Scaling up of highly active antiretroviral therapy in a rural district of Malawi: an effectiveness assessment

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Summary

Background **The recording of outcomes from large-scale, simplified HAART (highly active antiretroviral therapy) programmes in sub-Saharan Africa is critical. We aimed to assess the effectiveness of such a programme held by Médecins Sans Frontières (MSF) in the Chiradzulu district, Malawi.**

Methods **We scaled up and simplified HAART in this programme since August, 2002. We analysed survival indicators, CD4 count evolution, virological response, and adherence to treatment. We included adults who all started HAART 6 months or more before the analysis. HIV-1 RNA plasma viral load and self-reported adherence were assessed on a subsample of patients, and antiretroviral resistance mutations were analysed in plasma with viral loads greater than 1000 copies per mL. Analysis was by intention to treat.**

Findings **Of the 1308 patients who were eligible, 827 (64%) were female, the median age was 34·9 years (IQR 29·9–41·0), and 1023 (78%) received d4T/3TC/NVP (stavudine, lamivudine, and nevirapine) as a fixed-dose combination. At baseline, 1266 individuals (97%) were HAART-naive, 357 (27%) were at WHO stage IV, 311 (33%) had a body-mass index of less than 18·5 kg/m², and 208 (21%) had a CD4 count lower than 50 cells per μL. At follow-up (median 8·3 months, IQR 5·5–13·1), 967 (74%) were still on HAART, 243 (19%) had died, 91 (7%) were lost to follow-up, and seven (0·5%) discontinued treatment. Low body-mass index, WHO stage IV, male sex, and baseline CD4 count lower than 50 cells per μL were independent determinants of death in the first 6 months. At 12 months, the probability of individuals still in care was 0·76 (95% CI 0·73–0·78) and the median CD4 gain was 165 (IQR 67–259) cells per μL. In the cross-sectional survey (n=398), 334 (84%) had a viral load of less than 400 copies per mL. Of several indicators measuring adherence, self-reported poor adherence (<80%) in the past 4 days was the best predictor of detectable viral load (odds ratio 5·4, 95% CI 1·9–15·6).**

Interpretation **These data show that large numbers of people can rapidly benefit from antiretroviral therapy in rural resource-poor settings and strongly supports the implementation of such large-scale simplified programmes in Africa.**

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Introduction

In 2003, WHO launched the ambitious 3 by 5 strategy,[1] which recommends simplified management plans for the prescription and surveillance of antiretroviral therapy in resource-constrained settings, with the aim of ensuring that 3 million people receive treatment by the end of 2005.[2] An interim report in June, 2005, revealed that only 1 of the 6 million people currently in need of antiretroviral treatment were actually receiving them.[3,4] Most of these patients were living in middle-income countries such as Brazil, Thailand, and South Africa. The report concluded that the 3 by 5 programme would not reach its goal.

Scarce financial and human resources and inadequate health-care infrastructure are major challenges to the scaling up of treatment in sub-Saharan Africa. Models of care must be adapted to these circumstances, accounting for the few trained health personnel, different groups of patients compared with high-income countries (increased proportions of children and women of child-bearing age affected), restricted drug availability and procurement, inadequate access to monitoring equipment, and few extra funds. Data for ongoing experiences and patients' outcomes in different models of care are still scarce and could greatly contribute to the improvement and transfer of such models. The medical non-governmental organisation Médecins Sans Frontières (MSF) currently provides highly active antiretroviral therapy (HAART) to more than 56 000 patients in 56 projects worldwide and actively participates in implementing scaling-up and simplification procedures.[5,6]

This study aimed to assess the effectiveness of the most rapidly expanding and largest MSF programme in the rural district of Chiradzulu in Malawi by analysis of survival indicators, CD4 count evolution, virological response, and adherence.

