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ORIGINAL ARTICLE

HIV suppression was maintained during the COVID-19 pandemic in Malawi: a program-level cohort study

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Abstract

Background and Objectives: Measures introduced to reduce the spread of SARS-CoV-2 by the Malawi government and the national HIV care program might have compromised treatment outcomes of patients living with HIV on antiretroviral therapy (ART). We studied viral load (VL) outcomes before and during the COVID-19 epidemic in Malawi.

Methods: In this population-based cohort study, we included all routine VL measurements collected from July 2019 to December 2020 in about 650 ART clinics in Malawi. We examined differences between pandemic periods (before/during COVID-19) for i) VL monitoring, and ii) VL suppression (VLS: < 1,000 copies/ml). For i) we studied the number of VL measurements over time and assessed predictors of missed measurements before and during COVID-19 in logistic regression models. For ii) we estimated the odds of VLS before and during the COVID-19 epidemic stratified by treatment regimen using generalized estimation equations adjusted for age, sex, time on ART, and type of biological sample. We imputed missing treatment regimens by population-calibrated multiple imputation.

Results: We included 607,894 routine VL samples from 556,281 patients. VL testing declined during COVID-19 (243,729; 40%) compared to before COVID-19 (365,265; 60%), but predictors of missing tests were similar in the two periods. VLS rates increased slightly from 93% before to 94% during COVID-19. Compared to before COVID-19, the odds of VLS increased during COVID-19 for patients on protease inhibitor-based (PI) regimens (adjusted odds ratio [aOR] 1.22, 95% CI: 0.99–1.49) and for patients on integrase strand transfer inhibitor-based (INSTI) regimens (aOR 1.10, 95% CI: 1.03–1.17). There was no difference in VLS between the two periods among patients on nonnucleoside reverse transcriptase inhibitor-based (NNRTI) regimens. VLS varied by age, sex, regimen, and duration on ART, ranging from 45.1% (95% CI 40.3–50.0%) to 97.2% (95% CI 96.9–97.4%).

Conclusion: There was a significant decline in VL monitoring during COVID-19, but we did not find clear evidence that the pandemic reduced VL suppression rates. Routine scheduled VL monitoring, targeted adherence support, and timely regimen switches for patients with treatment failure remain critical to improving VLS. © 2022 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: HIV; COVID-19; ART; Suppression of HIV replication; Malawi; SARS-CoV-2

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Data sharing: De-identified data used for this study will be made available to interested parties after the Malawi Ministry of Health approves the data access agreement. Data dictionary and analysis script will be made available through a request by email to thokozani.kalua@students.unibe.ch.

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What is new?**Key findings**

- Routine viral load monitoring among patients on antiretroviral therapy (ART) declined during the COVID-19 pandemic in Malawi, but predictors of missing viral load measurements were similar before and during the pandemic.
- The odds of viral load suppression was higher during COVID-19 compared to before COVID-19 for patients on integrase strand transfer inhibitor (INSTI) and protease inhibitor (PI) based treatment regimens, with no difference between the two periods for patients on nonnucleoside reverse transcriptase inhibitors (NNRTI).
- The distribution of imputed treatment regimens matched the true distribution of treatment regimens known at the aggregate level better when using population-calibrated multiple imputation than with standard multiple imputation.

What this adds to what is known?

- There have been concerns that measures to reduce the spread of SARS-CoV-2 introduced at a national level and at the ART clinics could have affected virologic outcomes. We did not find clear evidence that the COVID-19 pandemic reduced viral load suppression rates.

What is the implication and what should change now?

- Monitoring viral load during any crisis is crucial because virological control can be poor in any patient, but especially in children and adolescents. COVID-19 mitigation measures such as appointment spacing may not affect viral load suppression in a well-run, mature ART program.
- When dealing with missing categorical data where the distribution is known on aggregate from an external source, population-calibrated multiple imputation is preferable to standard multiple imputation.

1. Introduction

In Malawi, the first cases of infection with SARS-CoV-2, the coronavirus that causes the COVID-19 disease, were confirmed on 2 April 2020 [1]. Two weeks earlier, on 20 March 2020, Malawi's State President declared COVID-19 a national disaster and implemented various preventive measures, including suspending scheduled passenger flights and restricting nonessential national travel and gatherings.

The national HIV program introduced additional measures to reduce the spread of SARS-CoV-2 and free up staff to screen for and manage COVID-19 patients [2]. These measures included suspension of some services and, like in other countries around the region, the extension of drug dispensing intervals from 3 months to 6 months [3].

As in many other countries, there were concerns about the pandemic's impact on public health and the health system [4]. Patients may change their care-seeking behaviour because of the pandemic [5,6]. Antiretroviral therapy (ART) interruption caused by COVID-19-related clinical service disruptions may increase the risk of virologic failure and ultimately HIV-related mortality [7]. The negative impact on outcomes could be sustained even after ART services are resumed because patients progressing to AIDS may not recover fully.

