



HIV viral load suppression following intensive adherence counseling among people living with HIV on treatment at military-managed health facilities in Uganda ☆☆☆☆



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ABSTRACT

Background: Uniformed service personnel have an increased risk of poor viral load suppression (VLS). This study was performed to evaluate the outcomes of interventions to improve VLS in the 28 military health facilities in Uganda.

Methods: This operational research was conducted between October 2018 and September 2019, among people living with HIV (PLHIV) in the 28 health facilities managed by the military in Uganda. Patients with a viral load (VL) >1000 copies/ml received three sessions of intensive adherence counselling (IAC), 1 month apart, after which a repeat VL was done. The main outcome was the proportion with a suppressed VL following IAC.

Results: Of the 965 participants included in this analysis, 592 (61.4%) were male and 367 (38.3%) were female. Average age was 35.5 ± 13.7 years, and 87.8% had at least one IAC session. At least 48.2% had a suppressed repeat VL. IAC increased the odds of VLS by 82% ($P = 0.004$), with adjusted OR of 1.56 ($P = 0.054$). An initial VL >10 000 copies/ml, being on antiretroviral therapy for at least 2 years, being male, and being <18 years of age were associated with repeat VL non-suppression.

Conclusions: IAC marginally improved VL suppression. There is a need to improve IAC in military health facilities.

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Introduction

Access to antiretroviral treatment (ART) has increased since the adoption of the World Health Organization (WHO) “test and treat all” policy (World Health Organization, 2016). In 2014, the WHO and Joint United Nations Programme on HIV/AIDS (UNAIDS)

adopted the 90–90–90 strategy (UNAIDS (a), 2014) to end the AIDS epidemic, which was upgraded to the 95–95–95 targets in 2018 (UNAIDS, 2015). The 95–95–95 targets aim to have 95% of those who are HIV-infected know their status, 95% of these put on ART, and 95% of those on ART virally suppressed (UNAIDS, 2018). To achieve the third 95% target of viral suppression, the WHO recommends 6-monthly HIV viral monitoring (WHO, 2016). This enables the early identification of individuals who are failing on ART and who are at risk of developing drug resistance to affordable first- and second-line regimens, for appropriate early interventions to improve adherence and treatment outcomes.

Prolonged undetected viremia is associated with an increased risk of opportunistic infections, an increased risk of transmis-

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sion of resistant virus, and death (Roberts et al., 2016). A review by the WHO found suboptimal levels of viral load suppression (VLS) among people living with HIV (PLHIV) on ART in 2013 in low and middle-income countries (McMahon et al., 2013), and these rates of non-suppression have not changed much following the rollout of the 2017 WHO HIV management guidelines (Agolory et al., 2018; Boerma et al., 2016a; Gaolathe et al., 2017; Humphrey et al., 2019; Kiweewa et al., 2019). In Uganda, a population-based HIV impact survey revealed that VLS among adults living with HIV aged 15–64 years was 59.6% in 2016 (Ministry of Health, 2019).

The two most recognized barriers to viral suppression are non-adherence to treatment and age, with younger patients having higher failure rates (Bulage et al., 2017). Having less than 89% adherence to therapy increases the risk of non-suppression and the development of resistance mutations as compared with perfect adherence (Bartlett, 2004; Lippman et al., 2020; von Wyl et al., 2013). Depression, alcohol use, and the cost of travel to the clinic have also been shown to increase the risk of non-suppression in some studies (Bukenya et al., 2019; Cerutti et al., 2016; Iacob et al., 2017; Williams et al., 2016). Other predictors of non-suppression include patient satisfaction with quality of care, time on ART, concurrent medications, especially anti-tuberculosis treatment, and baseline CD4 count (Bukenya et al., 2019). There have been inconsistent data on the association between VLS and the level of facility in which the patient received care, although one well-designed prospective study in Uganda showed that lower level facilities, including community-based providers, were more likely to have viral suppression among their patients when compared to hospital-based patients (Barnabas et al., 2020).