Methods

Setting

Malawi is one of the poorest countries in southern Africa with a yearly health-care expenditure of US$11·8 per capita. HIV prevalence was estimated at 19·8% in people attending antenatal clinics in 2003, and of a population of 10·5 million inhabitants, 900 000 were estimated to be infected with HIV by 2003.[7] HIV/AIDS is the leading cause of death in the most productive age group (20–49 years) and greatly affects life expectancy, which at 38·5 years is

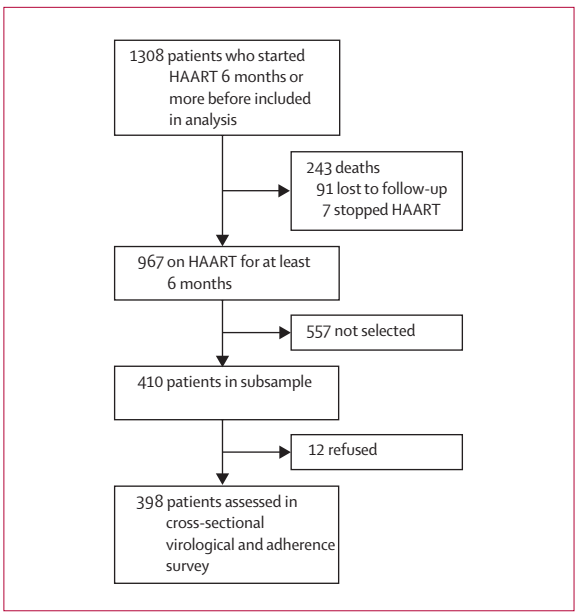

Figure 1: **Study profile**

one of the lowest in the world.[7] Chiradzulu district consists of 250 000 inhabitants, most of whom are poor self-sufficient farmers, with two hospitals and ten rural health centres. According to HIV prevalence and the proportion of patients with advanced disease, about 6000 people in the district are regarded to be in urgent need of HAART.

Study population

In collaboration with the Malawian Ministry of Health and Population, MSF began an HIV programme in Chiradzulu in 1997. HAART was begun free of charge in 2001 at the district hospital. HAART initiation criteria were WHO stage IV irrespective of CD4 count, and WHO stages I, II, or III with CD4 counts lower than 200 cells per µL according to WHO recommendations.[2] CD4 counts were initially measured by manual techniques (Dynabead, Dynal Biotech SA, Compiègne, France), and later by semi-automated techniques (Cyflow counter, Partec, Münster, Germany) that have been used since mid-2003. All laboratory tests took place at the laboratory of the district hospital by two technicians.

Of 2928 HIV-infected patients who were on HAART up to April 15, 2004, 1308 adults who started HAART 6 months or more before were included in the analysis (figure 1). Medical background and follow-up information were routinely obtained at every consultation on standardised forms and entered into FUCHIA monitoring software (follow-up and care of HIV infection and AIDS, Epicentre, Paris, France).

Treatment

The availability of an easy-to-use first-line regimen has been fundamental to the development of a large-scale programme with few resources. From October, 2002, treatment was based on the fixed-dose combination of stavudine (d4T), lamivudine (3TC), and nevirapine (NVP; Triomune, Cipla, Mumbai, India). MSF has been using this generic regimen for some time, well before WHO prequalification. This regimen was initially validated through internal MSF drug qualification procedures based on WHO recommendations and was then prequalified by WHO.[8,9] The regimen is now recommended by WHO and shown to have an excellent safety and efficacy.[2,10] When available, two doses of Triomune (d4T 30 mg or 40 mg) were used accordingly to patients' bodyweight to keep d4T-related toxic effects to a minimum. Patients who are intolerant to this combination are offered other regimens based on efavirenz (EFV; Merck Sharp Dohme, Manati, Puerto Rico) together with a d4T-3TC combination (Ranbaxy, Dewas, India).

From August, 2002, key steps were taken to adapt the programme towards scaling up (panel).[11] HAART was then initiated after decentralisation by the mobile HIV team during their bimonthly visits in the health centres and the peripheral hospital. Overall, these adaptations have allowed the programme to scale up from initially few monthly inclusions (mean 16 patients per month before August, 2002) to more than 100 patients in May, 2003 (mean 139 per month in 2003), and to almost 220 patients per month in 2004. At the time of the study

