Generic fixed-dose combination antiretroviral treatment in resource-poor settings: multicentric observational cohort

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Background: The use fixed-dose combination (FDC) is a critical tool in improving HAART. Studies on the effectiveness of combined lamivudine, stavudine and nevirapine (3TC/d4T/NVP) are scarce.

Objective: To analyse 6861 patients in a large observational cohort from 21 Médecins Sans Frontieres (MSF) HIV/AIDS programmes taking 3TC/d4T/NVP, with subcohort analyses of patients at 12 and 18 months of treatment.

Methods: Survival was analysed using Kaplan–Meier method and factors associated with progression to death with Cox proportional hazard ratio.

Results: Median baseline CD4 cell count at initiating of FDC was 89 cells/μl [interquartile range (IQR), 33–158]. The median follow-up time was 4.1 months (IQR, 1.9–7.3). The incidence rate of death during follow-up was 14.2/100 person-years [95% confidence interval (CI), 13.8–14.5]. Estimates of survival (excluding those lost to follow-up) were 0.93 (95% CI, 92–94) at 6 months ($n = 2,231$) and 0.90 (95% CI, 89–91) at 12 months ($n = 472$). Using a Cox model, the following factors were associated with death: male gender, symptomatic infection, body mass index < 18 kg/m^2 and CD4 cell count 15–50 cells/μl or < 15 cells/μl. Subcohort analysis of 655 patients after 1 year of follow-up (M12 FDC cohort) revealed that 77% remained on HAART, 91% of these still on the FDC regimen; 5% discontinued the FDC because of drug intolerance. At 18 months, 77% of the patients remained on HAART.

Conclusions: Positive outcomes for d4T/3TC/NVP are reported for up to 18 months in terms of efficacy and safety.

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Introduction

Limited antiretroviral treatment options for HIV-infected patients in many part of the world have emphasized the need for a potent, non-toxic and easy-to-take first-line regimen [1]. World Health Organization (WHO) guidelines recommend a combination of two nucleoside reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) as first-line regimen in resource-poor settings [2]. Fixed-dose combinations (FDC) are particularly important in effective scaling-up of HAART in such settings [3]. Quality FDC that combines two NRTI and one NNRTI (the standard treatment regimen worldwide) is both easy to use (one pill, twice a day) and affordable (less than $US300 per patient per year); these two advantages are

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particularly relevant to ensuring good long-term adherence to treatment.

Currently, only one WHO prequalified combination of NRTI/NNRTI is available as a FDC, combining lamivudine (3TC), stavudine (d4T) and nevirapine (NVP). Despite the obvious advantages, and at least one study proving the safety and effectiveness of this combination [4], the use of such d4T/3TC/NVP FDC is still not supported by all funding agencies, and its effectiveness, tolerability and quality continues to be questioned. For the rest of this article, this d4T/3TC/NVP regimen will simply be referred as triple FDC.

There are some potential weaknesses to this FDC: resistance is rapid to two drugs, 3TC and NVP; fatal rashes and hepatotoxicity are associated with NVP; and peripheral neuropathy and lipodystrophy are associated with d4T. Given the limited published literature but widespread use of this FDC, it is important to review the clinical experience in this large dataset.

As part of a simplified strategy for providing HAART in resource-poor settings, Médecins Sans Frontières (MSF) uses a d4T/3TC/NVP FDC in its HIV/AIDS programmes whenever possible. These are currently prescribed free of charge in the majority (78%) of newly treated patients. We report here clinicoimmunological outcomes of 6861 patients receiving d4T/3TC/NVP in a range of resource-poor settings as well as a subcohort analysis of safety data in 655 patients after 1 year of follow-up (M12 FDC cohort).

