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RESEARCH

Combination antiretroviral therapy in population affected by conflict: outcomes from large cohort in northern Uganda

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ABSTRACT

Objective To measure the clinical and immunological outcomes of HIV positive adult patients receiving combination antiretroviral therapy in conflict affected northern Uganda.

Design Prospective cohort study.

Setting Gulu District, northern Uganda.

Participants 1625 adults (aged over 14 years) receiving combination antiretroviral therapy.

Main outcome measures Primary outcome: all cause mortality. Secondary outcomes: impact of covariates (sex, age, CD4 count at start, adherence, tuberculosis at start, duration of treatment, and internally displaced person status) on mortality.

Results Sixty nine (4.2%) patients died during follow-up. The mortality incidence rate was 3.48 (95% confidence interval 2.66 to 4.31) per 100 person years. Patients started treatment with a median CD4 count of 157 (interquartile range 90-220) cells/μl; most (1009; 63%) had World Health Organization stage 2 defined illness. Sixty two patients had pulmonary tuberculosis at the start of treatment. Of the 1521 patients with adherence data, 118 (7.8%) had adherence of less than 95% and 1403 (92.2%) had adherence of 95% or above.

Conclusion Patients receiving combination antiretroviral therapy in conflict affected northern Uganda had a mortality comparable to that of patients in peaceful, low income settings and better adherence than patients in higher income settings. These favourable findings highlight the need to expand access to combination antiretroviral therapy in populations affected by armed conflict.

INTRODUCTION

Sub-Saharan Africa is home to two thirds of the global HIV/AIDS epidemic.[1] The continent simultaneously has the world's highest rate of armed conflict, which affects more than a third of African countries.[2] International policy guidelines for humanitarian responses previously intimated that the provision of combination antiretroviral therapy was not feasible in complex emergencies,[3 4] owing to associated population movements and poor access to basic health services.[5] As a consequence, populations affected by conflict continue to have very limited access to combination antiretroviral therapy.[1]

A recent consensus statement from many international agencies, including the World Health Organization and the United Nations High Commissioner for Refugees (UNHCR), indicated that provision of combination antiretroviral therapy to HIV infected people in emergency settings represents a public health and human rights imperative.[6 7] The UNHCR has since developed clinical and operational guidelines for the management of combination antiretroviral therapy in displaced populations.[8] The feasibility of distributing such therapy in complex humanitarian settings has been previously evaluated in the Eastern Democratic Republic of Congo.[9] A critical need exists for increased research in this area to inform evidence based humanitarian interventions.[10] We present clinical and immunological outcomes of a large cohort of adult patients receiving combination antiretroviral therapy in an ongoing complex humanitarian emergency.

METHODS

Setting

Northern Uganda has been in a state of humanitarian emergency for more than 20 years, in what has been called one of Africa's longest standing armed conflicts and a neglected humanitarian emergency. Of the estimated 1.6 million people displaced in northern Uganda between 2002 and 2004, most continue to reside in protected camps.[11] Over the past year, security in the region has been characterised by brief but violent attacks by the Lord's Resistance Army and neighbouring cattle rustling tribes, varying in intensity and geographic focus. As of June 2008, efforts towards peace were compromised and movement restrictions remain in place for those living in internally displaced persons' camps.

Between January and July 2005, Gulu district and municipality had a population of approximately 566 000 inhabitants. Most residents lived in internally displaced persons' camps. The crude mortality rate in the area was estimated to be high, reaching 1.22 (95% confidence interval 1.00 to 1.44) per 10 000 per day among camp residents and 1.29 (1.04 to 1.53) per

10 000 per day in the surrounding community. These rates exceed the emergency threshold of 1.0 per 10 000 per day.[12] In this period, violence was a leading cause of death in Gulu District, representing approximately 11% of all deaths. The overall violence specific mortality in Gulu District was approximately 0.17 (0.12 to 0.21) people per 10 000 per day.[10] Tenuous peace has been present since the last major fighting in December 2004. However, most Gulu residents have chosen not to leave the camp for fear of resurgent violence. The outskirts of Gulu municipality have experienced more recent violence.