The 2020 Ministry of Health of Uganda guidelines for the prevention and management of HIV (Ministry of Health, 2020) detail the interventions to be used in the management of PLHIV who are not suppressing the HIV virus. These include training health workers in the management of non-suppressed PLHIV, strengthening capacity for intensified adherence counselling (IAC), including the provision of job aides for IAC, establishing and strengthening switch teams to manage non-suppressed patients, line-listing all non-suppressed clients in 'non-suppressed' (NS) registers, and the follow-up of patients with non-suppressed viral load (VL) results to ensure that they are reached with intensified adherence interventions as soon as results are received. After these interventions, the VL of the non-suppressed individuals are repeated to inform further management decisions. The outcomes of these interventions have not been well investigated. For example Nasuuna et al. reported that only 23% of VL suppression was achieved among HIV-infected children and adolescents receiving IAC in public health facilities in Uganda in 2017, but this study mainly included children and adolescents (Nasuuna et al., 2018).

Uniformed service personnel are considered one of the major groups of persons for contracting HIV. Studies have shown HIV prevalence to be higher among uniformed service personnel than among the general population (Lloyd et al., 2014). Although military personnel are particularly at risk of poor treatment outcomes because of the nature of their deployment and lifestyles, studies in US military settings have shown that they can obtain good outcomes with well-managed care arrangements. There are, however, few studies outside of the US army on HIV treatment outcomes among military personnel (Matthews et al., 2015). The militaries in most African countries are frequently deployed, and failure to obtain good treatment outcomes might result in a high risk of spreading HIV within the communities surrounding military bases and their areas of operation. Some of the possible reasons for poor outcomes in the military include unpredictable duty schedules, long periods of deployment resulting in separation from families and primary care sites, high rates of transaction sex, and high rates

of alcohol and substance use by the service personnel (Deiss et al., 2016; Matthews et al., 2015).

There is a scarcity of data on the impact of treatment programs among the military in sub-Saharan Africa. Specifically, there are no data on VLS and treatment outcomes following IAC from populations served by military health facilities in Uganda. The aim of this study was to evaluate the outcomes of the interventions to improve VLS among non-suppressors in the 28 military health facilities in Uganda and to describe the facilitators and barriers to achieving VLS among these clients.

Study methods

Study design and population

This was an operational research study conducted among PLHIV with a first non-suppressed VL in the 28 health facilities managed by the military in Uganda. These health facilities serve the military, their family members, and civilian populations around the military bases, with about 55% of patients in treatment being military. All ART-treated children and adults with a VL >1000 copies/ml, with a test done between October 2018 and September 2019, and who had been receiving ART for at least 6 months, were included.

Project description

The Comprehensive HIV/AIDS Prevention, Care, Treatment and Support project with the Uganda People's Defence Force (UPDF) is a 3-year US Department of Defense (DoD) HIV/AIDS Prevention Program (DHAPP) implemented by the University Research Council (URC). It is part of the military-specific HIV/AIDS programs for the US President's Emergency Plan for AIDS Relief (PEPFAR)-funded countries. The project commenced in October 2018 in 28 military-managed health facilities across the country. The overall goal of the project is to reduce the number of new HIV infections and other sexually transmitted infections (STIs) and reduce associated mortality among members of the UPDF, their families, and the civilian communities served by UPDF health services.

The intervention

Between March 2019 and March 2020, URC provided technical assistance aimed at improving overall adherence to the Uganda national HIV treatment guidelines by the health workers in the Ugandan military-managed health facilities. The technical assistance included training of health workers in the Uganda HIV management guidelines, providing job aides for IAC, providing material support to follow up clients who missed appointments, and supporting sample transportation to the central laboratory for testing. Other areas supported included monitoring PLHIV on treatment, sample collection, labeling, dispatch, and utilization of the results. Health care workers were also specifically trained on the package of interventions recommended to manage viral non-suppression, which include line-listing all non-suppressed clients in registers, intensified adherence counselling, follow-up, and switch teams to manage non-suppressed patients (see Figure 1).