Methods

Sites and patients

As of March 2004, 12 058 adults started HAART in 21 HIV/AIDS programmes (patients per programme ranged from 21 to 1952) run by MSF in 11 countries (FDC MSF cohort) [5]. Among them, all adult patients who initiated HAART as a d4T/3TC/NVP FDC regimen between 1 October 2001 and the date of analysis (March 2004) were included in the present cohort analysis. The first-line treatment included two NRTI and one NNRTI. WHO prequalified FDC of 3TC/d4T/NVP was used, mainly from two sources: Triomune (Cipla, Mumbai, India) or Triviro (Ranbaxy, Dewas, India). In Thailand, GPO-vir (Thai Government Pharmaceutical Organization, Bangkok, Thailand) was used, in keeping with national guidelines [6]. Lead-in dosing of 200 mg/day NVP was used systematically during the first 15 days according to standard guideline, followed by a full dose escalation (400 mg/day). The dosing of d4T was adjusted for body weight using the appropriate FDC in all programmes. Only four women received single-dose NVP for the prevention of mother-to-child transmission, and those women were considered as not being naive for antiretroviral therapy. Treatment selection criteria required that patients be symptomatic (WHO clinical stage III or IV) and/or have a CD4 cell count of < 200 cells/μl. In some programmes, baseline CD4 cell count was not measured if obvious symptoms of AIDS-related illness were present. People meeting these criteria were given clinical care in primary healthcare settings in a district or referral hospital, following consultation protocols approved by local health authorities. Monitoring of CD4 cell count was available in all countries; viral load was not routinely assessed, except in the Khayelitsha programme in Cape Town, South Africa [7]. In programmes where CD4 cell count values were routinely available, MSF guidelines recommend a switch to second-line treatment when the CD4 cell count falls $> 50\%$ from the peak or if it falls to the level at baseline on entering the programme. The importance of strict adherence is emphasized in all programmes. MSF recommendations are to ensure a free and uninterrupted supply of antiretroviral therapy, to facilitate support groups for people living with AIDS, to train all health workers on adherence issues, and to provide support for patients before antiretroviral therapy initiation, for example by encouraging them to identify a treatment assistant. Adherence assessment is done on a monthly basis during the first 6 months of treatment.

Subcohort analyses after either 12 or 18 months of follow-up were also performed on treatment-naive adults who started FDC regimen between 1 February and 31 May 2003 (M12 FDC cohort) or between 31 July and 30 November 2002 (M18 FDC cohort).

Data collection

Information on medical background, baseline sociodemographic characteristics and selected clinical, biological, and therapeutic follow-up was routinely collected at each consultation on standardized forms and entered into FUCHIA monitoring software (Follow-up and Care of HIV Infection and AIDS, Epicentre, Paris, France). When appropriate, the toxicity grading scale of the AIDS Clinical Trial Group was used for reporting clinical and laboratory adverse events [8]. Lipodystrophy was reported by subjective assessment from the clinician. CD4 cell counts were performed using manual (Dynabead) or semi-automated (Cyberflow Partec) techniques [9]. Informed consent was obtained from all patients for data collection and analysis.

Statistical analysis

Clinicoimmunological outcomes included median changes in CD4 cell counts from baseline at various intervals. Baseline CD4 cell and haemoglobin counts were considered as valid if performed within 3 months prior and 15 days after the initiation of therapy. All data are reported as median and interquartile range (IQR).

Product-limit estimates (Kaplan–Meier) were computed to estimate the probability of survival and remaining in

Table 1. Baseline characteristic and outcomes of patients of the whole MSF FDC cohort (6961) and of the M12 FDC cohort (at 12 months; $n = 655$).

