Rapid scaling-up of antiretroviral therapy in 10 000 adults in Côte d'Ivoire: 2-year outcomes and determinants

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Objective: To assess the rates and determinants of mortality, loss to follow-up and immunological failure in a nongovernmental organization-implemented program of access to antiretroviral treatment in Côte d'Ivoire.

Methods: In each new treatment center, professionals were trained in HIV care, and a computerized data system was implemented. Individual patient and program level determinants of survival, loss to follow-up and immunological failure were assessed by multivariate analysis.

Results: Between May 2004 and February 2007, 10 211 patients started antiretroviral treatment in 19 clinics (median preantiretroviral treatment CD4 cell count, 123 cells/μl; initial regimen zidovudine–lamivudine–efavirenz, 20%; stavudine–lamivudine–efavirenz, 22%; stavudine–lamivudine–nevirapine, 52%). At 18 months on antiretroviral treatment, the median gain in CD4 cell count was +202 cells/μl, the probability of death was 0.15 and the probability of being loss to follow-up was 0.21. In addition to the commonly reported determinants of impaired outcomes (low CD4 cell count, low BMI, low hemoglobin, advanced clinical stage, old age and poor adherence), two factors were also shown to independently jeopardize prognosis: male sex (men vs. women: hazard ratio = 1.52 for death, 1.27 for loss to follow-up, 1.31 for immunological failure); and attending a recently opened clinic (inexperienced vs. experienced centers: hazard ratio = 1.40 for death, 1.58 for loss to follow-up). None of the three outcomes was associated with the drug regimen.

Discussion: In this rapidly scaling-up program, survival and immune reconstitution were good; women and patients followed up in centers with longer experience had better outcomes; outcomes were similar in zidovudine/stavudine-based regimens and in efavirenz/nevirapine-based regimens. Decreasing the rate of loss to follow-up should now be the top priority in antiretroviral treatment rollout.

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Introduction

At the end of 2006, the World Health Organization (WHO) and UNAIDS estimated that 28 million people were living with HIV/AIDS in sub-Saharan Africa, including almost one million in Côte d'Ivoire, one of the most affected countries in west Africa. Between 2002 and 2007, the number of HIV-infected patients receiving antiretroviral therapy (ART) increased from 100 000 to more than 2 million in sub-Saharan Africa and from 3000 to 30 000 in Côte d'Ivoire. These figures are expected to triple within 5 years [1].

Most of these African patients start ART in primary care centers with limited facilities. Patients who start ART need to continue the treatment for the course of their lives, all the while maintaining maximal adherence. At individual patient level, health care teams that are in charge should be able to detect treatment failures as soon as possible to reinforce adherence or to change the failing ART regimens whenever appropriate. At a public health level, program managers, drug suppliers and donors are looking for real-time data and indicators, including the exact number of patients lost to the program and of those remaining in care along with key indicators of ART efficacy. To reinforce the efficacy of the program, they will also need to know the determinants of the main treatment outcomes of patients in the program.

In February 2007, we estimated these indicators and outcomes and their determinants in a 3-year HIV care and treatment program in Côte d'Ivoire, West Africa.

Methods

Patients

Between the years 1996 to 2003, 723 HIV-infected adults were followed in the Agence Nationale de Recherches sur le SIDA (ANRS, Paris, France) 1203 Cotrame cohort study in Abidjan [2]. At the end of the study, health professionals associated with the project created a non-governmental association, Aconda [3]. In June 2004, Aconda, in partnership with the Institute of Public Health, Epidemiology and Development (ISPED, Bordeaux, France), launched a 5-year program for access to HIV care and treatment. This program was funded by the United States President's Emergency Plan for AIDS Relief (PEPFAR) through the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF, Washington, District of Columbia, USA).

The Aconda program relies on two types of HIV care centers: the CePReF clinic, formerly the Cotrame study center, now directly administered by Aconda and entirely dedicated to HIV care; a number of public and private healthcare facilities, not entirely dedicated to HIV care and not directly administered by Aconda. In these centers, the Aconda program trained personnel in standardized procedures of HIV care and treatment and implemented a computerized data management system. Clinical training consisted of an initial 1-week didactic course, followed by 1 week of work experience in the CePReF center, and then a long-term continuing education through repeated visits to each center by Aconda staff members. In each center, one staff member was identified to be responsible for the data management system. This person received specific training and was supported on-site and online by the central Aconda data management team.

In this study, we analyze data from all HIV-infected adults who started ART under the Aconda program from 27 May 2004 (the start of the program) to 1 February 2007.

