,50–53] Similarly, a study in South Africa showed that adolescents aged <15 years had higher risk of VF compared to older patients.[54] High pill burden among adolescents could also explain the lack of adherence leading to VF.[51] These findings have also been replicated elsewhere, with younger patients demonstrating poor adherence or higher levels of drug resistance mutations.[11,15,50–52,55]

In this study, patients taking Tenofovir (TDF) based ART regimens had lower odds of VF compared to those on zidovudine (AZT) or abacavir (ABC) based or other regimens. This corresponds to the research findings of a study in Uganda which showed that patients initiated on AZT-based regimens as compared with TDF-based ones were more likely to have VF.[56] TDF-based regimens have been shown to be better tolerated with fewer side effects and hence better adherence.[57] Nonetheless, one study reported that patients experiencing VF on a TDF-based regimen had higher rates of the NRTI-resistance mutation – K65R.[52] Some studies have reported that ART-experienced patients have higher odds of VF compared to ART-naïve patients.[58,59] Data suggests that drug resistance testing should be done for all patients with HIV RNA levels >1000 copies/ml.[16] The absence of drug resistance in these patients indicates poor adherence. Drug-related reasons such as toxicity, frequency of dosing and pill burden should be investigated and strategies of optimizing ART adherence discussed.

Patients tested for VF because of suspected clinical failure, repeat testers after suspected VF, breastfeeding mothers, those with no VL data, those undergoing routine viral loads and those with drug substitutions had overall reduced odds of VF compared to those tested at baseline. This is corroborated by the finding that patients on routine monitoring registered the lowest levels of VF[10] due to enhanced adherence counselling and support. A Kenya nationwide analysis showed that the odds of VF were reduced as the frequency of VL monitoring increased.[39] Contradictory findings were reported in Uganda where adolescents who had detectable VL at baseline testing were more likely to have VF upon a repeat viral load test regardless of their adherence level and change in ART regimen.[53] Moreover, repeat testers who had active tuberculosis co-infection had higher odds of VF.[10]

Sex was not associated with VF in this study (Table 4). This agrees with the findings in other resource-limited settings which found no association between sex and VF.[55,60,61] Other studies have however showed that being male was associated with higher risk of VF due to reluctance to access healthcare and poor adherence compared to women.[25,46,51] In particular, a study in rural Cameroon found that men had higher odds of VF, independent of their adherence behaviours, ascribable to biological differences where men took longer to regenerate their CD4 count while on ART compared to women.[62] Contrastingly, in Tanzania and UK, females were reported to be more likely to experience VF than males.[15,27]

Considering other study variables, the organizations partnering with the HIV care facilities did not emerge as significant predictors for VF. This was contrary to the findings of others studies where different levels of quality of care that the partners offer to the patients, program level differences or factors such as variations in policy and their implementation were attributed to higher odds of VF.[11,52] Moreover, task shifting - comprising of the redistribution of tasks from highly qualified to less specialized healthcare workers where appropriate, to efficiently utilize the available human resources for health[63,64] - was shown to be most successful in areas where the community health workers provided care under the supervision of experienced ART providers.[63,65]

The sample type collected was not independently associated with VF in this study. This is supported by findings from other studies that showed that using either DBS or plasma samples to quantify HIV viral loads resulted in findings that were reliable and comparable.[59,66,67] In Malawi, one study reported that using plasma samples increased the precision of VL monitoring but was plagued by logistical and financial barriers thus unappealing in resource-limited settings.[59] On the contrary, DBS samples were shown to be cost effective and easy to transport at ambient temperatures, but associated with reduced sensitivity with viral loads <5000 copies/ml.[56,68]

This study is not without limitations. The use of routine data that were not collected for research purposes handicapped the research since several exposure variables were not captured. The study did not analyze data on variables like income, education, or distance to the health facility that would have allowed for the control of more concealed sociodemographic confounders, because these are not routinely recorded in public health facilities. Additionally, some important factors leading to VF such as ART adherence, should be considered as potential factors in the study, but such information was not

available. Failure to control for these factors may have led to residual confounding that could have biased the estimated odds ratios towards null. Furthermore, the study was based on outcome data collected at a single time point. Therefore, we might have overestimated the virologic failure rate due to individual temporal variability in biological markers. Nevertheless, the strength of this study rests on its sizeable statistical power afforded by the large sample size. Further investigations using cohort studies may be necessary to validate the study's findings.