In Malawi, significant changes were introduced in first- and second-line ART treatment regimens following the introduction of dolutegravir (DTG) in January 2019 and the scale-up of ritonavir-boosted lopinavir (LPV/r) in children [8]. DTG-containing regimens were recommended for all eligible adult patients who newly started ART [8]. Patients already on ART were also routinely transitioned to DTG-containing regimens with no requirement for an additional viral load test [8]. It was expected that the regimen transition would lead to a measurable increase in viral load suppression rates at the program level. However, the arrival of the COVID-19 pandemic at the same time raised concerns that disruptions to health services might have undermined HIV treatment access and outcomes. We thus examined virologic monitoring and suppression of HIV replication by different treatment regimens before and during the COVID-19 pandemic in Malawi's national HIV program.

2. Methods*2.1. Setting and data*

We analyzed viral load measurement data from the Malawi Laboratory Management Information System, which covers about 650 ART clinics out of about 750 clinics in the country. The HIV program's routine viral load monitoring schedule included the first measurement at 6 months after starting ART and then every 12 months. We used all routine viral load samples drawn within 9 months before and after the first confirmed case of SARS-CoV-2 in Malawi (1 July 2019 to 31 December 2020). We restricted analyses to routine viral load measurements, excluding measurements reported to be follow-up tests after a high viral load in a routine test or targeted tests in a clinically unwell patient. In addition, we excluded measurements if the previous viral load was done less than 11 months earlier to exclude targeted or follow-up tests mistakenly reported as routine tests. If two routine

measurements were drawn more than 11 months apart, both measurements were included. Lastly, we excluded samples for which the patient identification number, age, or sex was missing.

Current treatment regimen information was only introduced into the information system between July and September 2019 and the data was incomplete for the first few months. However, the frequency distribution of treatment regimens was known precisely from quarterly cohort reports from all ART facilities in Malawi. Only aggregated data were reported, which could not be linked to individual patients or viral load samples.

2.2. Variables

Our main outcome of interest was virologic suppression, defined as a viral load $<1,000$ copies/ml. This cut-off was chosen because the limit of detection of tests done on dry blood spot samples (DBS) is just above 800 copies/ml. Furthermore, this cut-off is clinically relevant as it is the threshold used for decisions on treatment performance by the Malawi HIV program and WHO [8,9]. Explanatory variables included the pandemic period the sample was drawn, the treatment regimen, age and sex of the patient, time on ART, and the specimen type. The pandemic period was defined as “before COVID-19” and “during COVID-19” for samples drawn between July 2019 to March 2020 and April 2020 to December 2020. Treatment regimens were grouped into integrase strand transfer inhibitor-based regimens (“INSTI”), non-nucleoside reverse transcriptase inhibitor-based regimens (“NNRTI”), and protease inhibitor-based regimens (“PI”). Specimen types included “DBS samples”, “Plasma”, and “Other/Unknown”. Age was grouped into 0-9, 10-19, 20-29, 30-39, and ≥ 40 years. Time on ART was defined as “first year” on ART, “second year”, “3+ years”, and “unknown”.

2.3. Viral load monitoring

To study viral load monitoring, we examined differences in the number of routine viral load samples drawn before and during COVID-19. In addition, we assessed potential differences between the two periods by: 1) comparing patient characteristics of measurements between the two periods, and 2) comparing the predictors of “missing a scheduled viral load” between the two periods. As our dataset did not contain information about missed viral load tests, we could not assess 2) directly. However, the program’s schedule of 12 months between routine viral load tests allowed us to assess missed tests indirectly. We examined all viral load measurements reported during the year before our study period, i.e., between 01 July 2018 and 31 December 2019. All patients who had a measurement during this time should have had a second measurement either in the “before COVID-19” or the “during COVID-19” period. We then studied drivers of “missing a

scheduled viral load” by comparing patients with and without a second viral load measurement in logistic regression models including age, sex, time on ART, and virologic suppression at first measurement. We fitted the model separately for the period before and during COVID-19 to examine whether predictors of missing tests had changed with the advent of the pandemic.

2.4. Multiple imputation of unknown treatment regimens

We used the aggregate quarterly treatment distribution data to multiply impute missing treatment regimens by population-calibrated multiple imputation [10]. We used multinomial logistic regression stratified by pandemic period as imputation model and included covariates virologic suppression, sex, age, specimen type, time on ART, and quarter. The calibration to the aggregate “true” distribution of treatment regimens was done by quarter. We generated 50 imputed datasets and combined results using Rubin’s rules [11]. [Supplementary Text S1](#) gives details on the imputation approach used. An implementation in R software of the population-calibrated algorithm for both categorical and binary incomplete data is available from https://github.com/naninatamar/population_calibrated_multiple_imputation. It can be directly applied to other datasets containing missing categorical or binary data. We also included a simulation study illustrating the application of the approach and its superiority to standard multiple imputation in the context of a categorical variable “missing not at random” (MNAR) [12].