***Panel:* Adaptations of HAART programme towards scaling up**

- Disbanding of the previously established selection committee with immediate referring of the eligible patients to a counsellor
- Implementation of group HAART counselling sessions
- Because individual testing was not feasible, no systematic baseline CD4 count was done from 2003 and HAART was initiated according to clinical criteria only (WHO stage III or IV), as recommended by WHO when CD4 testing was not available[2]
- Yearly CD4 count for all the patients as the only routine monitoring blood test undertaken; other tests (cell blood count, chemistries) done only at initiation or if needed
- Introduction of a fixed-dose combination (Triomune), which is known to facilitate adherence (one pill twice a day) and drug supply
- Running of the HIV clinic in the district hospital 5 days a week
- Decentralisation of HAART consultations through a mobile HIV clinic from the district hospital to the ten rural health centres and the peripheral hospital since early 2003
- Monthly follow-up visits by a clinician until stabilisation on antiretroviral drugs
- Bimonthly visits by dispensing nurses after stabilisation on antiretroviral drugs (for symptom questioning, antiretroviral prescriptions, and pill counts). A clinician was seen if symptoms were reported on questioning

in April, 2004, 2928 patients had begun HAART in the programme.

Cross-sectional virological survey

Between Jan 1 and April 15, 2004, a cross-sectional survey was undertaken to assess the virological status of patients still on treatment. All patients aged 18 years or older, who had been receiving HAART for 6 months or more, and who presented to the HIV clinic during the study were regarded as eligible. With an expected prevalence of virological failure of 20%, a precision of 3%, and a type I error of 0·05, a sample size of 400 people was targeted. A subsample of patients with an even identification number from the patients' register was chosen. Plasma samples were obtained after blood sample centrifugation and immediately stored at –80ºC. All samples were sent in dry ice under strict cold-chain procedures to the Purpan Hospital Virology Unit (Toulouse, France), where plasma viral loads were measured with the Amplicor HIV-1 Monitor version 1·5 assay (Roche Diagnostics, Meylan, France), which measures non-clade B HIV-1 subtype RNA.[12] For viral loads greater than 1000 copies per mL, HIV-1 reverse transcriptase genotyping and identification of HIV subtypes were undertaken at the same time.[13,14] The resistance profiles to antiretroviral molecules were defined according to National Agency for AIDS Research (ANRS) algorithms.[15] Ethics approval for the survey was obtained from the ethics committee of the Malawi Ministry of Health and written consent was obtained from all participants.

Cross-sectional self-reported adherence survey

All patients included in the cross-sectional virological survey were also interviewed with a simple adherence questionnaire, given face-to-face in the local language by interviewers not linked to the medical team. The questionnaire was adapted from AIDS clinical trial group (ACTG) adherence follow-up questionnaires and the MASRI questionnaire.[16,17] Patients were asked to report the daily number of antiretroviral pills they had missed during the past 4 days, as well as their perceived adherence during the 28 days before the visit, as measured by a visual analogue scale. Patients were also asked the main reasons for non-adherence. We used three indicators to measure adherence with self-reports. First, patients were classified as highly adherent if they reported to have taken 100% of their prescribed dose during the past 4 days, moderately adherent if they have taken 80–99%, or non-adherent if they have taken 80% or less. A second measure of adherence in the previous 28 days was simply based on the visual analogue scale to classify patients into highly adherent (100%), moderately adherent (80–99%), and non-adherent (<80%) groups. We obtained a specific measure of high adherence with a third combined indicator, using an approach already adopted in studies with a similar way of questioning but based on self-administered questionnaires.[18] From the classification of adherence in the past 4 days, highly adherent patients were reclassified as moderately adherent if they reported to have inadequately followed the prescribed schedule of their prescriptions, or did not report 100% adherence in the previous 28 days on the visual analogue scale.

Another estimate of patients' adherence not based on self-report was derived from the examination of patients' pill boxes and the counting of pills actually taken with respect to the number of pills prescribed. We referred to this measure as the pill count.

Statistical analysis

Product-limit estimates (Kaplan-Meier) were calculated to assess the probability of survival and remaining in care at 12 and 24 months since HAART initiation, with all patients analysed by an intention-to-treat basis. Patients alive and in care on April 15, 2004, were right-censored on the date of their last visit before this date. At first, we calculated the probabilities of surviving at 12 and 24 months by just using death events. Patients with more than 2 months' delay with respect to the scheduled follow-up visit and who could not be traced were regarded as lost to follow-up. A second survival analysis to estimate the probability of patients remaining in care was done with events counted as patients who died or who were lost to follow-up.