Patient characteristics	MSF FDC cohort	M12 FDC cohort
Origin		
Africa	5175 (75.4)	460 (70.2)
Asia	1617 (23.6)	195 (29.8)
Central America	69 (1.0)	0
Demography		
Female [No. (%)]	4210 (61.4)	417 (63.7)
Median age [years (IQR)]	34 (29–40)	34 (29–41)
Naive for antiretroviral drugs [No. (%)]	6025 (87.8)	655 (100)
WHO stage [No. (%)]		
I/II	900 (13.1)	90 (13.7)
III	3643 (53.1)	307 (46.9)
IV	2318 (33.8)	258 (39.4)
Body mass index		
No. assessed	6094	581
< 18 kg/m^2 [No. (%)]	1950 (32.0)	185 (31.8)
≥ 18 kg/m^2 [No. (%)]	4144 (68.0)	396 (68.2)
Haemoglobin		
No. assessed	4646	532
< 80 g/l	372 (8.0)	51 (9.6)
80–99 g/l	1085 (23.3)	140 (26.3)
> 100 g/l	3189 (68.7)	341 (64.1)
CD4 cell count		
No. assessed	4893	578
Median [cells/μl (IQR)]	89 (33–158)	79 (26–143)
< 50 cells/μl [No. (%)]	1620 (33.1)	210 (32.1)
Median follow-up time on FDC [months (IQR)]	4.1 (1.9–7.3)	10.6 (9.7–11.5)
Outcomes [No. (%)]		
Deaths	413 (6.0)	82 (12.5)
Lost to follow-up	328 (4.8)	61 (9.3)
Stop HAART	128 (1.9)	9 (1.4)
Still on HAART	5992 (87.3)	503 (76.8)

FDC, fixed dose combination (see text); WHO, World Health Organization.

care at 6, 12 and 18 months since FDC initiation considering all patients on an intention-to-treat basis. Patients alive and in care on 31 March 2004 were right-censored at their last visit prior to this date. At first, the probabilities of survival were computed just considering death events. Patients with more than 2 month's delay with respect to the scheduled follow-up visit were considered as lost to follow-up and censored at the time of their last recorded visit to the clinic. A second survival analysis to estimate the probability of remaining in care was performed considering as events the patients who died or who were lost to follow-up.

Factors associated with progression to death were analysed using univariate and multivariate Cox proportional hazard models stratified per programme. The baseline covariates analysed for survival were: gender, age (over or under 35 years), WHO clinical stage (stage III–IV versus stage I–II), body mass index (BMI; above and below 18 kg/m^2), haemoglobin (< 80 or 80–99 versus > 100 g/l) and CD4 cell counts (< 50, 50–99, 100–199 versus > 200 cells/μl).

All variables associated with death with a P value < 0.25 in univariate analysis were included in the final multivariate model. All analyses were performed using Stata software (version 8.2; Stata Corp., College Station, Texas, USA).

Results

Among adult patients who initiated HAART in 21 MSF programmes, 6861 initiated an FDC regimen combining 3TC/d4T/NVP and were included in the analysis. Of them, 5175 (75.4%) originated from Africa, 1617 (23.6%) from Asia and 69 (1%) from Central America (Table 1).

Baseline characteristics of the population studied

Median age was 34 years [interquartile range (IQR), 29–40] and 61.4% were women (Table 1). There were 6025 patients naive of any antiretroviral treatment at FDC initiation (87.8%). Patients started FDC at an advanced stage of the disease, with 2318 (33.8%) already at WHO stage IV and 1950 (32.0%) having a BMI < 18 kg/m^2. Severe (< 80 g/l) and moderate anaemia (80–99 g/l) were found in 372 (8%) and 1085 (23.3%) of the patients, respectively. Of those patients with available CD4 cell count at baseline ($n = 4893$), median value was 89 cells/μl (IQR, 33–158); 1620 (33.1%) had a CD4 cell count < 50 cells/μl. Of all patients, 1968 (28.7%) had no CD4 cell count data available at baseline and initiated FDC upon clinical criteria only.

Clinical and immunological outcomes

Median follow-up was 4.1months (IQR, 1.9–7.3) after FDC initiation. At the date of analysis (March 2004),

413 patients (6.0%) had died, 328 (4.8%) were lost to follow-up, 128 (1.9%) had to stop HAART and 5992 (87.3%) were still on HAART (Table 1). Overall, 476 patients (6.9%) had to stop their FDC regimen during the course of the follow-up but 348 (84.7%) could continue another antiretroviral therapy regimen. Over two-thirds (69%) of deaths occurred during the first 3 months after initiation of therapy.