2.5. Virologic suppression

We examined the proportion of measurements with virologic suppression over time and by treatment regimen. We estimated the odds of virologic suppression using generalized estimation equations assuming an exchangeable correlation structure for within-patients measurements. We included covariates pandemic period, treatment regimen, age, time on ART, sex, and specimen type. To account for the changes in first-line treatment regimens over the study period (the scale-up of DTG, an INSTI drug in adults and of LPV/r, a PI drug, in children), we included an interaction term between the pandemic period and treatment regimen. As changes in first-line regimens differed between adults and children we did an additional analysis, where we fitted the model to children or adolescents (0-19 years) and adults (≥ 20 years) separately.

2.6. Sensitivity analyses

In sensitivity analyses, we compared the population-calibrated MI approach to standard MI without calibration to the aggregated data of the distribution of treatment regimens ([Supplementary Text S1](#)). In addition, we fitted the virologic suppression model both to the complete case data restricted to non-missing treatment regimens and to the

original data, including an “unknown” treatment regimen category for missing treatment regimens.

2.7. Ethical considerations

We obtained approval to use the data from the Ministry of Health and ethics approval from the National Health Sciences Research Committee (approval number 2653).

3. Results

3.1. Descriptive analyses and multiple imputation

Of 765,321 routine samples, we excluded 63,087 (8.2%) with missing patient ID, age, or sex, and 94,340 (12.3%) due to a previous measurement in the same patient less than 11 months earlier. Overall, we included 607,894 samples from 556,281 patients in the analyses. Most samples were from female patients (400,842; 66%) and patients aged 40 years and above (316,623; 52%) (Table 1). For most samples, the treatment regimen was not reported at the individual level (443,279; 73%), with a large difference between the before COVID-19 (92% unknown) and during COVID-19 period (44% unknown). Reporting of treatment regimens increased over time, from almost 100% of missing treatment regimens in the third quarter (Q3) 2019 to 31% missing in the fourth quarter (Q4) 2020 (Supplementary Fig. S1). The distribution of population-calibrated imputed treatment regimens matched the “true” aggregated distribution of treatment regimens closely (Supplementary Fig. S1).

3.2. Viral load monitoring

Fewer viral load samples were drawn during COVID-19 (243,729; 40%) compared to before COVID-19 (364,165; 60%) with an especially low number of samples in the first quarter of the pandemic (Fig. 1). Among measurements, most baseline characteristics were similar in the two periods (Table 1), with slightly more patients on ART for 3+ years during COVID-19. Only 2.4% and 1.7% of samples before and during COVID-19 were from people newly initiating ART in these periods. To study predictors of missing measurements, we included 746,360 previous viral load measurements that should have been repeated during the study period (Supplementary Table S1). Characteristics of those with and without subsequent viral load measurement available were similar in the before and the during COVID-19 period. The predictors for subsequent missing viral load were similar before COVID-19 and during COVID-19 (Fig. 2). The odds of missing viral loads was lower during the pandemic than before for younger patients (<20 years) and for patients with the previous measurement in plasma rather than DBS. Unsuppressed viral load in the previous measurement was strongly associated with a missing subsequent viral load, but the

strength of association did not change with the advent of the pandemic.

3.3. Virologic suppression

The proportion of measured viral loads that were suppressed increased over time from 92.5% (95%-CI 92.4–92.6%) in Q3 2019 to 95.1% (95%-CI 95.0–95.2%) in Q4 2020 (Fig. 1). Samples of patients on INSTI-based regimens showed the highest virologic suppression (>95%), while viral load was not suppressed in about 20% of samples from patients on PI-based therapies (Fig. 1). In line, estimated odds of virologic suppression were highest for INSTI-based regimens and lowest for PI-based regimens (Fig. 3). Regression analysis also suggested differences in virologic suppression between pandemic periods: The adjusted odds ratio (aOR) comparing the during COVID-19 to the before COVID-19 period was 1.10 (95% CI: 1.03–1.17) for INSTI-based and 1.22 (95% CI 0.99–1.49) for PI-based treatment regimens, while there was no difference for NNRTI-based regimens (aOR 1.00, 95% CI: 0.90–1.12). In addition, there was a substantial increase in the odds of virologic suppression by increasing age, by longer time on ART, in women compared to men, and in plasma compared to other samples.

When fitting the model to children or adolescents and adults separately, there was no difference in the odds of virologic suppression between pandemic periods for NNRTI-based regimens (Supplementary Fig. S2). In children and adolescents, only PI-based regimens showed a statistically significant increase in the odds of virologic suppression during COVID-19 (aOR 1.25, 95% CI 1.02–1.54) with no significant difference between the two periods for INSTI-based regimens (aOR 1.05, 95% CI 0.85–1.46). In adults, the opposite was the case with a significant increase in the odds of virologic suppression during COVID-19 in INSTI-based regimens and no statistically significant difference between pandemic periods in PI-based regimens (Supplementary Fig. S2). Predicted probabilities of virologic suppression varied widely, ranging from 45.1% (95%-CI 40.3–49.9) to 97.1% (95%-CI 97.0–97.3), with younger age being the most relevant predictor (with the largest estimated effect size) for virologic failure (Fig. 4).