Viral non-suppression was considered when the VL test results showed an HIV viremia of >1000 copies/ml, while suppression was considered if VL test results showed an HIV viremia of <1000 copies/ml. Patients with non-suppressed VL results were identified and invited to the facility as soon as results were received. They then underwent three sessions of IAC, each done 1 month apart, during which barriers to adherence were identified and addressed. After completion of the recommended IAC sessions, a repeat VL was done to ascertain if there was re-suppression. For those still

- When viral load result of not suppressed (VL >1000 copies/ml), is received at facility the following interventions are recommended:**
1. Sort all NS VL results from the laboratory from the suppressed for rapid action by ART clinic
 2. Apply the red stickers for non-suppressed clients to flag non-suppressed client files and record NS patients in NS registers for tracking and reporting
 3. Conduct 1st Intensive adherence counselling within 7 days of result return
 4. Intensive Adherence Counseling (IAC) **at least 3 sessions 1 month apart should be done**
 5. Record IAC sessions on IAC counselling forms to support completion of 3 IAC sessions
 6. Repeat VL test after one month of having good adherence rating in the 3 IAC sessions
 7. Form viral load focal teams with clinical–lab interface for routine review of NS files
 8. If patient on 1st line, evaluate and switch to 2nd line if repeat VL is still NS.
 9. If patient is on 2nd line and repeat VL is NS, do genotype testing and switch to 3rd line.
 10. If patient is on 3rd line, switch to a more potent regimen (salvage regime)
 11. Continue intensive adherence support throughout this period.
 12. Repeat VL at 6months after regimen switch and then follow steps 4, 9 and 10 if still NS
 13. Engage multidisciplinary switch team at health facilities to discuss failing patients
 14. Integrate viral load monitoring talks into morning health education sessions
 15. Linkage with community structures for peer support and client tracking as appropriate
 16. Implement viral load continuous quality improvement (CQI) site-level initiative

Figure 1. Steps followed in the package of interventions recommended to manage viral non-suppression: URC-DHAPP HIV care and treatment standard operating procedures, 2020.

not suppressing, ART failure was diagnosed, and the client was referred to the ART switch committee for further evaluation and possible switch to a second- or third-line ART regimen. For this study, a person was considered to have received IAC if there was a filled-out IAC form on their file.

The outcome

The main outcome was the proportion of PLHIV with suppressed VL following IAC interventions to manage the initial non-suppressed VL. The co-factors examined included age, sex, and the barriers and facilitators of virological suppression among participants who had received the IAC following non-suppression. The secondary outcomes included the proportion of PLHIV who were completing recommended IAC sessions and the most frequently identified barriers to adherence.

All non-suppressed results from 25 of the 28 military ART clinics were considered. The three sites not included had missing data because of administrative reasons.

Selection of participants

All clients with a non-suppressed VL from 25 military facilities were considered. A master list of all PLHIV who had a VL >1000 copies/ml was generated from the 'non-suppression' (NS) register and a review of the participants' files at each facility. A list of participants to be included in the study was then generated from the master list and by confirming a clinical record in their files. Individuals who were listed in the non-suppressed master list but whose file could not be retrieved, whose file lacked clinical records for at least 6 months, or who had been on ART for less than 6 months were not included in the study. The files of those

Table 1
Characteristics of and reasons for non-adherence among participants with a viral load >1000 copies/ml in the military health facilities in Uganda

Characteristic		Frequency (N = 965)	Percentage (%)
Adult/child (2 missing)	Adult (>18 years)	831	86.3
	Child (<18 years)	132	13.7
Sex	Female	367	38.3
	Male	592	61.7
Duration on ART (53 missing)	6 months–1 year	67	7.3
	1–2 years	123	13.5
	2–5 years	326	35.8
	5+ years	396	43.4
Current regimen	EFV-based	475	49.2
	NVP-based	395	41.9
	PI-based	52	5.4
	Others	43	4.5
First high VL level (copies/ml)	<10 000	535	55.4
	10 000–100 000	204	21.1
	100 000–250 000	117	12.1
	>250 000	109	11.4
Identified barriers to adherence		Frequency, (N = 847)	Percentage (%)
	Gender-based violence	No	805
	Yes	42	5.0
Alcohol use and mental health challenges	No	678	80.1
	Yes	169	19.9
Lack of food	No	655	77.3
	Yes	192	22.7
Non-disclosure and stigma	No	727	85.8
	Yes	120	14.4
Other social issues/ problems	No	514	60.7
	Yes	333	39.3

ART, antiretroviral therapy; EFV, efavirenz; NVP, nevirapine; PI, protease inhibitor; VL, viral load.

patients with an initial non-suppressed VL and who fulfilled the eligibility criteria were retrieved for data abstraction. Data were abstracted using a pre-designed data abstraction tool.