St Mary's Lacor Hospital, a large non-governmental hospital in Gulu, reports HIV/AIDS as the most common reason for death in 2005.[13] A sero-surveillance study among women attending antenatal clinics in Gulu District in 2006 found a prevalence of HIV infection of 10.3%. Women living in communities surrounding internally displaced persons' camps had a higher prevalence of HIV infection than did those living in the camps (11.6% *v* 6.3%), indicating that these camps may have had a protective effect on transmission of HIV in Gulu.[14] Prevention of mother to child transmission programmes in northern Uganda indicate that the prevalence of HIV infection may be lower in rural areas.[15] A geographic information system assessment of HIV/AIDS health services in northern Uganda in 2007 found that Gulu District had 14 HIV voluntary counselling and testing sites, five clinics for the prevention of mother to child transmission, and six sites providing combination antiretroviral therapy to eligible patients. Most of these health services are located in the (urban) municipality.[16]

Demographic, clinical, and immunological characteristics of patients (n=1625). Values are numbers (percentages) unless stated otherwise

Characteristic	Overall (n=1625)	Women (n=1162)	Men (n=463)
Median (IQR) age (years)	39 (33-46)	38 (33-45)	41 (36-47)
Internally displaced persons' camp resident:			
Yes	227 (14.0)	157 (13.5)	70 (15.1)
No	1398 (86.0)	1005 (86.5)	393 (84.9)
WHO stage at start:	(n=1591)	(n=1140)	(n=451)
1	13 (0.8)	10 (0.9)	3 (0.7)
2	1009 (63.4)	749 (65.7)	260 (57.7)
3	482 (30.3)	322 (28.3)	160 (35.5)
4	87 (5.5)	59 (5.2)	28 (6.2)
Tuberculosis at start:	(n=1623)	(n=1160)	
Yes	62 (3.8)	32 (2.8)	30 (6.5)
No	1561 (96.2)	1128 (97.2)	433 (93.5)
Adherence:	(n=1521)	(n=1094)	(n=427)
<95%	118 (7.8)	80 (7.3)	38 (8.9)
≥95%	1403 (92.2)	1014 (92.7)	389 (91.1)
Died:			
Yes	69 (4.3)	45 (3.9)	24 (5.2)
No	1556 (95.8)	1117 (96.1)	439 (94.8)
CD4 cell count	(n=982)	(n=704)	(n=278)
>200/µl at start:			
Yes	318 (32.4)	247 (35.1)	71 (25.5)
No	664 (67.6)	457 (64.9)	207 (74.5)
Median (IQR) at start	157 (90-220)	166 (99-232)	143 (80-201)
Median (IQR) change	0 (0-0)	0 (0-0)	0 (0-0)

IQR=interquartile range.

Programme

The AIDS Support Organization (TASO) began providing HIV/AIDS services in Gulu in 2004. Before this, no combination antiretroviral therapy was provided publicly and private provision of care was limited. Since 2004, TASO has started combination antiretroviral therapy in 1625 adults and 57 children in this setting, becoming the largest provider in the region. Patients initially received combination antiretroviral therapy at the TASO clinic in Gulu. In 2005 TASO began a home based treatment programme for patients who need home based care or outreach in rural areas of Gulu District and camps. The primary initiation regimen is based on non-nucleoside reverse transcriptase inhibitors. At the time of data collection first line treatment typically comprised nevirapine, lamivudine, and stavudine, and second line treatment comprised boosted lopinavir, didanosine, and zidovudine. Criteria used for starting treatment when these data were gathered included WHO stage 3 or 4 illness or a CD4 cell count below 200 cells/µl. HIV-1 RNA concentrations are not used in this setting, as no facilities to measure viral load exist in the region. Given the infrastructure constraints and pressing clinical needs, many patients will start combination antiretroviral therapy on clinical presentation and may not have CD4 evaluations.

Apart from patients receiving services at the main TASO clinic in Gulu town, outreach programmes to the internally displaced persons' camps in Pabbo, Bobbi, and Awach also exist. The mobile combination antiretroviral therapy clinics take place every fortnight in the camps, and patients schedule appointments to meet with field workers and clinicians. Mobile clinics take place in public settings, as well as in individual households in the camps. Field workers manage drug distribution, and clinicians provide clinical care. Field officers who document and report outcomes to the combination antiretroviral therapy team leaders in the camps or camp elders manage side effects and adherence. In anticipation of any rebel attacks, patients are given a hotline mobile number; patients who need combination antiretroviral therapy or have clinical problems are escorted by military transport to the nearest safe TASO clinic or receive military intelligence of safe routes. Stigma remains a major reason for not using voluntary counselling and testing.