We used a Cox model to identify independent predictors of deaths occurring in the first 6 months after HAART initiation. Factors included in the model were baseline data such as age, sex, CD4 cell count or WHO clinical stage if CD4 counts were missing, body-mass index, drug regimen used, decentralised follow-up, and year of HAART initiation. According to the evolution of the treatment programme, years 2001 and 2002 were compared with 2003 (the year when follow-up of patients had been simplified). Because some patients started HAART on the sole basis of clinical assessment (with no baseline CD4 count), we used a variable defining patients' clinico-immunological status based either on baseline CD4 count if available or on WHO staging when CD4 cells were not counted. For this variable, CD4 counts greater than 50 cells per µL were used as the reference category. We used logistic regression analysis to identify factors associated with virological failure (viral load >1000 copies per mL).

A logistic regression analysis was done on treatment-naive patients to identify which indicator among the pill counts and the three self-reported adherence measures was the best predictor of detectable viral load (>400 copies per mL). We used Stata 8.2 software for analysis (Stata Corp).

Role of the funding source

MSF participated in the study design and data collection. The Sidaction did not participate in any part of the study process. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Whole cohort (n=1308)	Survey group (n=398)
Demography		
Female	827 (64%)	275 (69%)
Median age (years [IQR])	34·9 (29·9–41·0)	34·0 (28·9–40·3)
HAART-naive	1266 (97%)	384 (96%)
Clinico-immunology		
WHO stage at HAART initiation		
Stage I/II	232 (18%)	72 (18%)
Stage III	718 (55%)	230 (58%)
Stage IV	357 (27%)	96 (24%)
Body-mass index (n)	943	303
Median (kg/m^2 [IQR])	19·8 (17·9–22·1)	20·0 (18·3–22·2)
<18·5 kg/m^2	311 (33%)	84 (28%)
CD4 T-cell counts at initiation (n)	980	327
Median number of cells per µL (IQR)	112 (59–176)	114 (66–177)
Count <50 cells per µL	208 (21%)	56 (17%)
Treatment		
Initial antiretroviral treatment		
d4T/3TC/NVP	1023 (78%)	299 (75%)
AZT/3TC/NVP	256 (20%)	90 (23)
AZT/3TC/EFZ	12 (1%)	5 (1%)
d4T/3TC/EFZ	14 (1%)	2 (0·5%)
AZT/3TC/IND	2	2 (0·5%)
d4T/3TC/RIT	1	..
Follow-up time on HAART		
Median for all patients (months [IQR])	8·3 (5·5–13·1)	9·5 (7·4–15·2)
Outcomes		
Deaths	243 (19%)	..
Loss to follow-up	91 (7%)	..
Stopped treatment	7 (0·5%)	..
Still on HAART	967 (74%)	..

Data are number of patients (%) unless stated otherwise.

Table 1: **Baseline characteristics of patients**

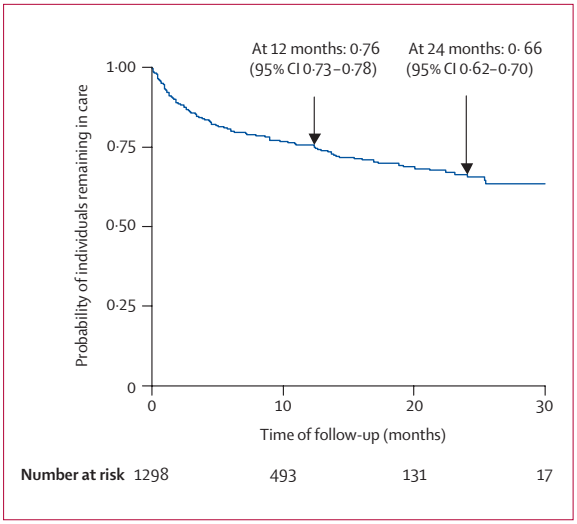

Figure 2: **Kaplan-Meier curve of patients who started HAART 6 months or more before and remaining in care in the Chiradzulu programme, Malawi (n=1298)**

Results

Of the 1308 adults who started HAART 6 months or more before and who were included in the analysis (figure 1), 68 (5%) started HAART in 2001, 300 (23%) in 2002, and 940 (72%) in 2003. For 501 (47%) of 1076 patients for whom the information was available, a decentralised follow-up in the health centres was implemented. Table 1 summarises the baseline characteristics of all the patients in our study.