3.4. Sensitivity analyses

The distribution of imputed treatment regimens from standard multiple imputation matched the “true” aggregate distribution of treatment regimens worse than population-calibrated imputation, especially for the before COVID-19 period (Supplementary Fig. S1). Point estimates of the standard multiple imputation approach were similar to the ones from the population-calibrated imputation approach, but confidence intervals were narrower (Supplementary Fig. S3). Compared to model fits to imputed data, model

Table 1. Viral load suppression and baseline characteristics of patients of routine viral load measurements overall and by pandemic period

	Overall	Before COVID	During COVID
No. of samples	607,894	364,165	243,729
Viral load suppression			
Suppressed	568,756 (94%)	338,467 (93%)	230,289 (94%)
Unsuppressed	39,138 (6%)	25,698 (7%)	13,440 (6%)
Sex			
Female	400,842 (66%)	241,560 (66%)	159,282 (65%)
Male	207,052 (34%)	122,605 (34%)	84,447 (35%)
Age [yr]			
0-9	17,062 (3%)	10,436 (3%)	6,626 (3%)
10-19	32,175 (5%)	18,896 (5%)	13,279 (5%)
20-29	71,281 (12%)	44,431 (12%)	26,850 (11%)
30-39	170,753 (28%)	106,230 (29%)	64,523 (26%)
40+	316,623 (52%)	184,172 (51%)	132,451 (54%)
Treatment regimen			
Original data			
INSTI-based	147,448 (24%)	21,006 (6%)	126,442 (52%)
NNRTI-based	12,500 (2%)	6,845 (2%)	5,655 (2%)
PI-based	4,667 (1%)	707 (0%)	3,960 (2%)
Unknown	443,279 (73%)	335,607 (92%)	107,672 (44%)
Population-calibrated MI data			
INSTI-based	475,584 (78%)	247,225 (68%)	228,359 (94%)
NNRTI-based	111,403 (18%)	104,252 (29%)	7,151 (3%)
PI-based	20,906 (3%)	12,688 (3%)	8,219 (3%)
Time on ART			
1st year	51,740 (9%)	33,332 (9%)	18,408 (8%)
2nd year	37,008 (6%)	23,069 (6%)	13,939 (6%)
3+ years	335,008 (55%)	192,429 (53%)	142,579 (58%)
Unknown	184,138 (30%)	115,335 (32%)	68,803 (28%)
Specimen type			
DBS	309,756 (51%)	242,651 (67%)	67,105 (28%)
Plasma	83,338 (14%)	44,372 (12%)	38,966 (16%)
other/unknown	214,800 (35%)	77,142 (21%)	137,658 (56%)

fits to the original data and the complete case data differed mainly in the estimated interaction between pandemic period and treatment regimen (Supplementary Fig. S4). In both model fits, there was some evidence for a worse virologic suppression in NNRTI- and INSTI-based regimens during COVID-19, while there was no change for PI-based regimens. On the other hand, “unknown” treatment regimens showed a substantial increase in the odds of virologic suppression during COVID-19.

4. Discussion

4.1. Main findings

In the Malawi national HIV program, the number of routine viral load measurements decreased by about one-third during the COVID-19 pandemic. Predictors of missing scheduled viral load measurements were similar

before and during the COVID-19 pandemic. Virologic suppression rates in the measurements done remained high, close to 95%, with slightly higher odds of virologic suppression during COVID-19 compared to before COVID-19. The higher suppression rate during the pandemic was mainly observed in adults on INSTI-based regimens and children or adolescents on PI-based regimens.

4.2. Strengths and limitations

With an estimated 87% of all people living with HIV on ART in Malawi in 2020 and over 600,000 viral loads included in the analyses, our study’s findings are likely to be robust and representative of the whole country. The routine data lacked detailed clinical information such as missed visits. Thus, we could not directly assess if patients who missed a viral load test during the COVID-19 pandemic differed from those who missed visits before