Data management system

The Aconda data management system was directly derived from the ANRS 1203 Cotrame cohort study information system [2] and approved by the National Ethics Committee of Côte d'Ivoire. It has been recently presented at a PEPFAR meeting [4]. In summary, standardized forms are used at all program sites to record the following variables: initial visit; date, sex, date of birth (or age), height, weight, type of HIV positivity (HIV-1, HIV-2 or dual); subsequent visits; date, weight; at ART initiation; date, WHO clinical stage, weight; for each drug prescription (either antiretroviral or non-antiretrovirals); date, names and quantity of drugs delivered; at each CD4 cell count and blood cell count measurement; date, CD4 number, CD4 percentage, hemoglobin level, platelet, granulocyte and leukocyte counts; each time a patient is contacted by phone or through home visits, and for each death reported to the care center team, the date of death or, for patients not known to be dead, the date the last time the patient was known to be alive. The CePReF Aconda-managed HIV care center collects further variables, not included in this analysis [4].

Standardized follow-up procedures

In Côte d'Ivoire, the standard serologic testing algorithm for primary care centers consists in a series of two rapid HIV assays, the Determine HIV-1/HIV-2 (Abbott Diagnostics, Abbott Park, Illinois, USA), followed by the Geni II HIV-1/HIV-2 (Bio Rad Laboratories, Marne-La-Coquette, France) [5]. During the study period, all HIV-infected adults followed either off-ART or on-ART in the Aconda program had biannual CD4 cell count measurements. ART was started when the following criteria were met: WHO clinical stage 4, CD4 cell count of less than 200 cells/μl or WHO stage 3 and CD4 cell count at 200–350 cells/μl. Antiretroviral drugs and biannual CD4 measurements were provided to the patient under a monthly package price of US$ 2. For all nonantiretroviral drugs, patients were required to pay an additional package price of US$ 1 per

drug prescription, irrespective of the number and type of drugs prescribed. Antiretroviral drugs were provided on a monthly basis. Cotrimoxazole prophylaxis was prescribed in all HIV-infected patients with a CD4 cell count of less than 500 cells/μl. For patients who did not keep their monthly scheduled appointment, telephone calls or home visits were made by a community-based team, composed of experienced social workers and members of associations of people living with HIV/AIDS [6]. A patient was defined as lost to follow-up if his last contact with the care center was at least 3 months (patients who ever started ART) or at least 6 months (patients who never started ART) while he was not known to be dead or transferred out.

Statistical analysis

For all patients who started ART, we considered three outcomes: death, loss to follow-up (when the time since last contact with program was at least 3 months on 1 February 2007, in a patient not known to be dead before this date), and immunological failure of ART at month 6 (defined as a difference between the baseline and the 6-month CD4 cell counts lower than +50 cells/μl). Baseline was the date of ART initiation. Data were censored on 1 February 2007 for patients who were still alive, on the date of death for patients who died before 1 February 2007 or on the date of last contact with the care center for patients whose last contact was before 1 February 2007 and who were not known to be dead. We used multivariate Cox proportional hazard regression models to analyze the association between death or loss to follow-up and the following determinants: characteristic on ART initiation: sex, age, WHO clinical stage, hemoglobin level, BMI, CD4 cell count, type of HIV seropositivity (HIV-1, HIV-2 or dual); the initial ART regimen; the type of care clinic (CePReF-dedicated HIV care center, compared with all other care centers); the medication possession ratio (MPR), defined as the number of days of treatment actually given to the patient at the pharmacy during the study period divided by the follow-up time between ART initiation and last visit at the care center (or 1 February 2007 if the last visit was posterior to this date). Finally, all patients who were still alive and actually followed-up at month 6 were included in a multivariate logistic regression model to analyze the association between immunological failure at month 6 and the explanatory variables listed above. Analyses were conducted using the SAS software, version 8.2 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patients

From program initiation to 1 February 2007, 20 474 HIV-infected adults (72% women) had at least one contact with one of the 19 centers participating in the Aconda program (17 urban centers in Abidjan and two rural centers) (Fig. 1). Of these patients, 1018 had already started ART prior to their first contact, and 19 456 were not on ART at their first contact with the program. Of the latter, 10 211 had started ART before the end of the study period, 968 had died before ART initiation, 218 had been transferred to another care center before ART initiation, 2612 had been lost to follow-up before ART initiation (last contact with program ≥6 months), and 5447 were still followed up without ART (last contact with program <6 months) at the end of the study period. Among the 5447 latter patients, the last available CD4 cell count was less than 200 cells/μl in 772 patients, between 200 and 350 cells/μl in 1048, more than 350 cells/μl in 2431, and nonavailable in 1196 patients. During the overall study period, the 6-months probability of starting ART in patients off-ART with a CD4 cell count lower than 200 cells/μl was estimated at 0.94 (95% confidence interval, 0.93–0.95).