Figure 1 shows the study profile, for clinico-immunological outcomes; median duration of follow-up was 8·3 months (IQR 5·5–3·1). Most deaths (187 [77%] of 243) occurred in the first 6 months after HAART initiation (median time to death 2·6 months, IQR 1·0–5·6). Of the 967 patients still on HAART, 757 (78%) were on d4T/3TC/NVP, 151 (16%) on AZT (zidovudine)/3TC/NVP, 29 (3%) on d4T/3TC/EFZ, 18 (2%) on AZT/3TC/EFZ, nine (1%) on an nelfinavir-protease-inhibitor-based second-line regimen, and three had other prescriptions.

Overall, 879 (91%) individuals were still on their original regimen and 88 (9%) had to change one or two antiretroviral drugs (47 for drug intolerance). Of the 1308 patients in the cohort, 66 (5%) were reported to have stopped their treatment because of severe drug intolerance, of which 27 stopped AZT (21 for anaemia, one for neutropenia, three for other reasons, two for unknown reasons), 15 stopped d4T (11 for peripheral neuropathy, one for myopathy, three for unknown reasons), 22 stopped NVP (13 for skin toxic effects, six for hepatotoxic effects, three for unknown reasons), and two stopped EFV (one for skin rash, one for insomnia).

With only death events accounted for, Kaplan-Meier probability of survival was 0·81 (95% CI 0·79–0·83) at 12 months and 0·72 (0·68–0·76) at 24 months. With both death and loss to follow-up events accounted for, the probability of remaining in care was 0·76 at 12 months and 0·66 at 24 months (figure 2).

Of patients with available CD4 counts at baseline (n=980), median gain of CD4 cells was 139 cells per µL (IQR 63–234) at 6 months (n=102) and 165 (67–259) at 12 months (n=192). At 12 months, only eight (4%) of 215 patients with a CD4 test available had a CD4 count still lower than 50 cells per µL whereas 144 (67%) had CD4 counts higher than 200 cells per µL.

After factors associated with early deaths (occurring in the first 6 months of HAART initiation) were analysed by a multivariate Cox model (n=925), four baseline factors could be independently identified: body-mass index of less than 18·5 kg/m^2, male sex, baseline CD4 count lower than 50 cells per µL, and WHO stage IV without CD4 test at baseline (table 2). Age at initiation, type of antiretroviral treatment used, period of initiation, and care from health centres (rather than care from hospitals) were not associated with early death in this analysis.

Of the 967 patients still on treatment after 6 months, a subsample of 410 patients was chosen for virological

	Univariate analysis	Multivariate analysis
Age		
>35 years	1	..
≤35 years	1·09 (0·80–1·49)	..
HAART initiation		
2003	1	..
2002	1·35 (0·97–1·88)	..
2001	0·70 (0·28–1·79)	..
Antiretroviral regimen		
AZT-based	1	..
d4T-based	1·03 (0·70–1·52)	..
Follow-up		
Centralised process	1	..
Decentralised process	1·26 (0·91–1·74)	..
Sex		
Female	1	..
Male	1·76 (1·29–2·39)	1·63 (1·15–2·31)
Body-mass index*		
≥18·5 kg/m2	1	..
<18·5 kg/m2	3·56 (2·42–5·26)	2·92 (2·04–4·17)
CD4 at baseline		
≥50 cells per µL	1	..
<50 cells per µL	2·19 (1·51–3·19)	1·64 (1·07–2·53)
No CD4, WHO stage I/II	1·07 (0·42–2·74)	0·72 (0·18–2·94)
No CD4, WHO stage III	1·14 (0·68–1·91)	0·96 (0·55–1·68)
No CD4, WHO stage IV	3·04 (1·95–4·75)	2·47 (1·45–4·20)

Data are hazard ration (95% CI). *At baseline.