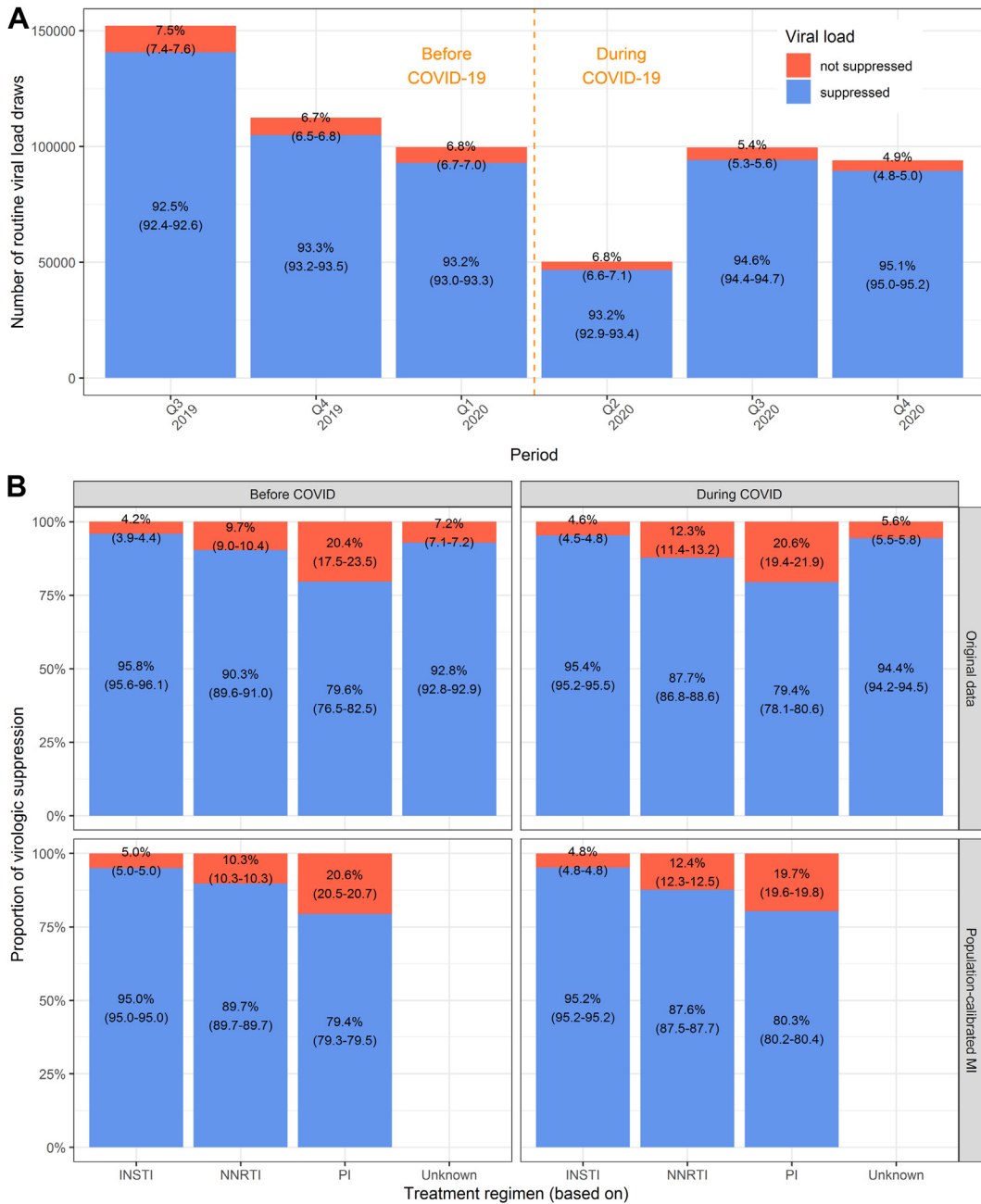


Fig. 1. Viral load measurements before and during COVID-19. Panel A shows the total number of samples drawn, and the proportion (95% confidence interval [CI]) suppressed and unsuppressed by quarter. Panel B shows the proportion (95% CI) of viral load suppression by period and treatment regimens for the original data and the population calibrated multiple imputation (MI) data.

the pandemic. However, the schedule of 12 months between routine viral load tests allowed us to assess this indirectly. In addition, calendar months differed between the two periods, and seasonal effects may thus have affected our results. The season has been shown to affect the number of viral load measurements in the Malawi national ART program, but not the probability of virologic suppression [13].

Data on treatment regimens were missing at the individual level for many samples but were available aggregated for all people on ART quarterly at the clinic level. This

allowed applying population-calibrated multiple imputation, assuming that the distribution of treatment regimens among the viral load measurements did not systematically differ from the distribution of treatment regimens of all people on ART. Although this assumption cannot be verified, it is reassuring that for the last two quarters (when fewer treatment regimens were missing) the distribution of non-missing regimens was similar to the distribution on the aggregate level. As shown in the simulation study in the supplementary material, in situations where data