Among patients with available data, a progressive CD4 cell gain was observed over time with a median gain of 102 cells/μl (IQR, 58–154; $n = 695$) at 6 months, 144 cells/μl (IQR, 75–233; $n = 209$) at 12 months and 173 cells/μl (IQR, 126–278; $n = 45$) at 18 months.

Survival analysis

The overall incidence rate of death during the follow-up was 14.2/100 person-years [95% confidence interval (CI), 13.8–14.5]. Estimates of survival were 0.93 (95% CI, 0.92–0.94) at 6 months ($n = 2231$), 0.90 (95% CI, 0.89–0.91) at 12 months ($n = 472$) and 0.89 (95% CI, 0.87–0.90) at 18 months ($n = 83$). In an intent-to-treat analysis, when lost to follow-up events were taken as deaths, estimates of remaining alive in care were 0.82 (95% CI, 0.81–0.84) at 12 months (Fig. 1). For patients still alive and followed in the programmes 3 months after FDC initiation, estimates of remaining in care at 12 months were 0.90 (95% CI, 0.88–0.91).

Estimates of survival at 12 months according to baseline CD4 cell count groups of < 15, 15–50, 50–99, 100–199 and > 200 cells/μl were 0.81 (95% CI, 0.76–0.85), 0.86 (95% CI, 0.82–0.89), 0.94 (95% CI, 0.92–0.96), 0.94 (95% CI, 0.92–0.96) and 0.96 (95% CI, 0.93–0.97), respectively ($P < 0.0001$; Fig. 2).

A multivariate Cox proportional hazard ratio (HR) analysis stratified by programme showed the following baseline characteristics significantly associated with death (Table 2): male gender, HR 1.75 (95% CI, 1.34–2.27); WHO stage III, HR 2.07 (95% CI, 1.04–4.12); WHO stage IV, HR 3.86 (95% CI, 1.93–7.70); BMI < 18 kg/m^2, HR 2.38 (95% CI, 1.82–3.11); CD4 cell count < 15 cells/μl, HR, 3.63 (95% CI, 1.95–6.75); CD4 cell count 15–50 cells/μl, HR 2.54 (95% CI, 1.38–4.67); haemoglobin < 80 g/l, HR 2.62 (95% CI, 1.80–3.81); and); haemoglobin 80–100 g/l, HR 1.48 (95% CI, 1.09–2.01).

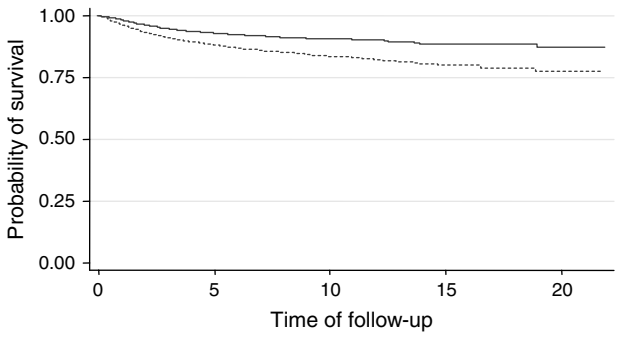

Fig. 1. Kaplan–Meier curves of the whole MSF FDC cohort ($n = 6,861$) giving the probability of survival (—) and the probability of remaining in care (- - -).

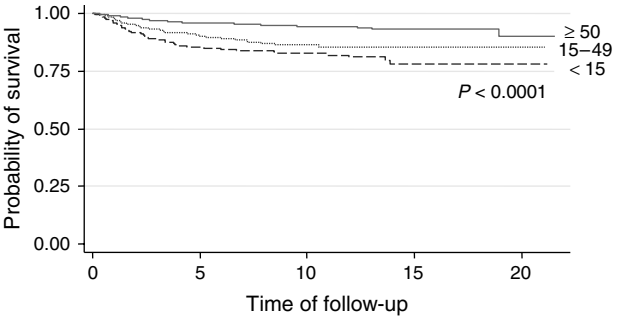

Fig. 2. Kaplan–Meier curves of the whole MSF FDC cohort giving the probability of survival according to baseline CD4 cell count (≥ 50, 5–49 and < 15 cells/μl).