Conclusions

This study showed that around 13% of HIV patients on ART in Makueni County had VF during the period between October 2018 and June 2019. The factors associated with VF were lower age (≤15 years), the type of ART regimen and the justification for VL measurement.

Consequently, (1) youth-friendly ART initiatives are warranted in this setting to reduce the VF prevalence among younger patients, (2) adherence support in patients taking regimens that are not TDF-based should also be prioritized, particularly in cases of suspected VF and before treatment switches, (3) routine viral load measurements should be conducted to ensure treatment success and prevent VF. However, if VF is confirmed, targeted HIV drug resistance testing to prevent unnecessary/premature switches should be considered.

Data availability

Underlying data

The viral load data for Makueni county used in this study is accessible upon placing a formal request to NASCOP, Kenya Dashboard (nascop.org).

Extended data

The virologic failure analysis script for this manuscript is available from Figshare: Makueni_Data_Analysis_0123.R. https://doi.org/10.6084/m9.figshare.22633552.v2.[41]

This project contains the following extended data:

- Makueni_Data_Analysis_0123.R (virologic failure Rscript)

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Keywords

- the idea here is to make it easy for anyone to use the keywords to search and find your article Online. But more than anything, keywords should help widen your search and retrieval of your article. These should not necessarily be the same words as in your title. Predictors, HIV patients are therefore not good keywords.

- Instead of 'Makueni County', i would put in 'Kenya'.

Introduction

- Authors should include recent VF rates. 2008-2011 is over 10 years ago.

- Authors are saying little has been published, but this is more than little. There is over 5 citations in this paragraph and part of it addresses the objectives of this current study? Unless authors rephrase this passage, there is no sufficient justification why this study is conducted since there are already findings from other studies reporting similar findings.

Methods

- It would be ideal to include some variables collected.

- To avoid repetition with the first paragraph of the results, I would suggest that authors remove this.

- For qualitative variables, frequencies and proportions were computed-How did authors achieve this in qualitative variables? Was this a mixed method study or quantitative study?

- Is figure 1 not supposed to be part of the results?

Results

- The results will need to be re-written detailing the available findings and linking with what is described in the methods. As is, the result section is not detailed enough.

- While this is probably important in other studies, what is the significant of analysing sample type in this case?

- Tables 3-4: p values for other response options are missing in the univariate analysis unless this is chi squared tests.

Discussion

- Authors should detail what could have led to such improvement?

- It would have been best to compare current regimens based on the current Kenyan ART guidelines. Is the country not initiating DTG as their first line option?

- Reference 57 is old and may not help in creating strong points for your argument? Beside, some of these regimens or drugs are probably not in the option list anymore.

- Authors should revise this paragraph 3 (of discussion) based on the results or include lack of data for other regimens or drugs as limitations.

- What is the difference between a detectable VL and VF?

- Does Kenyan MoH recommend VL testing at baseline?

- On reasons why males are likely to experience VF than females. The discussion does not provide underlying reasons for VF among males. What is causing men's reluctance to access healthcare services?

- Supporting partners are most likely to provide high quality care and subsequently improving quality of care within public health settings. There is a need to elaborate on how and why this could be associated to VF?

- Sample type: This study may not to be sufficient to report on this. I would remove anything to do with this from this study. This is also because authors do not provide possible reasons for such findings. If authors decide to keep this in the paper, they should provide more information on sample storage, sample preparation and RNA extraction? It might also be ideal to present some of the related findings in Pearson correlation analysis or related type of analysis.

Conclusion

- Drug resistance testing: This might be an expensive route than assessing and addressing adherence first. Please reconsider this statement

Data availability

- It is better to say data not necessarily specify VL data. Being specific to VL may prompt questions on where do we obtain the other data, unless that is what you are referring to, then you may need to be specific on where data for the other variables is?

See annotated PDF.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: ART drug optimization, adherence to ART or chronic medication, Systematic reviews, scoping reviews,

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.