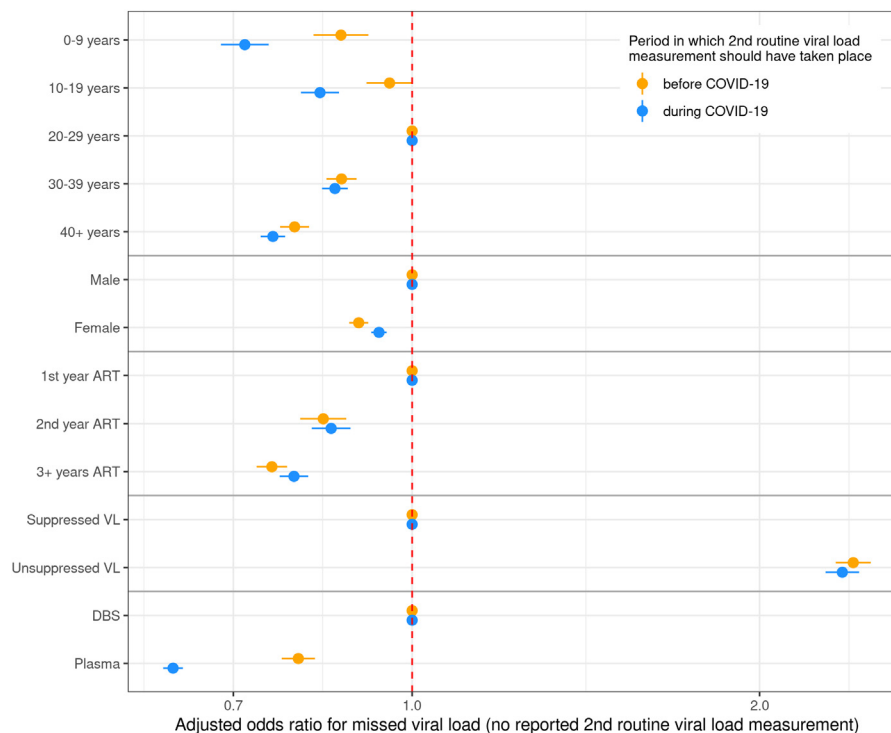


Fig. 2. Adjusted odds ratios and 95% confidence intervals for no reported second routine viral load measurement 12 months after the initial one. The logistic regression includes all variables listed and was stratified by period in which the second viral load measurement should have taken place. All variables included are measured at the time of the initial viral load measurement.

are MNAR population-calibrated multiple imputation can be superior to standard multiple imputation, which assumes “missing at random” (MAR). MAR makes the strong assumption that missingness is entirely dependent on the covariates included in the multiple imputation model [12]. In our study assuming MAR for treatment regimens is particularly risky for the first two quarters of our study, when only few treatments were recorded. Standard multiple imputation led to too many imputed PI-based treatment regimens in the first quarter (12% PI for the standard multiple imputation data compared to 3% PI in the aggregated data) and to narrower confidence intervals of estimates in the virologic suppression regression model. Nevertheless, point estimates were broadly similar, suggesting that treatment regimens might in fact have been MAR.

4.3. Interpretation and comparison with other studies

The high virologic suppression rates observed during the COVID-19 pandemic are plausible as worsening virologic control would most likely be due to treatment interruptions caused by supply challenges [14]. The Malawi HIV treatment program maintained the supply of antiretroviral drugs at all facilities. In some instances, drug stocks were moved between facilities to ensure uninterrupted supply [13,15,16]. Further, the continued high levels of virologic suppression during the first wave of the COVID-19 pandemic will likely have been facilitated by the introduction of differentiated care models to respond to the

reallocation of health system resources in the context of the COVID-19 response and the resumption of interrupted services as soon as possible, in line with recommended practice [17].

Although predictors of missing viral load measurements were generally similar before and during the pandemic, there were some differences. In both periods, patients with measurements from DBS were more likely to have missing viral loads than those with measurements in plasma, but this difference increased in the pandemic. The use of plasma or DBS is related to the setting: plasma in urban and DBS in rural settings. People from rural areas likely had more difficulties meeting scheduled visits than those living in urban settings. Of note, there was no difference between the two periods regarding the importance of patients’ history of viral load suppression. This implies that the decline in viral load testing during COVID-19 was not driven by more patients with poor viral load history missing their tests.

The increase in the odds of virologic suppression we observed during COVID-19 for INSTI and PI-based regimens could have resulted from selection bias, due to viral load measurements missing not at random. However, this is unlikely as we adjusted for all predictors of missing viral load tests that were somewhat more important in one period and less important in the other. Although we can exclude selection bias, the increase was probably driven by the concomitant change in ART regimens. DTG-based regimens in adults and LPV/r-based regimens for children were