Table 2: **Cox model analysis of factors associated with early death in the Chiradzulu programme, Malawi (n=1308)**

	Number of individuals (%) (n=397)	95% CI	Cumulative %
<40 copies per mL	275 (69%)	65–74	69%
40–400 copies per mL	59 (15%)	11–18	84%
400–1000 copies per mL	11 (3%)	1–4	87%
1000–5000 copies per mL	19 (5%)	3–7	92%
5000–30 000 copies per mL	14 (3%)	2–5	95%
≥30 000 copies per mL	19 (5%)	3–7	100%

Table 3: **Viral load measures of 397 patients in cross-sectional virological survey**

assessment. Of these individuals, 12 refused to participate (figure 1). Baseline characteristics for the 398 people in the cross-sectional virological survey did not differ significantly from those in the entire cohort (table 1). No women had previously received single-dose NVP to prevent mother-to-child transmission. 299 (75%) initiated the 3TC/d4T/NVP regimen as a fixed-dose combination. Median follow-up duration was 9·5 months (IQR 7·4–15·2), with 245 (62%) patients already on HAART for 6–12 months, 80 (20%) for 12–18 months, 39 (10%) for 18–24 months, and 34 (9%) for more than 24 months. Median CD4 gain was 138 cells per µL (IQR 69–219) at 6 months (n=45) and 176 cells per µL (97–282) at 12 months (n=79).

Viral loads could be measured for 397 patients; 334 (84%) had less than 400 copies per mL and 345 (87%) had less than 1000 copies per mL. Of the 52 (13%) patients with a viral load higher than 1000 copies per mL, only 19 (5%) had counts of more than 30 000 copies per mL, a threshold indicator for major virological failure (table 3). In the multivariate logistic regression model, only previous exposure to antiretroviral treatment (odds ratio 5·06, 95% CI 1·34–19·1), when compared with HAART-naive patients, was associated with virological failure (viral load >1000 copies per mL). Other baseline characteristics (age, sex, WHO stage, body-mass index, CD4 count), period of HAART initiation, time of follow-up, gain of CD4 count at 6 months, or body-mass index at the time of the survey were not statistically associated with virological failure in the model.

HIV reverse transcriptase genotyping was done for the 52 patients who had viral loads higher than 1000 copies per mL; two samples were not interpretable because of failed PCR amplification. According to reverse transcriptase sequences, all viruses were identified as the HIV-1C subtype. Three (6%) interpretable sequences did not show any mutations, 42 (84%) presented NRTI (nucleoside reverse transcriptase inhibitor) mutations, and 47 (94%) non-NRTI mutations. The most frequent NRTI mutation was the 3TC-induced Met184Val mutation (n=38, 76%), whereas the Thr215Tyr/Phe mutation induced by d4T was rarely seen (n=6, 12%). The Lys65Arg mutation, known to confer resistance to tenofovir, was recorded in five (10%) patients taking non-tenofovir-based regimens.

Of the non-NRTI mutations, Lys103Asn (n=22, 44%) and Tyr181Cys/Ile (n=14, 28%) were more frequently identified than Lys101Glu/Gln (n=9, 18%), Gly190Ala/Ser (n=9, 18%), or Val106Met/Ala (n=7, 14%). According to ANRS algorithms, 42 patients with viral loads greater than 1000 copies per mL were resistant to both 3TC and NVP/EFV (of which six individuals were also resistant to d4T), and five were resistant to NVP/EFV only.[15]

For adherence analysis with the pill count (n=367), 334 (91%) patients were classified as highly adherent (235, 64%) or moderately adherent (99, 27%) and 33 (9%) as non-adherent. By use of self-reported adherence in the past 4 days (n=398), 383 (96%) patients were regarded as highly adherent (375, 94%) or moderately adherent (8, 2%), and 15 (4%) as non-adherent. With the combined indicator based on self-reports (n=398), 365 (92%) patients could be classified as highly adherent (301, 76%) or moderately adherent (64, 16%) and 33 (8%) as non-adherent.

Self-reported adherence in the past 4 days was the best predictor of detectable viral load (odds ratio 5·4, 95% CI 1·9–15·6) whereas the combined indicator was only marginally associated with this outcome (2·3, 1·0–5·2). However, the pill count (1·7, 0·7–4·1) and visual analogue scale (1·9, 0·8–4·5) were not significantly associated with detectable viral load; neither variable was

significant after adjustment for possible confounders or predictors. By contrast, the strength of the association between adherence in the past 4 days and viral load did not change even after adjustment for the duration of follow-up and other possible cofactors (sex, age, baseline body-mass index, and CD4 count). Of potential causes for missing pills (n=398), individuals being away from home (n=137), forgetting to take drugs (n=119), running out of pills (n=36), feeling sick (n=31), or trying to avoid side-effects (n=17) were the most frequently reported.