Efficacy and safety of the fixed-dose combination at 12 months

In the M12 FDC cohort of the 655 antiretroviral therapy-naive adults assessed after 12 (± 2) months of follow-up, baseline characteristics were not significantly different compared with those of the global cohort (Table 1) except that more patients were at WHO stage IV at HAART initiation ($P = 0.047$) and had a CD4 cell count of < 50 cells/μl ($P < 0.001$). Median CD4 cell count at baseline ($n = 578$) was 79 cells/μl (IQR, 26–143). Clinical outcomes at 12 (± 2) months of follow-up revealed that 82 patients (12.5%) had died, 61 patients (9.3%) were lost to follow-up, 9 (1.4%) had stopped HAART and 503 (76.8%) were still on HAART. Overall, among those patients still on HAART at 1 year, 460/503 (91.4%) were still on their initial FDC regimen. Almost two-thirds (62.2%) of the deaths occurred during the first 3 months. The median gains in CD4 cells for the patients in the M12 FDC cohort were 113 cells/μl (IQR, 67–163) at 6 months ($n = 184$) and 133 cells/μl (IQR, 75–208) at 12 months ($n = 67$). During this first year of treatment, no patients had to switch to second-line regimen owing to clinical or immunological failure.

During follow-up, 52 patients (8%) had to discontinue FDC, most (51) could continue HAART and were switched to another antiretroviral therapy combination, while one patient had to stop his treatment definitively. FDC discontinuations were for severe drug toxicity (grade 3 or 4) for 30 patients (5%), initiation of a rifampicin-based antituberculosis treatment for 15 patients (2%) and for unknown reasons for 7 patients (1%). The drug mostly responsible for stopping FDC regimen was NVP ($n = 42$) because of initiation of rifampicin-based antituberculous

Table 2. Cox model analysis showing hazard ratio of factors associated with death of 6861 patients of the MSF FDC cohort.

	Univariate analysis		Multivariate analysis ($n = 4175$)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Male	1.61 (1.32–1.86)	< 0.001	1.75 (1.34–2.27)	< 0.001
Age (years)				
< 35[a]				
≥ 35	1.19 (0.98–1.44)	0.087	1.25 (0.97–1.61)	0.09
WHO stage				
I/II[a]				
III[a]	1.98 (1.25–3.13)	0.003	2.07 (1.04–4.12)	0.038
IV	5.21 (3.32–8.18)	< 0.001	3.86 (1.93–7.70)	< 0.001
Body mass index (kg/m^2)				
≥ 18[a]				
< 18	3.09 (2.48–3.85)	< 0.001	2.38 (1.82–3.11)	< 0.001
CD4 cell count (cells/μl)				
≥ 200[a]				
< 15[a]	5.29 (3.22–8.69)	< 0.001	3.63 (1.95–6.75)	< 0.001
15–49	3.03 (1.84–4.96)	< 0.001	2.54 (1.38–4.67)	0.003
50–99	1.32 (0.77–2.25)	0.310	1.52 (0.80–2.90)	0.20
100–199	1.02 (0.61–1.71)	0.942	1.26 (0.67–2.36)	0.47
Missing[b]	2.06 (1.28–3.32)	0.003	1.44 (0.76–2.72)	0.258
Haemoglobin (g/l)				
≥ 100[a]				
< 80[a]	3.52 (2.49–4.96)	< 0.001	2.62 (1.80–3.81)	< 0.001
80–99	2.00 (1.52–2.65)	< 0.001	1.48 (1.09–2.01)	0.012

CI, confidence interval; HR, hazard ratio; WHO, World Health Organization.
[a]Reference group.
[b]Group who initiated the fixed-dose combination only on clinical criteria without baseline CD4 cell count available.