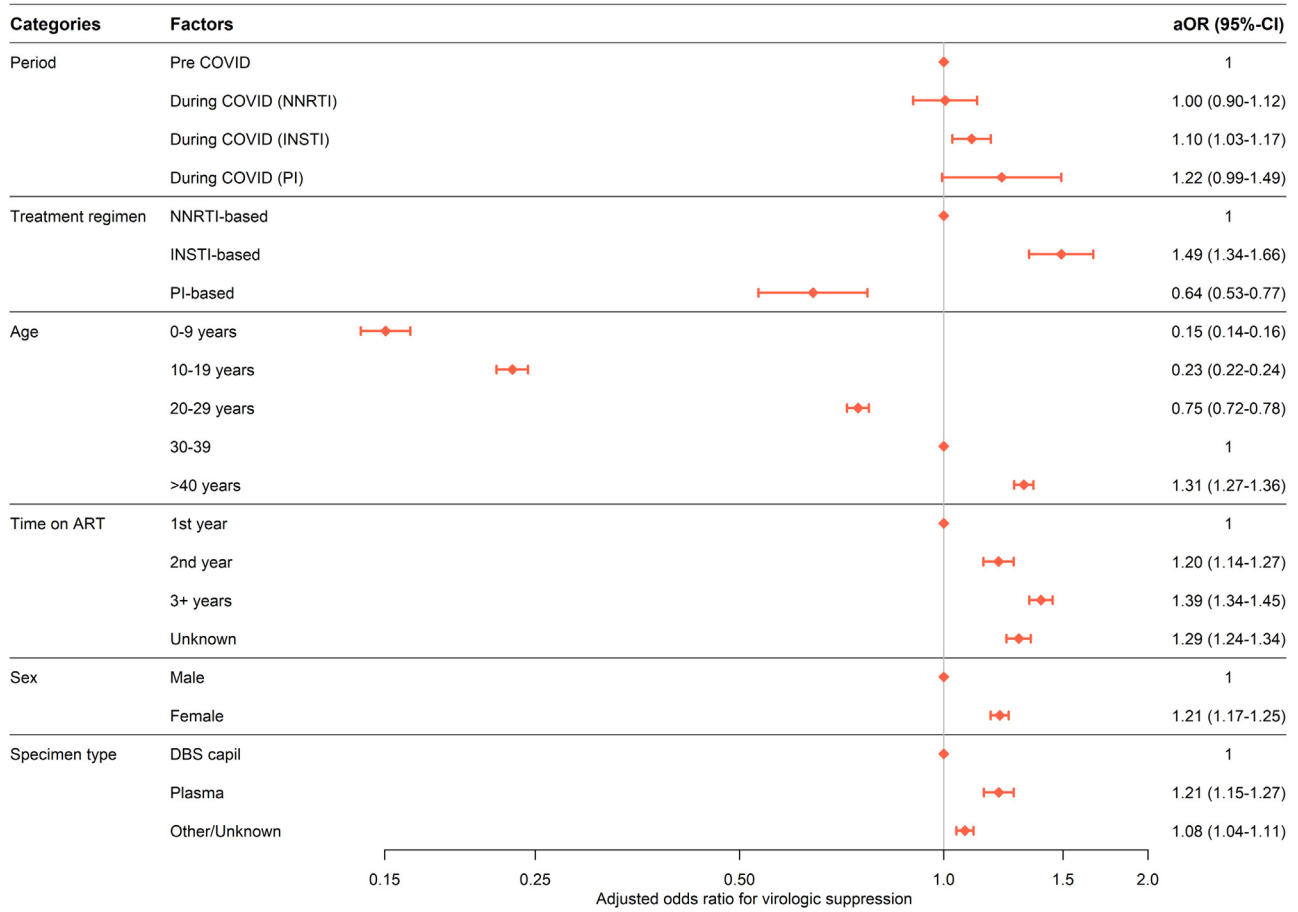


Fig. 3. Adjusted odds ratios and 95% confidence intervals (CI) for viral load suppression. Model fitted to the population-calibrated multiple imputation (MI) data. The regression model includes all variables listed as well as an interaction between period and treatment regimen.

scaled up during the study period. Thus, many measurements in patients on INSTI- and PI-based regimens before COVID-19 were from adults and children who had newly transitioned to DTG and LPV/r and who might not yet have achieved viral suppression if their previous regimen failed to suppress HIV viral replication. In contrast, during COVID-19, most measurements on INSTI- and PI-based regimens were from adults and children who had been on these regimens for longer. This is supported by the fact that there was no difference in virological suppression between the two periods for NNRTI-based regimens and that children and adolescents mainly showed an improvement for PI-based regimens and adults only for INSTI-based regimens.

The pandemic may have affected other aspects of HIV treatment and care than viral load monitoring or virologic suppression. Patients with advanced HIV disease may die because of delayed ART initiation, and increased HIV transmission during the disruptions may increase the burden of HIV long-term [18]. A study from the KwaZulu-Natal province of South Africa found no change in ART collection and visit frequency during the COVID-19 pandemic compared to before. Still, the number of HIV tests and ART initiations was lower [19]. In another study from the Western Cape,

South Africa, HIV infection was associated with a higher risk of dying from COVID-19 [20].