Discussion

Our study of a large-scale simplified HAART programme revealed that more than three-quarters of patients remained in care at 12 months with a median CD4 gain of 165 cells per µL. Low body-mass index, WHO stage IV, male sex, and a low baseline CD4 count were associated with early mortality. Of assessed patients still on HAART for more than 6 months, more than 80% had undetectable viral loads (<400 copies per mL). Self-reported adherence during the past 4 days was the best predictor of detectable viral load.

The Chiradzulu programme differs from most HAART programmes described so far in Africa with respect to the scaling-up and simplification procedures used and the number of patients already on treatment.[19–21] Currently, very few data from programmes currently involved in scaling-up HAART have been reported.[21–24] Clinical, immunological, and virological treatment outcomes obtained in our study are comparable with those described in cohorts from developing as well as developed countries,[21–26] and indicate that despite scarce medical and monitoring resources, a large cohort of patients with advanced stages of HIV disease could clearly benefit from first-line antiretroviral treatment.

Similar to other regions of Malawi, the Chiradzulu district health system is chronically short-staffed and MSF has had to employ five clinical officers, three dispensing nurses, seven counsellors, a pharmacy technician, and a medical doctor to provide outpatient antiretroviral services in collaboration with personnel from the Ministry of Health (two clinical officers, and nurses from health centres). Clinicians mostly focus on patients who are to begin or who have just begun antiretroviral treatment. Dispensing nurses' tasks are to detect poorly adherent patients and dispense the drugs. They also have the role of triage for patients who have already been stabilised on antiretroviral drugs. One MSF nurse was also in charge of tracing followed up patients. Counsellors deal with patients' education and psychological support. In the health centres during bimonthly visits, the MSF mobile HIV team was working in collaboration with Ministry of Health nurses who were in charge of the patients on all the other days.

We believe that free treatment is an important reason for assuring retention in antiretroviral treatment and sustained long-term immuno-virological response. This benefit is well illustrated by the situation in Brazil, where a free national programme has had wide coverage with very satisfactory outcomes.[27–29] However, the scaling-up process has not been without major challenges, and several institutional and individual beliefs and attitudes about provision of HIV care have had to be overcome. Doctors were initially uncomfortable in shifting responsibility towards nurses, although acceptance came quickly with the benefits of the treatment of such a large number of patients. Such a shift was necessary because of the chronic shortage of medical staff in the district and despite the input of substantial human resources by MSF. Similarly, the scarcity of trained laboratory staff is one of the factors preventing individual immunological and virological monitoring in this and other settings.

The high initial death rate recorded in our programme was similar to that seen in other African cohorts and in developed countries during the early HAART era for severely immunocompromised patients.[20,21,23,30] Death and loss to follow-up events mostly occur in the first 6 months after HAART initiation. Indeed, most patients die at home and the ultimate causes of death remain often unspecified. As expected, factors associated with early mortality are those indicating an advanced stage of the disease at HAART initiation. Other factors inherent to the programme itself, such as the period of inclusion and follow-up in the health centres (decentralisation), did not affect survival. Thus, this early death rate might show the late presentation of the patients to the clinic with overwhelming opportunistic infection or early immune reconstitution syndrome induction.[31] Serial changes in body-mass index are important prognostic indicators of survival in resource-rich settings.[32,33] In sub-Saharan Africa, the burden of intercurrent infections differs substantially, and whether body-mass index is a useful simple clinical marker of survival is debatable. Our data and recent studies suggest that body-mass index at the time of HIV diagnosis or at HAART initiation remains an important survival predictor in resource-poor settings.[33,34] Unexpectedly, male sex was also independently associated with early death. Since such an effect has not been reported previously in other African cohort studies,[19–21] unidentified confounding factors could also contribute to early death.

Such early mortality rates represent important challenges faced by the HIV programmes in sub-Saharan Africa to rapidly and efficiently treat large numbers of patients. Strategies are needed to help earlier access to HAART, to improve the diagnosis of opportunistic infections, and to better identify and manage immune reconstitution syndromes. Further studies are also needed to investigate nutrition strategies to reduce early mortality for patients with very low body-mass index.