Data collection

Clinicians and field workers complete standardised forms detailing patients' demographics, as well as clinical, psychosocial, and drug use data at each visit. These data are then hand entered, in duplicate, into the TASO database. Patients are given a unique confidential identifying number.

A field adherence monitoring team equipped with motorcycles is responsible for active retention and follow-up of patients. The field adherence monitoring team visits patients who fail to attend any appointment and those who have requested home based care. The team consists of medical attendants who do adherence counselling and clinical observation and provide combination antiretroviral therapy. TASO has a rigorous method for measuring adherence, which far surpasses most Western standards. It involves a composite of pharmacy monitored drug possession ratio, pharmacy refill records, and a three day recall report by patients or care givers. TASO defines adequate clinical adherence to combination antiretroviral therapy as ≥95%.

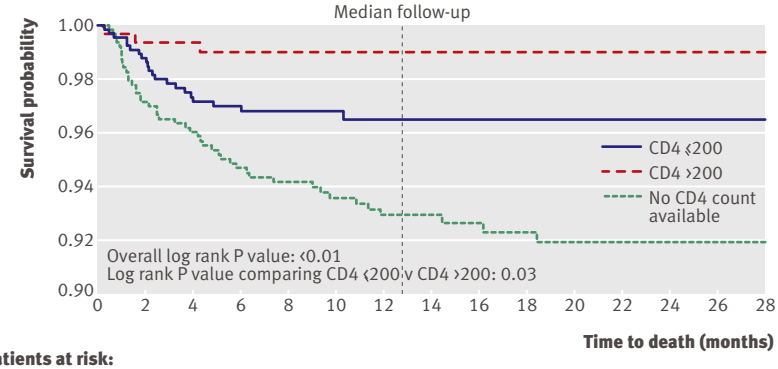
Patients began receiving combination antiretroviral therapy from 8 June 2005 and were followed until 29 January 2008. The median numbers of patients who entered the programme were 47 (interquartile range 23-72) monthly, 129 (54-221) every three months, and 287 (49-358) every six months.

Outcomes

The primary outcome of interest was all cause mortality. Secondary outcomes analyses included assessment of immunological status at start of combination antiretroviral therapy and patients' characteristics. Covariates in our analysis included age, sex, CD4 count at start of treatment, presence of tuberculosis, internally displaced person status, and adherence defined as above.

Analysis

We used Kaplan-Meier methods to assess survival over time. We used Cox proportional hazards to determine if covariates determined in advance affected mortality. Our covariates included sex, age, CD4 count at start (≤200 *v* >200 cells/μl), adherence, duration of treatment, tuberculosis at start, and internally displaced person status. We explored the effect of missing CD4 counts at baseline on the relation between adherence and mortality in sensitivity analyses. The final adjusted model used a backward selection process based on the Akaike information criterion. We checked the proportional hazards assumption for this model by using a test based on the weighted residuals and found no evidence of deviation from this assumption. We used the Hosmer-Lemeshow test to test the final model for fit and found no evidence of a lack of fit. We additionally examined whether CD4 count at the start of treatment was affected by sex, internally displaced person status, or the presence of tuberculosis. We formally tested these by using the χ^2 test and Fisher's exact test. All P values are exact. All tests of significance are two sided, and $P<0.05$ indicates that an association is statistically significant. We used SAS (version 9.0) for all calculations.



No of patients at risk:

CD4 ‹200	664	570	448	281	109	99	53	32
CD4 ›200	318	285	251	188	133	131	104	64
No CD4 count available	643	588	506	414	276	258	207	86

Fig 1 | Kaplan-Meier plot for survival in patients with CD4 cell count at start of treatment >200 cells/μl or ≤200 cells/μl and in those with no CD4 data available

RESULTS

The table describes the demographic, clinical, and immunological characteristics of patients included in the analysis. Of 5625 adults (aged >14 years) receiving clinical care from TASO in Gulu District, a total of 1625 are receiving combination antiretroviral therapy and were included in our analysis—100% of all patients who ever received combination antiretroviral therapy from TASO in Gulu District. The cohort represented a cumulative 1981 patient years of follow-up. Most (72%) patients were women, and the median age was 39 (interquartile range 33-46) years. Of all internally displaced people in the study, 14.0% resided in official government camps and the rest resided in outlying areas. All patients were started on non-nucleoside reverse transcriptase inhibitor based regimens.