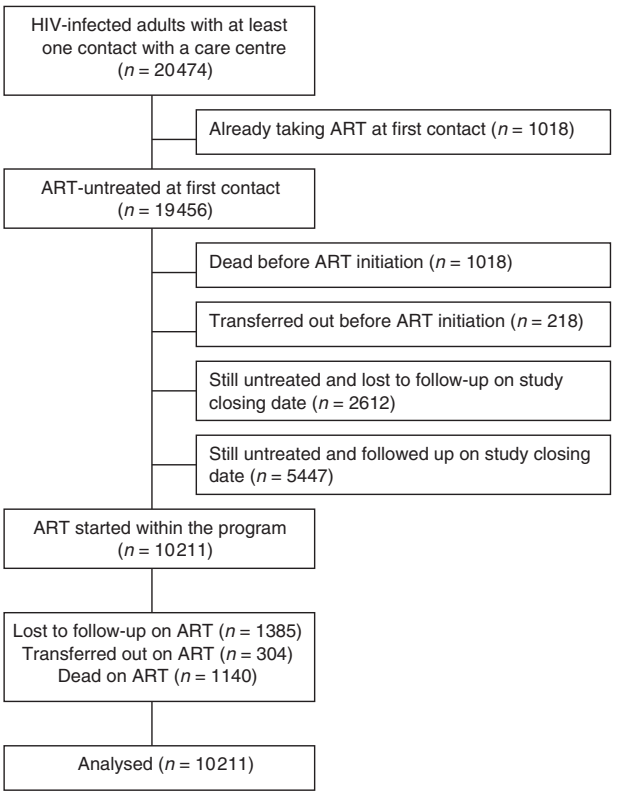

Fig. 1. Flow diagram of enrolment and retention, Aconda Program, Côte d'Ivoire, May 2004–January 2007. Study closing date: 1 February 2007. Lost-to follow-up: patients not known to be dead or transferred out and whose last contact with the care center was at least 3 months [patients who ever started antiretroviral therapy (ART)] or at least 6 months (patients who never started ART) on study closing date.

Table 1 shows the main pre-ART characteristics of the 10 211 treatment-naive patients who started ART in the program. Their median pre-ART CD4 cell count was 123 cells/μl, 26% of them had a CD4 cell count less than 50 cells/μl, their median body mass index was 19.1 kg/m^2

Table 1. Pre-antiretroviral therapy (ART) and follow-up characteristics (patients who started ART within the Aconda program, Côte d'Ivoire, May 2004–January 2007, $n = 10\,211$).

Pre-ART characteristics	
Time since first contact with program, months, median, (IQR),	9.6 (3.9; 17.2)
Sex male, number (%)	3024 (30%)
Age (years), median (IQR)	36 (30; 42)
Body mass index (kg/m^2), median (IQR)	19.1 (17.1; 21.4)
Time since last weight measurement[a], months, median (IQR),	0.0 (−0.2; 0.0)
Type of HIV seropositivity, number (%)	
HIV-1	9117 (94%)
HIV-2	214 (2%)
Dual	381 (4%)
WHO clinical stage, number (%)	
Stage 1 or 2	1714 (19%)
Stage 3	6222 (69%)
Stage 4	1163 (12%)
Last available CD4+ cell count (cells/μl) median (IQR)	123 (47; 207)
Time since last CD4 measurement[b], months, median (IQR)	−0.4 (−0.8; −0.2)
Hemoglobin level (g/l), median (IQR)	94 (82; 107)
Initial ART regimen, number (%)	
ZDV-3TC-EFV	2024 (20%)
d4T-3TC-EFV	2226 (22%)
d4T-3TC-NVP	5343 (52%)
Others	618 (6%)
Follow-up after ART initiation	
Follow-up time	
Cumulative (person-years)	8157
Median (IQR), months	7.7 (2.6–15.5)
Medication possession ratio during follow-up[c]	
Median (IQR)	0.98 (0.78–1.00)
<80%, number (%)	2704 (26%)

Missing values: type of HIV seropositivity ($n = 499$), BMI ($n = 2787$), CD4 cell count ($n = 488$), WHO clinical stage ($n = 1112$), hemoglobin ($n = 696$). ART, antiretroviral therapy; IQR, interquartile range; WHO, World Heath Organization; 3TC, lamivudine; d4T, stavudine; EFV, efavirenz; NVP, nevirapine; ZDV, zidovudine.
[a]Time between last available weight measurement and ART initiation. Only weights measured the day when ART was started or within the preceding 15 days were taken into account.
[b]Time between last available CD4 cell count and ART initiation. Only CD4 cell counts performed the day when ART was started or within the preceding 3 months were taken into account.
[c]Medication possession ratio: number of days of treatment given to the patient divided by number of days from ART initiation to last visit at the care center (or to 1 February 2007 if the last visit is posterior to this date).

and 81% of them were at WHO stage 3 or 4, including 470 patients (4.6%) with a past history of successfully treated tuberculosis and 556 patients (5.5%) with an ongoing episode of active tuberculosis when ART was started. The three most frequently prescribed ART regimens were zidovudine-lamivudine-efavirenz (ZDV-3TC-EFV) (20%), stavudine-lamivudine-efavirenz (d4T-3TC-EFV) (22%), and stavudine-lamivudine-nevirapine (d4T-3TC-NVP) (52%).