We were concerned that changes in contact time between patients and clinicians due to the increasing number of patients rapidly enrolled in the scaled-up programme could affect adherence. Our finding that

most (84%) patients who survived the first 6 months had viral loads lower than 400 copies per mL, was similar to that obtained in better-resourced settings and in other reported African settings for treatment-naive patients.[19,20,26,35,36] We recorded that self-reported adherence in the past 4 days with a cutoff of 80% best predicted detectable viral loads (>400 copies per mL) in treatment-naive patients. Our results confirm that even for the fixed-dose combination regimen, adherence of less than 80% is detrimental for long-term virological response in the maintenance phase of treatment.[37] Additionally, our results underline that the most appropriate questions for adherence measurement could depend on how patients are questioned (face-to-face or self-administered) and in the sociocultural context, since social desirability or recall bias could modulate the answer to some questions. These results also show that, in simplified programmes, self-reported adherence combined with other indicators can be regarded as an important proxy of treatment outcome. Our result will help define a simple questionnaire to detect poorly adherent patients in such settings.

The high adherence to HAART treatment recorded in survivors from our cohort indicate early success of the scaling-up approach, and further confirm the effectiveness of generic fixed-dose combinations. Studies in resource-rich settings show that poor adherence in the maintenance phase is crucial for long-term immunovirological success. However, the median follow-up time of our patients studied is still short (9·5 months, table 1) and because adherence to HAART is a dynamic process,[18,37] further investigation is clearly needed to assess such adherence in the medium-term and long-term in this setting.

HIV genotyping of viral loads higher than 1000 copies per mL (13%) revealed the presence of mutations expected for HIV-1B subtype with respect to the antiretroviral drugs prescribed, whereas all viruses analysed were of the HIV-1C subtype, for which little is known, since most of the current knowledge relates to HIV-1B.[38,39] Viral resistance is an inevitable consequence of HAART, even in resource-rich settings with very high adherence, and should not be regarded as a barrier to scaling up but as another challenge to be faced.[40,41] Although legitimate concern exists about the spread of viral resistance during scaling up, the potential for chaotic drug supply and subsequent resistance in the absence of formal programmes is the probable alternative. In countries where few patients are exposed to suboptimum treatment and a public-health approach is taken to HIV management, the potential for widespread viral resistance could be less likely than that in resource-rich settings.[42–44] Sentinel monitoring approaches to follow HIV resistance emergence in HAART programmes should be implemented where possible.[45]

Our study presents several limitations mainly because it analyses the outcomes of an observational cohort with routine data monitoring. Indeed, the nature of opportunistic infections and comorbidities were incompletely recorded and could not be appropriately analysed. Standardisation and particular focus on these data in MSF programmes should allow more accurate analysis in the near future. Causes of death were incompletely recorded mainly because patients either died at home or could not be diagnosed (because of a lack of appropriate diagnostic procedures). Since tracing is not easy, and access to the clinic might be difficult for many patients, loss to follow-up was most likely in patients with negative outcomes. To consider this problem, we used analyses with a combined endpoint of death or loss to follow-up. Finally, with a median at 9·5 months, the follow-up on HAART of the patients studied was still restricted and long-term analyses are clearly needed to fully assess the effect of scaling-up procedures on global outcomes of the programme and to allow some generalisability of the results.

In conclusion, our study indicates that key steps for simplification and scaling up can be safely implemented to rapidly and efficiently treat large numbers of patients even if trained personnel availability will still remain to be an important limiting factor.[46]

Contributors

C Brasher, G Fédida, L Ferradini, P Guérin, D Odhiambo, E Szumilin, and J-M Tassie contributed to the study concept and design. L Ferradini was the study coordinator. S Balandine, A Jeannin, G Karungi, and L Mankhambo collected data. L Ferradini and L Pinoges did the statistical analysis. J Izopet did the virological assessment. B Spire and P Carrieri participated in the adherence assessment. C Brasher, L Ferradini, A Jeannin, and N Ford led the writing of the paper, and all investigators participated in its writing and editing.

Conflict of interest statement

We declare that we have no conflict of interest.

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