Patients started treatment with a median CD4 count of 157 (interquartile range 90-220) cells/μl, and most (63%) had WHO stage 2 disease. A total of 62 patients had been diagnosed as having pulmonary tuberculosis at baseline. The median follow-up time was 12.8 (7.7-23.1) months; 69 (4.2%) patients died during follow-up, giving a mortality incidence rate of 3.48 (95% confidence interval 2.66 to 4.31) per 100 person years.

Of the 982 patients with available baseline CD4 counts, 664 (68%) had CD4 counts of 200 cells/μl or less. Median follow-up was similar by baseline CD4 count: 10.5 (interquartile range 6.3-15.0) months for patients with CD4 counts 200 cells/μl or less and 14.4 (9.3-27.5) months for those with CD4 counts above 200 cells/μl. Mortality varied by baseline CD4 cell count: 21/664 (3.2%, 3.22/100 patient years) patients with CD4 counts of 200 cells/μl or less died compared with 3/316 (0.9%, 0.68/100 patient years) patients with CD4 counts above 200 cells/μl. For the 643 patients with no initial CD4 count available, the median follow-up time was 14.3 (9.1-26.1) months and 45 patients died (7.0%, 50.8/100 person years). Patients without CD4 counts were less likely to be in a camp and were less likely to have tuberculosis at the start of treatment than were patients who had CD4 cell counts available (internally displaced persons' camp: 69/643 (10.7%) *v* 158/982 (16.1%), P=0.002; tuberculosis: 5/643 (0.8%) *v* 57/980

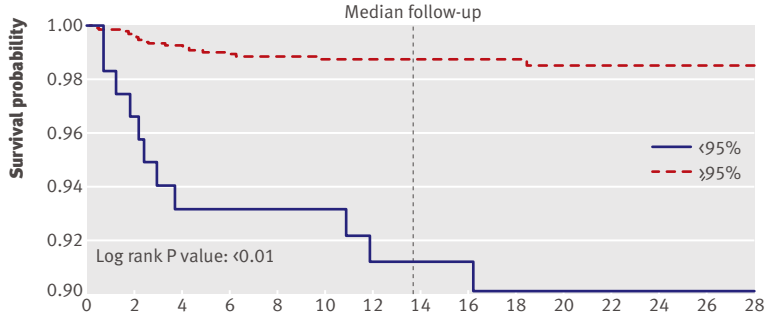
(5.8%), P<0.0001). We found no significant difference between patients without or with cell counts in terms of sex: 458/643 (71.2%) *v* 704/982 (71.7%) (P=0.8). Figure 1 shows the Kaplan-Meier plot for survival in patients with CD4 counts of 200 cells/µl or lower and above 200 cells/µl and for those without CD4 cell evaluations.

The median follow-up time for the 1521 patients who had complete adherence data was 13.7 (8.4-23.6) months. Of the 1521 patients with complete data for adherence, 118 (7.8%) patients had adherence below 95% and 1403 (92.2%) had adherence of 95% or above. The median follow-up was 26.0 (14.4-28.4) months for patients with adherence below 95% and 12.8 (8.1-22.4) months for those with adherence of 95% or above. A total of 11/118 (9.3%, 5.24/100 patient years) patients with less than 95% adherence died compared with 17/1403 (1.2%, 1.00/100 patient years) patients with at least 95% adherence. Figure 2 shows the Kaplan-Meier plot for survival of patients defined as adherent or not adherent (<95% or ≥95%).

Of the 69 people who died, the shortest time between the start of treatment and death was eight days. Of the deaths, 17 (25%) occurred within 1. 3 months of starting treatment, 35 (50%) within 2. 5 months of starting treatment, and 52 (75%) within 5. 1 months of starting treatment. No violent deaths occurred in this cohort.