Antiretroviral treatment regimens

Figure 2a illustrates the changing importance of each ART regimen during the 2.5-year study period. The monthly number of patients who started ART increased from around 100 in June 2004 to more than 400 at the beginning of 2007. During the first few months, the two most frequently prescribed ART regimens were ZDV-3TC-EFV and d4T-3TC-EFV. From May 2005 onward, d4T-3TC-NVP became the first regimen, accounting approximately for two-thirds of the new ART regimens prescribed. During the follow-up, 1410 patients (14%) experienced 2006 changes in their ART regimen, including 307 patients (16%) with 467 changes among those whose initial regimen was ZDV-3TC-EFV, 345 patients (16%) with 465 changes among those whose initial regimen was d4T-3TC-EFV and 558 patients (11%) with 733 changes among those whose initial regimen was d4T-3TC-NVP. Among the 9592 patients who started one of the three most frequent regimens, the most frequent reasons for the 1665 changes were toxicity (55%), pregnancy (11%), tuberculosis (12%) and treatment failure (3%). Among the 595 HIV-2 and HIV dually reactive patients, the initial regimens were two nucleoside reverse transcriptase inhibitors (NRTIs) and one protease inhibitor in 301 patients (50%), three NRTIs in 69 patients (12%), and two NRTIs and one nonnucleoside reverse transcriptase inhibitor (NNRTI) in 225 patients (38%). Among the latter, 53 patients (24%) switched to protease inhibitor-based or three NRTIs regimens during follow-up, and the remaining 172 patients (76%) remained on NNRTI until the study closing date.

Follow-up on antiretroviral treatment

Patients were followed up for a median of 7.7 months after ART initiation [interquartile range (IQR) 2.6–15.5]. During the overall study period, the median MPR was 0.98 (IQR 0.78–1.00) and 5402 (53%) of patients had an MPR less than 100%, including 44% with an MPR less than 95%, 37% with an MPR less than 90%, 26% with an MPR less than 80%, 16% with an MPR less than 65% and 9% with an MPR less than 50%. At the end of the study period, 1385 patients (14%) who initiated ART during the study period were lost to follow-up, 1140 (11%) were known to be dead, 304 (3%) had been transferred to another HIV care program, and 7382 (72%) were still receiving ART in the program. Of the latter, 5681 patients (77%) had renewed their last prescription of antiretroviral drugs as scheduled, and 1701 (23%) were late in renewing their supply of drugs. Figure 2b shows the temporal evolution of the proportion of patients dead, lost to follow-up and still actively followed up on ART.

Outcomes on antiretroviral treatment

Overall, the 18-month probability of death regardless of baseline CD4 cell count was estimated at 0.15 and the 18-month probability of being lost to follow-up was at 0.21.

Figure 3a and Table 2 show the probability of survival by baseline CD4 cell count. Survival estimates were systematically lower with lower pre-ART CD4 cell count, with a 15–17% crude difference in survival at the three time points between those patients starting ART at less than 50 CD4 cells/μl and those starting at more than