Data management and analysis

The data abstraction tools were pre-tested before data collection. Data were entered into a database using Microsoft Excel, cleaned, and then imported into Stata 14.0 for analysis. Socio-demographic characteristics of the different groups (suppressed, non-suppressed) were also analyzed and presented as frequencies and mean values. Continuous data were compared using the mean values and *t*-test, while categorical data were compared using proportions and the Chi-square test. Logistic regression was used to determine the odds of VLS following IAC and the associated cofactors.

Results

Characteristics of the study population

A total of 1026 non-suppressed results were identified from the non-suppressed registers. Of these, 71 (6.7%) were dropped: 56 had missing files, 10 had VL done before 6 months of ART, and five had incomplete clinical records. Of the 965 participants included in the analysis, 592 (61.4%) were male and 367 (38.3%) were female. Twenty-seven (7.2%) of the female participants were either pregnant or breastfeeding. The average age was 35.5 ± 13.7 years; 827 (86.2%) were >18 years old and 58.3% were between 30 and 50 years old. With regard to time on treatment, 398 (41.4%) had been on treatment for more than 5 years, while only 7.0% had received treatment for less than 1 year. At the time of the VL test, 49% of the participants were on an efavirenz-based regimen and 41% on a nevirapine-based regimen; the rest were on other regimens including protease inhibitors or dolutegravir (5%). Slightly more than half of the study participants (55.4%) had a VL <10 000 copies/ml

and 103 (10.7%) had VL of >250 000 copies/ml of blood. [Table 1](#) reports details of the participant characteristics.

[here]

Intensive adherence counselling (IAC)

Overall, 847 (87.8%) of the study participants had at least one IAC session before the repeat VL test was done: 323 (33.5%) had only a documented first IAC session, 336 (34.8%) had two documented IAC sessions, and 323 (33.5%) had all three sessions documented.

Viral load suppression following intensive adherence counselling

Of the 965 participants who had an initial detectable VL, a total of 463 (48.2%) had a suppressed repeat VL (95% confidence interval (CI) 44–51%). Receiving at least one session of IAC increased the odds of suppressing the VL by 82% (odds ratio (OR) 1.82, 95% CI 1.22–2.75; *P* = 0.004), while two IAC sessions increased the odds of suppressing the VL by 3.6 times (OR 3.64, 95% CI 1.00–13.3; *P* = 0.05). Pregnancy and breastfeeding did not affect VLS after IAC.

Factors associated with viral load non-suppression

As shown in [Table 2](#), an initial VL >10 000 copies/ml, being on an ART for at least 2 years on a regimen that was not efavirenz- or protease inhibitor-based, being male, and being <18 years of age were all associated with repeat VL non-suppression.

After adjusting for confounding, the odds of suppressing VL after IAC among participants who received at least one IAC was 1.56 (95% CI 0.99–2.49), with a borderline *P*-value of 0.054. After multivariate analysis, an association with repeat VL non-suppression was found for participants below the age of 18 years (OR 0.33, 95% CI 0.22–0.51; *P* < 0.001) and those who had an initial VL of >10000 copies/ml. There was no statistically significant association between repeat non-suppression and sex, type of regimen, or duration on ART.

Table 2
Multivariate analysis of factors associated with viral non-suppression on repeat viral load after intensive adherence counseling