Lower mortality was associated with female sex (hazard ratio 0.70, 95% confidence interval 0.55 to 0.91, P=0.02), higher baseline CD4 count (hazard ratio per 100 cell increase 0.14, 0.06 to 0.34, P<0.0001), and at least 95% adherence (hazard ratio 0.14, 0.10 to 0.21, P<0.0001). Residence in a camp (0.39, 0.14 to 1.05, P=0.06) and age (hazard ratio per year increase 1.00, 0.99 to 1.02) were not associated with mortality outcomes.

Female sex was associated with higher CD4 cells counts at baseline (odds ratio 1.56, 1.15 to 2.13, P=0.005). Presence of tuberculosis at baseline was associated with lower CD4 counts (0.49, 0.25 to 0.95, P=0.04). Residence in a camp was not associated with CD4 counts at start of treatment (0.84, 0.58 to 1.22, P=0.34).



No of patients at risk:

Adherence <95%	118	106	100	91	84	82	65	34
Adherence ≥95%	1403	1266	1056	764	415	389	290	144

Fig 2 | Kaplan-Meier plot for survival in patients defined as adherent or not adherent (<95% or ≥95% adherence)

DISCUSSION

Our study represents the first effort to assess outcomes of treatment among a large cohort of patients receiving combination antiretroviral therapy in a complex emergency setting. Adults receiving such treatment in Gulu, northern Uganda, showed clinical outcomes better than those found in the only other existing study of patients receiving combination antiretroviral therapy in a conflict setting.[9] The results compare favourably with those found in peaceful regions of Uganda and other low income countries.[17-20] The high median age (39, interquartile range 33-46, years) of patients clinically eligible for and receiving combination antiretroviral therapy suggests that many people are infected with HIV in their late 20s. The predominance of women (72%) in our cohort might be explained by the comparatively low number of men in Gulu District.[12] These findings are consistent with UNAIDS estimates of age specific HIV prevalence and access to combination antiretroviral therapy in Uganda.[1]

Findings in context with other studies

The mortality incidence rate among adult patients receiving combination antiretroviral therapy in our cohort—3.48 (95% confidence interval 2.66 to 4.31) per 100 person years—was about half of that found in Bukavu, Democratic Republic of Congo (7.9 (3.6 to 12.1) per 100 person years), a setting with ongoing active violence and noticeably fewer aid agencies available.[9] Interestingly, this is also lower than the mortality found in better resourced, politically stable areas of Uganda, such as Rakai, where the mortality has been 5.2 per 100 person years among patients receiving combination antiretroviral therapy.[17] We found that residence in a camp did not predict worse outcomes than urban dwelling. This is consistent with WHO and Ugandan government reports about crude mortality in Gulu District,[12] and it supports the view that communities surrounding internally displaced persons' camps may be more vulnerable than populations living within them.[21]

Strengths and limitations

Several strengths and limitations need to be considered in interpreting our study. Strengths include the retention of patients in our cohort. Whereas many programmes in Africa are affected by considerable loss to follow-up,[22] our programme uses a special counselling team on motorcycles to consistently track patients. This model is now being implemented by other organisations throughout Africa. Our adherence counselling is superior to that found in more developed settings, as TASO has specifically employed adherence counsellors and database managers at each TASO site.

Regarding limitations, this is a prospective cohort. As with any cohort study, confounding variables of which we are unaware may be present. We have tried to control for these by using a priori explanations of bias. We did not have routine CD4 counts for all patients, which is common in emergency humanitarian settings

WHAT IS ALREADY KNOWN ON THIS TOPIC

Early guidelines suggested that antiretroviral therapy for populations affected by conflict was untenable

Access to antiretroviral therapy for conflict affected populations remains low

WHAT THIS STUDY ADDS

Patients receiving antiretroviral therapy had favourable outcomes in mortality and adherence

Innovative strategies to retain patients in care may contribute to positive health outcomes and reduce mortality and loss to follow-up

Expansion of antiretroviral care to other conflict affected populations is warranted

and in resource limited settings. Given resource constraints, we do not do viral load evaluations. We use clinical signs and treatment interruptions, which have been shown to be possibly equally effective for monitoring patients' outcomes.[19 23]

In clinical monitoring, mortality provides the strongest inference of treatment successes. We did a sensitivity analysis in which the Cox proportional hazards survival analysis was re-done with adjustment for all variables except CD4 at start of treatment. This increased the sample size from 947 to 1519, and we found the same magnitude of association between adherence and mortality as in the previous analysis that excluded patients without CD4 counts. Indeed, this is common circumstance in many resource poor settings.[24]

Possible explanations of findings

Our finding that only 14% of patients receiving combination antiretroviral therapy resided in internally displaced persons' camps may reflect a bias specifically in access to HIV treatment. Internally displaced people residing in camps often provide protection and support to their neighbours. Among patients residing outside camps, we were unable to differentiate those forcibly displaced by conflict from those who voluntarily migrated to Gulu District for other reasons. The reality remains that all of Gulu District and Municipality's population has been affected by armed conflict.