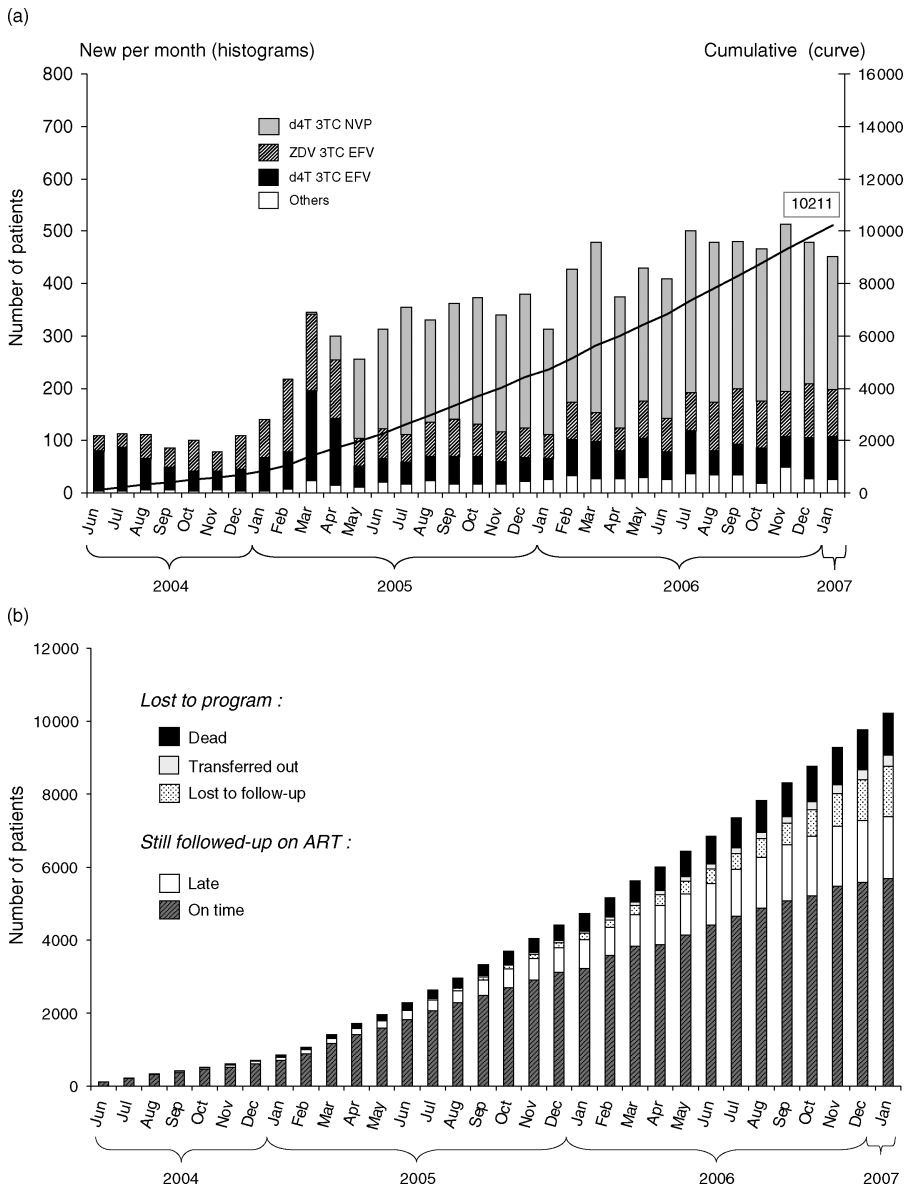

Fig. 2. Antiretroviral therapy (ART) initiation and retention into program over time, Aconda program, Côte d'Ivoire, May 2004–January 2007. (a) Number of patients who started ART over time, by initial ART regimen. Aconda program, Côte d'Ivoire, May 2004–January 2007. ZDV, zidovudine; d4T, stavudine; EFV, efavirenz; NVP, nevirapine; 3TC, lamivudine. (b) On-ART patients status at the end of each month between the date when the program was launched and the study closing date. Aconda program, Côte d'Ivoire, May 2004 – January 2007. Late: patients who where late in renewing their supply of antiretroviral drugs but who were not considered as lost to follow-up. Lost to follow-up: patients whose last contact with the care center was at least 3 months and who were not known to be dead or transferred out.

150 CD4 cells/μl. Overall, the median time between ART initiation and death was 1.9 months (IQR 0.7–4.6).

Figure 3b and Table 3 show the probability of being lost to follow-up over time, by type of care center, with much lower figures at all time points in the most experienced center, the CePREF clinic, compared to those opened in the course of the program. The median gain in CD4 cells since ART initiation was +136 cells/μl (IQR +71; +218), +166 cells/μl (+84; +249) and +202 cells/μl (+107; +314) at 6, 12 and 18 months, respectively for patients with adequate follow-up and repeated measurements. At 6 months, 645 patients (19%) had a gain in CD4 of less than 50 cells/μl.

As shown in Table 4 the risk of mortality, the risk of being lost to follow-up, and the risk that the CD4 gain at 6 months would be less than 50 cells/μl were higher in men and in patients with low hemoglobin level. Older age, low CD4 cell count, advanced clinical stage and low BMI