Many of our other findings were consistent with previous studies. For example, DTG-based treatment regimens achieved better suppression of HIV replication than efavirenz-based regimens, confirming the results of a randomized controlled trial from Cameroon [21]. Adolescents have previously been shown to have poorer virologic outcomes than adults, likely due to lower adherence [22]. A report showed that during 2016-2018 one out of three children were not virally suppressed in Malawi, Uganda and Zimbabwe [23]. Similarly, a study from South Africa showed non-suppression rates of around 30% in children [24]. Furthermore, women living with HIV are more likely to suppress HIV viral replication on ART than their male peers [25]. Finally, below 1,000 copies/ml on plasma samples, viral load results on DBS samples can be discordant and higher—leading to lower rates of viral load suppression [26].

5. Conclusion

In conclusion, we showed that in the national HIV program in Malawi, there was a decline in viral load

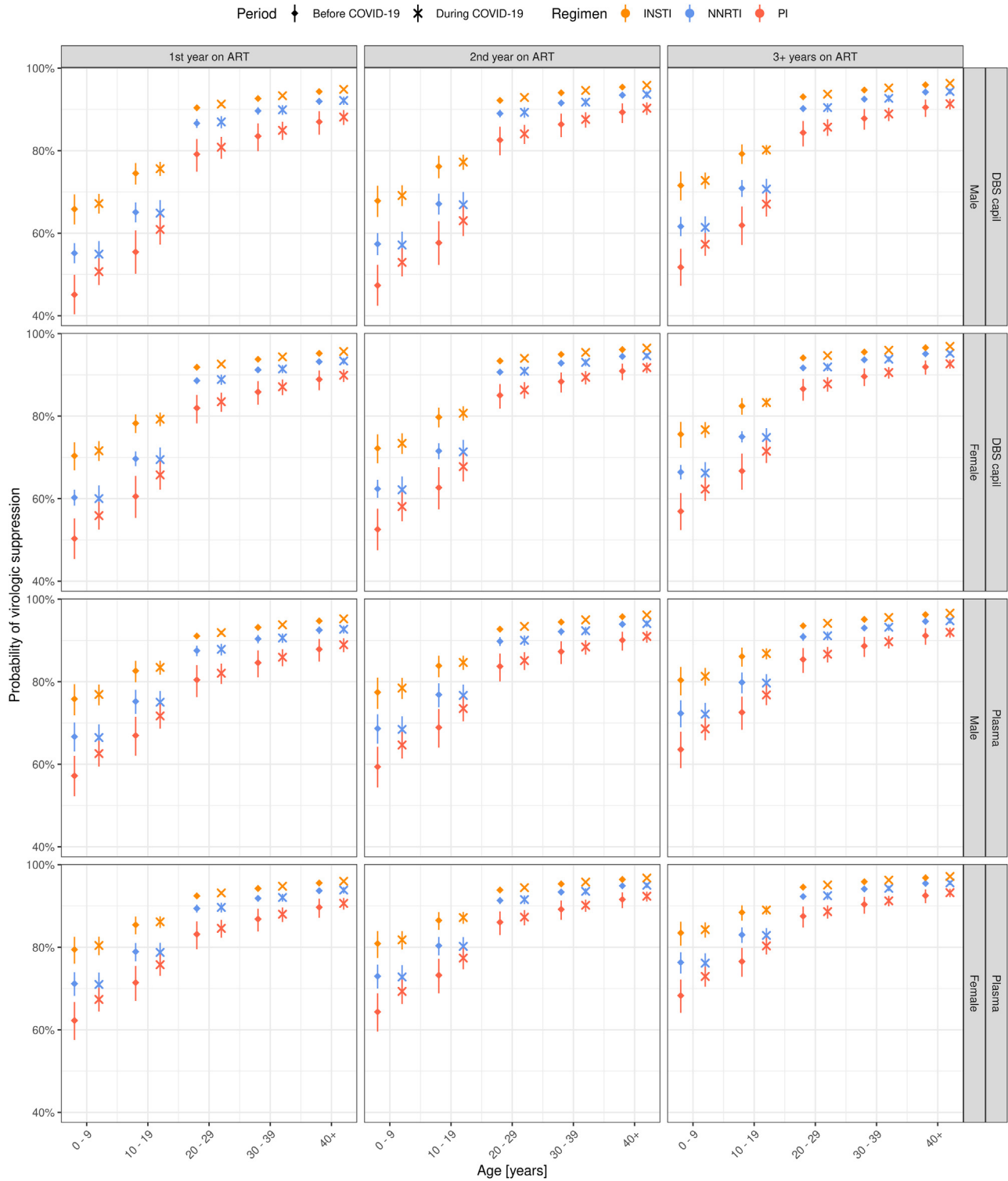


Fig. 4. Predicted probabilities of virologic suppression by treatment regimen (color), period (shape), age, time on ART, sex and specimen type. Results based on the population-calibrated multiple imputation (MI) data from the regression model fitted separately to children/adolescents and adults.

monitoring, but no clear evidence for a worsening of virologic suppression due to the measures taken in response to the COVID-19 pandemic.

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Appendix B

Supplementary Data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jclinepi.2022.06.019>.

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