The adherence to treatment among our cohort of adult patients receiving combination antiretroviral therapy was high. This compares favourably with levels of adherence reported from studies involving patients in well resourced, politically stable areas of Uganda or the rest of the world. Whereas 92% of our patients had at least 95% adherence, the reported adherence in the capital, Kampala, is 82%.[18 19] The adherence among our patients in Gulu is particularly striking when compared with pooled adherence rates across sub-Saharan Africa and North America, where 77% and 55% of patients adhered to combination antiretroviral therapy.[25] Duration of clinical follow-up may contribute to adherence, as the median follow-up time for patients with good adherence was 12.8 months, compared with 26.0 months among patients with poor adherence.

Implications

These impressive clinical outcomes may largely be possible owing to the stability of the population in Gulu after the influxes of 2002 and 2004.[11] Compared with other districts affected by conflict in northern Uganda, Gulu has the largest number of health facilities and thus better access for internally displaced people and resident communities.[16] Maintaining positive clinical outcomes among patients receiving combination antiretroviral therapy may be challenging in the face of anticipated movements of population. In 2008 optimistic international organisations expected that 35% of internally displaced people in northern Uganda would relocate "home," 45% would be in transit, and 20% would remain in camps.[26] In early June 2008, the optimistic peace process between the Lord's Resistance Army and the government broke down. Steps will need to be taken to ensure that combination antiretroviral therapy is not disrupted as a result of the relocation of people from the camp to their homes and vice versa.[8 27] This should include cooperation with HIV treatment facilities in neighbouring districts and delivery of additional emergency "relocation" stock of combination antiretroviral therapy and the creation of treatment information cards and duplicate medical records for patients.[9]

Unanswered questions and future research

Humanitarian and government agencies should use the anticipated repatriation of internally displaced people as an opportunity to investigate different modalities of combination antiretroviral therapy programmes for displaced and returning populations. Research in this area would facilitate the development of international best practices for sustaining drug distribution, for the monitoring of clinical and viral outcomes, and for the management of adverse outcomes and opportunistic infections among displaced and returning patients.[8] Development of programmes and policies in this area is particularly important in light of the fact that 330 000 refugees and 33 000 internally displaced people returned home in 2005.[28] Identifying programmatic strategies for maintaining access to combination antiretroviral therapy during movements of populations would also be applicable to newly displaced populations. The need for development of policies and programmes in this area is highlighted by situations such as Zimbabwe's 2005 forced displacement of 700 000 urban residents, including 79 500 HIV positive adults and children, during the Operation Murambatswina[29]; and by continued arrivals of refugees from sub-Saharan African countries such as Kenya, Sudan, the Democratic Republic of Congo, Somalia, Cote D'Ivoire, Burundi, and Liberia.[28]

Conclusions

Our study describes the first outcomes among a large cohort of patients receiving combination antiretroviral therapy in northern Uganda. Our findings show that the provision of such treatment in contexts with armed conflict is both feasible and potentially highly successful. Our study validates recent policies set out by the

WHO and UNHCR about HIV treatment in complex emergencies and shows the imperative of expanding access to combination antiretroviral therapy to populations affected by armed conflict.

Contributors: AK, CN, AA, CLC, JSGM, and EJM developed the concept of the study, and all authors designed it. AK, RJN, CN, CLC, and EM were responsible for data acquisition. AK, CLC, KAF, JSGM, and EJM analysed the data. All authors interpreted the results, drafted the manuscript, and approved the final manuscript. EJM is the guarantor.
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Competing interests: None declared.
Ethical approval: The administrative headquarters of TASO Uganda, Kampala, and the Mbale Regional Referral Hospital Review Board approved the study.

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