	Suppressed (%)	Non-suppressed (%)	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
At least one IAC session						
No	41 (34.8)	77 (65.2)	1.86 (1.25–2.79)	0.002	1.56 (0.99–2.49)	0.054
Yes	422 (49.8)	425 (50.2)				
Adult/child						<0.001
>18 years	423 (50.1)	408 (49.1)				
<18 years	38 (28.8)	94 (71.2)	0.39 (0.26–0.58)	<0.001	0.33 (0.22–0.51)	
Sex						0.299
Female	192 (52.3)	175 (47.7)				
Male	271 (45.8)	321 (54.2)	0.77 (0.59–0.99)	0.049	0.86 (0.65–1.14)	
Duration on ART						0.244,
6 months–<1 year	41 (61.2)	26 (38.8)				0.094,
1–<2 years	60 (49.2)	63 (50.8)	0.61 (0.34–1.12)	0.114	0.68 (0.35–1.30)	0.153
2–<5 years	146 (44.5)	180 (55.5)	0.51 (0.30–0.87)	0.014	0.61 (0.34–1.09)	
>5 years	186 (47.0)	210 (53.0)	0.56 (0.33–0.95)	0.033	0.66 (0.37–1.17)	
Current regimen						0.893,
EFV-based	253 (53.3)	222 (46.7)				0.206,
NVP-based	172 (43.5)	223 (56.5)	0.68 (0.52–0.89)	0.004	0.97 (0.72–1.34)	0.479
PI-based	22 (42.3)	30 (57.7)	0.52 (0.27–0.99)	0.136	0.79 (0.42–1.50)	
Others	16 (37.2)	27 (62.8)	0.64 (0.36–1.14)	0.047	0.63 (0.31–1.28)	
First VL level (copies/ml)						0.063,
<10 000	294 (55.2)	239 (44.8)				<0.001,
10 000–100 000	106 (51.2)	101 (48.8)	0.85 (0.62–1.17)	0.333	0.72 (0.51–1.01)	<0.001
100 000–250 000	38 (32.8)	78 (67.2)	0.40 (0.26–0.60)	<0.001	0.36 (0.23–0.57)	
>250 000	25 (22.9)	84 (77.1)	0.24 (0.15–0.39)	<0.001	0.22 (0.13–0.37)	

ART, antiretroviral therapy; CI, confidence interval; EFV, efavirenz; IAC, intensive adherence counseling; NVP, nevirapine; OR, odds ratio; PI, protease inhibitor; VL, viral load.

Table 3
Association of reasons for non-adherence with viral load non-suppression after intensive adherence counseling

Reason identified for non-adherence	Suppressed (%)	Non-suppressed (%)	OR (95% CI)	P-value
Lack of food				
No	366 (55.9)	289 (44.1)	0.33 (0.23–0.46)	<0.001
Yes	56 (29.2)	136 (70.8)		
Alcohol use/mental health				
No	345 (50.9)	333 (49.1)	0.81 (0.58–1.13)	0.216
Yes	77 (45.4)	92 (54.4)		
Non-disclosure/stigma				
No	364 (50.1)	363 (49.9)	0.93 (0.63–1.37)	0.725
Yes	58 (48.3)	62 (51.7)		
Gender-based violence				
No	403 (49.8)	406 (50.2)	0.92 (0.49–1.70)	0.781
Yes	20 (47.6)	22 (52.4)		
Other social problems				
No	302 (58.8)	212 (41.2)	0.40 (0.30–0.52)	<0.001
Yes	120 (36.0)	213 (64.0)		

CI, confidence interval; OR, odds ratio.

The most commonly reported barrier among non-suppressing clients was general social problems including lack of income, reported by 261 (30.7%) clients. This was followed by limited access to food, which was reported by 192 (22.6%) clients. One hundred and seventy (20.0%) clients reported using alcohol or having experienced mental health challenges, while 120 (14.1%) reported having challenges with disclosure or having experienced stigma (Table 3). Only 42 (4.9%) clients reported experiencing gender-based violence (Table 1). Comparison of these barriers among those who had a suppressed or non-suppressed VL after IAC showed that not having access to adequate food and other social problems significantly reduced the odds of a repeat VL suppression following IAC (OR 0.33 and 0.40, respectively), with a P-value of <0.001 for both. There was no statistically significant association among the other barriers and a repeat VL suppression.

Discussion

This study sought to evaluate the outcomes of programmatic support to activities aimed at improving VLS in health facilities managed by the UPDF. Almost half (48.2%) of the participants who

had an initial non-suppressed VL had a repeat suppressed VL. This result is higher than the 23% that was reported in a similar study done on children living with HIV in Uganda ([Nasuuna et al., 2018](#)). This is not surprising, as studies have previously reported poor VLS among children compared to adults ([Bulage et al., 2017](#)). The result is also higher than that reported in Zimbabwe ([Bvochora et al., 2019](#)), where only a third of the patients were reported to have VLS after counselling. The latter study, however, was conducted in a general hospital of a country going through very challenging political and social times, compared to the present study, which was conducted in facilities supported by the military and after intervention by the DHAPP project. On the other hand, the result of the present study is much lower than that reported by Matthews from South Africa (64%) ([Fox et al., 2016](#)) in a study that was conducted in a public health facility that received PEPFAR support like the health facilities included in the present study. However, their study population were participants failing on second-line regimens. The present study result is also lower than the WHO target of 70% ([Bonner et al., 2013](#); [World Health Organization, 2016](#)), which may point to gaps in the quality of IAC, or content revision of counselling sessions.