treatment ($n = 15$), skin toxicity ($n = 12$), liver toxicity ($n = 11$) or unknown reason ($n = 4$) (Table 3) [10]. In these cases, NVP was replaced by efavirenz (39) or lopinavir (3) while d4T and 3TC were continued with other formulations. Only nine patients had to stop FDC because of d4T toxicity, five because of severe neuropathy, two for lipodystrophy and two for unknown reason. In these cases, d4T was replaced by zidovudine while 3TC and NVP were continued with other formulations. No death was attributed to an adverse event. The median time before FDC discontinuation was 38.5 days (IQR, 21–156) after HAART initiation; 28 days (IQR, 19–114) when stopping because of NVP toxicity and 215 days (IQR, 155–287) when stopping because of d4T toxicity. No patients had to switch to a second-line regimen because of clinical or immunological failure during this 1 year period.

Table 3. Drug responsible and reasons for stopping FDC among patients of the M12 FDC cohort who continued HAART ($n = 51$).

Drug	No.	Reasons (No.)
Nevirapine	42	Tuberculosis (15) Skin toxicity (12) Liver toxicity (11) Unknown (4)
Stavudine	9	Neuropathy (5) Lipodystrophy (2) Unknown (2)
Total	51	

Efficacy and safety of the fixed-dose combination at 18 months

In the M18 FDC cohort ($n = 126$) at 18 months of follow-up, 22 (17.5%) patients had died, 6 patients (4.8%) were lost to follow-up, 1 (0.8%) had stopped HAART and 97 (77.0%) were still on HAART. Among these, 75/97 (77.3%) were still on their initial FDC regimen. For 39 patients with available CD4 cell counts, the median CD4 cell count gain at 18 months was 165 cells/μl (IQR, 127–247).

Discussion

All the 6861 patients who initiated HAART as FDC in MSF programmes and analysed in the present study received the generic FDC d4T/3TC/NVP and were followed using simplified procedures without viral load monitoring [11,12]. The use of FDC greatly simplifies pill burden for patients (one pill twice a day), improving the chances of good adherence, and also helps drug supply procedures. Despite the fact that these patients were severely immunocompromised (median baseline CD4 cell count 79 cells/μl), we found that 76.8% of the patients were still on HAART at 1 year. Only 9.3% had been lost to follow-up and 12.5% of these severely ill patients had died, mostly during the first months of therapy. Previous studies on more limited numbers of patients and in settings where virological monitoring was available found viral

suppression similar to that observed in developed countries [13,14]. The present study shows that the benefit of FDC extends beyond satisfactory surrogate markers, giving survival results comparable to those reported in patients with very low CD4 cell count initiating antiretroviral therapy in developing countries [15–16] and in developed countries in the early era of HAART [17]. One may argue that the lack of routine viral load and AIDS event assessment in our programmes does not allow a complete comparison with results from previously published cohorts. Nevertheless, the very satisfactory clinical outcomes and the extent of the immunological restoration observed in our study were found to be comparable to those seen elsewhere [4], providing further convincing evidence that generic FDC regimens clearly benefits people with advanced-stage HIV infection.

Analysis of a subcohort of 655 patients who initiated FDC 1 year previously (M12 FDC cohort) also revealed positive clinicoimmunological outcomes and allowed us to analyse severe side-effects reported on FDC. Only 8% of these patients had to stop FDC during their follow-up, 5% for severe drug toxicity. A second important reason for discontinuing FDC was the initiation of rifampicin for tuberculosis treatment (2%). At 1 year, rates of severe skin and liver toxicities linked to NVP appear comparable to those observed in the 2NN study (8·3% of liver-associated laboratory toxicity), the ATLANTIC study (7% of severe rash) and the INCAS study (4% of severe rash), which did not use FDC [18–20]. Only few FDC discontinuations because of d4T toxicity (mainly neuropathy) were reported. Of note, Steven–Johnson's syndrome has not been reported in our cohort. However, the rate of adverse effects might have been underestimated because of the absence of routine laboratory examination, with diagnosis performed only clinically, or because of poorly documented causes of deaths and lost to follow-up, which might also be caused by severe side-effects. Improvements of routine diagnosis and data collection over longer periods are clearly needed to improve documentation of side-effects in such open observational cohorts.