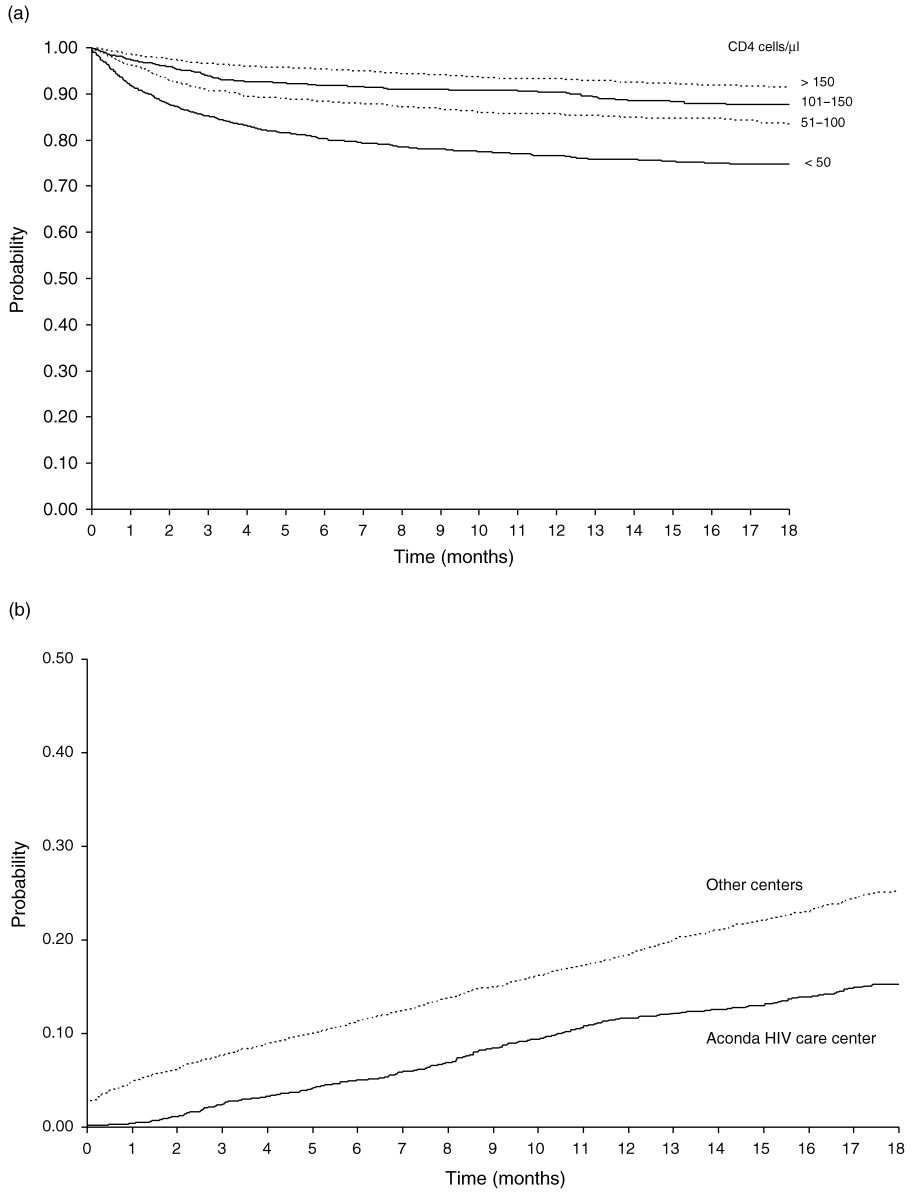

Fig. 3. Survival and loss-to-follow-up, Aconda program, Côte d'Ivoire, May 2004–January 2007. (a) Survival after antiretroviral therapy (ART) initiation, by pre-ART CD4 cell count. Aconda program, Côte d'Ivoire, May 2004–January 2007. CI, confidence interval. (b) Probability of being lost to follow-up after ART initiation, by type of care center. Aconda program, Côte d'Ivoire, May 2004–January 2007. Lost to follow-up: patients whose last contact with the care center was at least 3 months and who were not known to be dead or transferred out.

were associated with a higher risk of death only. The risk of death and the risk of loss to follow-up were lower in the CePReF clinic compared with the other less experienced centers. A low MPR (<80%) was associated with a higher risk of loss to follow-up and a higher risk of immunological failure. The risk of loss to follow-up was independent of the CD4 cell count. Importantly, none of the three outcomes was associated with the initial

Table 2. Survival after antiretroviral therapy (ART) initiation, by pre-ART CD4 cell count (complement to Fig. 3a).

	Baseline CD4 cell count			
Probability (95% CI)	≤50	51–100	101–150	>150
Month-6	0.81 (0.79; 0.83)	0.89 (0.87; 0.91)	0.92 (0.90; 0.94)	0.96 (0.94; 0.97)
Month-12	0.77 (0.75; 0.80)	0.86 (0.84; 0.89)	0.91 (0.89; 0.93)	0.94 (0.92; 0.95)
Month-18	0.76 (0.73; 0.78)	0.84 (0.82; 0.87)	0.88 (0.86; 0.91)	0.92 (0.90; 0.93)

CI, confidence interval.

Table 3. Probability of being lost to follow-up after antiretroviral therapy initiation, by type of care center (complement to Fig. 3b).

	Type of care center		
Probability (95% CI)	Aconda care center (CePReF care center, exclusively dedicated to HIV care)	Other centers (recently opened, and not exclusively dedicated to HIV care)	Overall
Month-6	0.05 (0.04; 0.06)	0.11 (0.10; 0.12)	0.09 (0.08; 0.11)
Month-12	0.11 (0.09; 0.13)	0.18 (0.16; 0.20)	0.16 (0.16; 0.18)
Month-18	0.15 (0.13; 0.17)	0.25 (0.23; 0.27)	0.21 (0.21; 0.23)

CI, confidence interval.

ART regimen. Finally, the risk of immunological failure was higher in patients infected with HIV-2 or dually reactive than in those infected with HIV-1 only.

Discussion

This routinely collected data from an nongovernmental organization (NGO)-implemented HIV care program in West Africa provide encouraging information and raise several concerns.