While receiving at least one IAC session was high (87.8%) in this study, only a third had documentation of completing all of the required three IAC sessions by the time a repeat VL was done. This implies possible non-adherence to the standard, as guidelines recommend that repeat VL testing should only be done after completion of at least three IAC sessions. This is low compared to what was reported by Nasuuna et al (Nasuuna et al., 2018), who reported up to 77% of children receiving three IAC sessions. The high number with a single session of IAC received and the drastic reduction in the subsequent sessions might be explained by the highly mobile nature of the military. The 323 (33%) participants who received all three IAC sessions is a very small proportion; therefore almost two thirds of the study participants remained at an increased risk of continued poor adherence, resulting into drug resistance and increased HIV transmission. Barriers to the completion of IAC and the quality of the IAC should be investigated and interventions instituted to improve the proportion of PLHIV suppressing the virus in this population.

As expected, IAC increased the odds of having a suppressed repeat VL, with unadjusted OR of 1.82; however after adjusting for age, sex, and other factors, this reduced to 1.56 with a borderline *P*-value of 0.054. This finding is not consistent with what would be expected and needs further investigation to understand it. As most studies report the proportions of participants with suppressed virus following IAC, there is a need for more studies to examine the effect of IAC on VL suppression. The low suppression after IAC could have been due to the majority of the study population receiving a nevirapine- or efavirenz-based regimen; these regimens have been shown to have a low genetic barrier to resistance (Gregson et al., 2017; WHO, 2012). A recent review reported a prevalence of 7.6% pre-treatment non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance in Eastern Africa in 2016, with yearly increases in the odds of treatment drug resistance of 17% (Gupta et al., 2018).

Sex, the duration on ART, and the current regimen were not found to confound the effect of IAC on VLS.

Reasons for non-suppression

Lack of food and other social problems (lack of income) were found to be associated with repeat VL non-suppression. Similarly, in a qualitative study done by Nasuuna et al. (Nasuuna et al., 2018), some of the reported challenges faced by caregivers in supporting adherence of children were financial, i.e., lack of food and transport. A unique challenge for the military was frequent unplanned travel due to deployments. Forging solutions around economic problems, travel planning for those on ART, and psychological support is required in improving adherence of PLHIV to ART, thereby improving VL outcomes. Other factors not investigated in this study, such as exposure to antiretrovirals through prevention of mother-to-child transmission, pre-treatment resistance, and high levels of resistance among those failing first-line regimens, have been found by others (Boerma et al., 2016b; Kuhn et al., 2014; Possomato-Vieira and Khalil, 2016) and need to be investigated in military settings.

Conclusions and recommendations

Although IAC improved VLS by 56% (OR 1.56), this was marginal, with only 48% of the participants having suppressed VL following IAC. Efforts are needed to improve coverage of IAC in health facilities managed by the military, as only 33% of the participants received the recommended three sessions. Nonetheless, these results also highlight other factors such as being a child, lack of food, and other social problems contributing to non-suppression of the VL following IAC. These results also point to the limitations

of health care system-based interventions in addressing viral suppression in highly mobile populations. HIV drug resistance testing among those failing first-line ART regimens may also need to be considered.

Study limitations

This study was conducted just before the country introduced dolutegravir as a first-line regimen. The current population has largely switched to dolutegravir-based regimens and the effect of this might limit the application of the study findings to the current population on ART.

Some of the information that was needed for this study was missing in the participants' files. This was because routine systems were used to collect the data for this study, which carries a risk of 'incomplete data'. However, the proportion of files with missing information was small.

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Ethical approval

The study was approved by both the TASO Uganda IRB (Protocol # TASOREC/048/2020-UG-REC-009) and the Uganda National Council for Science and Technology (Reg. No HS959ES), and permission was obtained from the Uganda People's Defence Force (UPDF) and study site management to conduct the study.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijid.2021.08.057](https://doi.org/10.1016/j.ijid.2021.08.057).

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