Almost a third of FDC discontinuations were because of the initiation of antituberculosis treatment. Indeed, it is known that both rifampicin and NVP interact with cytochrome P450 and that by modifying NVP metabolism rifampicin might dramatically decrease NVP plasma levels and potentially its virological efficacy [21]. In addition, both drugs can lead to hepatotoxicity, which could be amplified in coadministration. Consequently, NVP, and, therefore, the d4T/3TC/NVP FDC, is commonly interrupted when initiating rifampicin-based anti-tuberculosis treatment. However, there are very limited data on the actual clinical and virological impact [10] and research is needed to provide clear recommendations regarding the use of NVP in patients coinfected with tuberculosis and HIV. This could help to avoid inappropriate interruption of FDC treatment.

The overall incidence rate of death in our cohort during follow-up was still high (14.2/100 person-years; 95% CI, 13.8–14.5) compared with what is observed in developed countries, where HAART became more beneficial over time [22]. Two international cohort collaborations, ART-CC and ART-LINK, also found a discrepancy when comparing the death rate in developed countries (1.3/100 person-years) with that in resource-poor settings (5.2/100 person-years) [23]. Nearly 70% of deaths occurred during the first 3 months after initiation of antiretroviral therapy treatment, and this most probably could be explained by undiagnosed opportunistic infections at the time of HAART initiation and/or the advanced stage of the disease in those patients by the time they had entered the health facility. Immune reconstitution inflammatory syndrome (IRIS) is certain to occur in our cohort given the low CD4 cell count prior initiation of HAART, which is associated with development of IRIS [24], and the fact that tuberculosis is found to be the most frequent opportunistic infection. However, as diagnosis is still difficult to confirm clinically, we are unable to assess the relative contribution of IRIS to the high rate of death at the first trimester.

As expected and already described in Asian [15] and in African [16] settings, baseline BMI, WHO stage III and IV, CD4 cell counts and haemoglobin level were all significantly associated with death. Anaemia below a threshold of 80 mg/l was also found to be strongly associated with death in our analysis (HR, 2.62; $P < 0.001$), which is in accord with observations in America [25] and Europe [26].

In keeping with European cohorts [27], risk of death is strongly associated with CD4 cell count at baseline: patients with a baseline count < 50 cells/μl had a higher risk of death (odds ratio, 2.54; $P = 0.003$) and those with baseline < 15 cells/μl were even worse (odds ratio, 3.63; $P < 0.001$). Interestingly, patients with baseline CD4 cell count 50–200 cells/μl have almost the same probability of survival at 1 year as those with a baseline CD4 cell count > 200 cells/μl. However, these data need to be interpreted cautiously because of the short follow-up time and the absence of reliable information related to intercurrent AIDS events. In particular, we have no reference group with CD4 cell count > 200 cells/μl. It would be interesting to see if this survival benefit of patients with a baseline CD4 cell count of 50–200 cells/μl will persist over time, and to conduct prognosis analysis of AIDS events and death in a reference group of patients with CD4 > 200 cells/μl and without a previous AIDS-defining illness.

We also observed that being male was significantly associated with early death (HR, 1.75; 95% CI, 1.34–2.27) independent of other factors. However, previous large cohort studies have failed to report such significant gender differences in disease progression on HAART

[28,29] and it is possible that, in our cohort, other unidentified confounding factors may exist besides gender.

Overall, these MSF cohort results confirm the efficacy and safety of generic FDC in preventing AIDS-related death in resource-poor settings. Funding and implementing agencies should support without reservation the rapid scale up of this simple first-line treatment in resource-poor settings.

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