On the one hand, in only 3 years, 19 care centers, mostly primary health care units, of which 18 had no previous experience in HIV care, could be mobilized to initiate ART in more than 10 000 adult patients. An easy-to-manage computerized data monitoring system could be implemented in each site, providing real-time indicators for the number of patients in care and for treatment effectiveness. At 18 months, the estimates of survival and immune reconstitution were as good as in industrialized countries [7], as previously shown in several other large programs throughout Eastern and Southern Africa [8–11].

On the other hand, these good clinical indicators were achieved despite a worrying rate of patients lost to the program in the background. Any definition of loss to follow-up can be seen as arbitrary as a patient who is late can never be considered as definitively lost unless he is

Table 4. Factors associated with death, loss to follow-up, and CD4 cell count evolution on antiretroviral therapy (ART) (multivariate analysis).

	Death			Loss to follow-up[c]			Gain in CD4 <50 cells/μl at 6 months[d]		
	HR	95% CI	*P*	HR	95% CI	*P*	OR	95% CI	*P*
Sex male (ref. women)	1.52	1.29–1.80	<0.0001	1.27	1.09–1.48	0.002	1.31	1.03–1.65	0.02
Age (for 1 year older)	1.01	1.00–1.02	0.02	0.99	0.98–1.01	0.08	1.00	0.99–1.02	0.47
CD4 cell count (ref. >150 cells/μl)			<0.0001			0.74			<0.0001
101–150 cells/μl	1.32	1.01–1.72		1.10	0.91–1.33		0.60	0.45–0.81	
51–100 cells/μl	1.63	1.29–2.07		1.00	0.83–1.21		0.63	0.47–0.84	
≤50 cells/μl	2.72	2.23–3.32		1.01	0.85–1.20		0.45	0.33–0.60	
WHO clinical stage 3 or 4 (ref. 1 or 2)	1.61	1.32–1.96	<0.0001	1.25	1.01–1.55	0.03	1.01	0.69–1.47	0.95
ART regimen (ref. ZDV-3TC-EFV)			0.88			0.28			0.07
d4T-3TC-EFV	1.03	0.82–1.30		1.00	0.82–1.22		0.89	0.66–1.18	
d4T-3TC-NVP	1.15	0.92–1.43		1.14	0.95–1.36		0.72	0.56–0.93	
Others	1.11	0.65–1.86		1.20	0.79–1.80		1.00	0.56–1.79	
Type of HIV seropositivity (ref. HIV-1)			0.50			0.40			0.03
HIV-2	0.87	0.45–1.72		0.78	0.41–1.35		2.06	0.97–4.37	
Dual	0.91	0.59–1.40		1.11	0.79–1.56		1.79	1.08–2.95	
Hemoglobin level (for 10 g/l lower)	1.22	1.14–1.29	<0.0001	1.07	1.03–1.13	0.0006	1.08	1.01–1.16	0.02
Body mass index (ref. >25.0 kg/m^2)			<0.0001			0.05			0.08
18.5–25 kg/m^2	0.93	0.59–1.46		0.93	0.69–1.25		1.22	0.82–1.82	
<18.5 kg/m^2	1.93	1.23–3.02		1.11	0.82–1.50		0.96	0.62–1.48	
Type care center (ref. CePReF)[a]	1.40	1.18–1.67	<0.0001	1.58	1.36–1.84	<0.0001	1.15	0.93–1.41	0.19
Medication possession ratio[b] <80%	0.87	0.73–1.04	0.12	1.19	1.03–1.38	0.01	2.11	1.66–2.67	<0.0001

Patients who started ART within the Aconda program, Côte d'Ivoire, May 2004–January 2007. Ref., reference; HR, hazard ratio (Cox proportional hazard model); OR, odds ratio (Logistic regression); CI, confidence interval; WHO, World Heath Organization; 3TC, lamivudine; d4T, stavudine; EFV, efavirenz; NVP, nevirapine; ZDV, zidovudine.

[a]CePReF: The HEART program relies on two types of care centers: the CePReF clinic, formerly the Cotrame study center between 1996 and 2003, now directly administered by the NGO Aconda and entirely dedicated to HIV care; a number of public and private health care facilities, not entirely dedicated to HIV care and not directly administered by Aconda.

[b]Medication possession ratio: number of days of treatment actually given to the patient divided by number of days from ART initiation to last visit at the care center (or to 1 February 2007 if the last visit is posterior to this date).

[c]Loss to follow-up: patients were defined as lost to follow-up when their last contact with the care center was at least 3 months on 1 February 2007 if they were not known to be dead or transferred out before this date.

[d]Gain in CD4 at 6 months: difference between the pre-ART CD4 cell count and the CD4 cell count measured 6 months after ART was started.

reported to be dead. However, it is crucial that any report of program indicators include the proportion of patients who have lost contact for a significant period of time. This is for two reasons: first, some of these patients are likely to be dead, and the rate of loss to program reflects to a certain extent the degree of underestimation of mortality [6]; and second, even if the proportion of dead patients among patients lost to follow-up is unknown, loss to program can undoubtedly be seen as a program failure indicator. In our study, the overall 18-months probability that the time interval since last contact exceeded three months was estimated at 21%. This is equivalent [12] or lower [13] than previously reported in some pilot programs, but recent reports of home-based programs have clearly shown that a lower rate of loss to follow-up can be achieved [14]. Assessing the determinants of a prolonged treatment interruption in low-resource settings should be a top priority in the near future at international level.

A major strength of our study was its power to investigate the determinants of major outcomes.

First, we found in a single large data base a series of determinants that were previously separately shown to be associated with impaired outcomes in sub-Saharan Africa: low CD4 cell count, low BMI, advanced WHO stage, and low hemoglobin [9–11,13,15–25]. These variables mostly reflect advanced immunosupression, suggesting that mortality could be substantially decreased by starting ART earlier. More than half of the documented deaths occurred within the first 2 months of treatment, a period of time during which the hazard ratio of mortality has been shown to be higher in low-resource settings than in industrialized countries [16]. In the African context, many patients start ART with a CD4 cell count much lower than currently recommended by WHO, even in settings where access to antiretroviral drugs has become easier in the past 3 years [9–11,14–16,20,21,23,26–28].

Second, in our study, older age was independently associated with a higher risk of death. Though most studies previously done in Africa have failed to show a significant association between age and prognosis [9–11,16,18,19,22,23], our finding is probably a result of a higher statistical power to demonstrate this association and is consistent with reports from industrialized countries [7].

Third, we found a strong association between male gender and impaired outcomes. Some previous studies in sub-Saharan Africa had already reported a significant association between male gender and a higher risk of mortality [9–11,22] or between male gender and a higher risk of withdrawal from programs [8]. Other studies did not find any association between gender and prognosis [13,16,23,26]. In South Africa, men have been reported to have poorer adherence to ART than women [12]. The fact that, in our study, male gender was associated not only with immunological failure and mortality but also with the rate of withdrawal from program might suggest that the association between gender and treatment failure may have been mediated by adherence.

Fourth, in our program, we did not measure adherence. Nevertheless, we calculated the medication possession ratio by dividing the number of patient-days of treatment actually given to the patients by the number of days of follow-up. A low MPR has been previously shown to predict treatment failure in Uganda [14]. In South Africa, a low rate of pharmacy claims, another type of pharmacy-based indicator, has been shown to predict mortality in adults on ART [12]. These pharmacy-based indicators are easy to monitor. In our experience, the strong association between a low MPR and poor outcomes confirms that the MPR is a valuable key indicator both at the individual and program level. A good MPR does not exempt physicians from looking for symptoms of bad adherence. But a poor MPR always reflects a failure in accessing to drugs.

Fifth, in our study, the rate of lost to program and the mortality were dramatically lower in the HIV care center with the most extensive experience. In industrialized countries, the positive impact of sites and physicians' experience on HIV-infected patients outcomes has been reported for quite a long time but has leveled off over time [29,30]. However, these findings are also thought-provoking in terms of ART effectiveness, as a lot of economical, managerial, logistical and organizational characteristics may make a given care center different from another. Cost-effectiveness analyses should take up the challenge of identifying the characteristics that make an HIV care center more efficient than others, in order to generalize the best practices [31].

Finally, in an intent-to-treat multivariate analysis, we did not find any difference in terms of outcomes between ZDV-based and d4T-based regimens on the one hand, or between NVP-based and EFV-based regimens on the other. Regarding the latter, these findings are consistent with comparisons performed between NVP-based and EFV-based regimens in the 2NN international trial [32]. A limitation, however, is that we did not measure virological outcomes, and NVP-based regimens have been shown to be independently associated with higher rates of virological failure [33]. Moreover, in the ART-CC collaboration based on 12 cohorts from industrialized countries, clinical outcomes were poorer in NVP-based regimens compared to EFV-based regimens and in d4T-based regimens compared to ZDV-based regimens [34]. Though our findings may be globally interpreted as reassuring from a programmatic point of view, they cannot prove that all these ART regimens are equivalent at the individual level.

In conclusion, our report documents the efforts to expand a national ART program from a clinically experienced, preexisting program of care and treatment

in one location. Two concerns were raised by the available data collected on the first 10 000 patients starting ART: treatment initiation occurs late in general and opportunities to save lives are clearly missed; once in the program, too many patients are subsequently lost at relatively early phases, leading again to missed opportunities. Individual patient characteristics may explain some of the losses to program but it is likely also that program characteristics and organization contribute significantly to this phenomenon that impairs the true success story of ART introduction in sub-Saharan Africa.

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