

Mortality of HIV-Infected Patients on Antiretroviral Therapy in a Large Public Cohort in West Africa, Burkina Faso: Frequency and Associated Factors

Armel Poda^{1,2*#}, Arsène Hema^{2#}, Jacques Zoungrana², Nongodo Firmin Kaboré²,
Bebar Euloges Kamboulé², Ibrahim Soré², Guillaume Bado², Abdoul-Salam Ouédraogo^{1,3},
Nicolas Meda^{4,5}, Adrien Bruno Sawadogo^{2,3}

¹School of Medicine, University of Bobo Dioulasso, Bobo Dioulasso, Burkina Faso; ²Day Care Hospital for HIV-Patients of Bobo Dioulasso, Department of Infectious Diseases, Souro Sanou Teaching Hospital, Bobo Dioulasso, Burkina Faso; ³Department of Virology and Bacteriology, Souro Sanou Teaching Hospital, Bobo Dioulasso, Burkina Faso; ⁴School of Medicine, University of Ouagadougou, Ouagadougou, Burkina Faso; ⁵Muraz Center, Bobo Dioulasso, Burkina Faso.
Email: *armelpoda@yahoo.fr

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ABSTRACT

Background: In sub Saharan Africa, small size surveys have demonstrated early high mortality among infected patients on antiretroviral therapies (ART). Few studies have been conducted in large cohorts of HIV-patients in public health care system in West Africa. **Objectives:** Our study aims to determine mortality rate and its predictors in a cohort of patients on ART in a public daycare hospital in Burkina Faso. **Methods:** We have carried out a retrospective cohort study. All HIV-infected patients on ART between January 1st 2008 and December 31st 2011 were included in the study. Survival probability was estimated by the Kaplan-Meier method. Cox regression analysis was used to identify associated factors to mortality. **Results:** A total of 2243 HIV-infected patients were included in the study. During the follow-up, 218 patients representing 9.7% were lost. About 104 patients representing 4.6% were transferred and 1691 representing 75.4% were still in the therapeutic cohort. There were 230 death cases for a total of 4282 persons-years, (5.4 deaths for 100 persons-years; 95% CI: 4.8 - 6.3). The survival probabilities after 6 months, 1 year and 2 years were 92.6%, 91% and 88.9% respectively. For the multivariate analysis, the following factors were independently associated to death: male gender, BMI < 18.5 kg/m², WHO stage 3 and 4, HIV-2, T-CD4 lymphocytes < 200/μl, haemoglobin rate < 8 g/dl and creatinine clearance < 60 ml/m². **Conclusions:** Our study provides for the first time mortality rates and its predictors among HIV-patients on antiretroviral treatment in a large cohort in public health sector in Burkina Faso. It highlights the importance of early HIV screening to limit ART initiation at advanced HIV infection stages.

Keywords: Antiretroviral Therapy; Burkina Faso; HIV; Mortality; West Africa

1. Introduction

Nowadays, antiretroviral treatments (ART) do not only aim to reduce morbidity and mortality caused by HIV infection and improving infected patients' life. They also aim to prevent HIV infection [1], therefore, they have the interest of reaching universal access to ART goals (ART coverage superior or equal to 80% to those in need among infected patients). Few African countries were able to make it [2]. However, in sub Saharan Africa, the number of

patients on ART is increasing [2]. Landlocked West African country, Burkina Faso is also part of this trend with 36,248 patients on ART in December 2011 [2]. Obviously, ART have drastically reduced HIV-related morbidity and mortality [2-6]. However, one can note residual mortality among HIV-patients both in Southern and Northern countries [7]. The Souro Sanou Teaching Hospital is a public reference health centre in Burkina Faso and in West Africa for the ambulatory care to HIV-infected patients [8]. Few studies have been carried out among large cohorts in West Africa on mortality during ART in public health care system. In such conditions where patients on ART

*Corresponding author.

#These authors have contributed equally to the work.

are increasing, we found it necessary to make investigations among the Bobo-Dioulasso cohort which includes 3089 patients on ART at the day of December 31st 2011. The objective of this study was therefore to determine mortality rates and related factors among a cohort of ART patients in Burkina Faso, West Africa.

2. Methods

2.1. Study Area

The study was conducted at the Teaching Hospital in Bobo-Dioulasso and specifically at the Day Care Hospital for HIV-patients. Bobo-Dioulasso is the second major city after Ouagadougou the capital city, in Burkina Faso

2.2. Study Design

We conducted a retrospective cohort study. We included all HIV patients on ART between January 1st 2008 and December 31st 2011. These patients were followed up from the initiation of the ART to June 30th 2012 (cut off point).

2.3. Data Collection

Data have been collected during medical examinations with ESOPE software (Epi concept). ESOPE is software for monitoring patients with HIV infection in limited resources countries. Data collected at the first visit included: socio-demographic data, medical history, WHO classification, biological and clinical examinations, data such as weight, height, etc. Samplings for biological examinations were carried out on patients with empty stomach. Examinations carried out at the first visit included haemogram, TCD4 lymphocytes counting, and creatinine checking. Data collected on ESOPE software were transferred to STATA-12 Corporation, Texas for analysis.

2.4. Statistical Analyses

Patients' socio-demographic, clinical and biological characteristics were described in number and percentage for qualitative variables. Quantitative variables were described through their medians and inter-quartile intervals (IQR). The Pearson chi2 test was used to compare proportions. The Student t test was used to test equality between the two averages (signification threshold 5%). To calculate the mortality rate we used at the numerator the total number of deaths that occurred during the follow up and at the denominator how long patients were followed up in the cohort from the first day of the treatment.

Survival probability was evaluated by the Kaplan-Meier method. The association between socio-demographic, clinical and immunologic factors of mortality was assessed with the Iogrank test (signification threshold = 5%).

The effect of predictors significantly associated to the prognosis was then studied through a multivariate analysis with Cox proportional risks model.

2.5. Ethical Issues

This study was done in the process of routine clinical care. Collected information was kept confidential and names of patients were not included in the data collection process.

3. Results

3.1. Characteristics of the Study Population

A total of 2243 HIV infected patients were on ART between January 2008 and December 2011. These included 636 males (28.4%) and 1607 females (71.6%) aged between 16 to 78 years with an average age of 37 (IQR 32 - 45) (**Table 1**). Married patients represented 54.3%, uneducated ones were 46.4% and 58.1% were unemployed.

HIV-1 was the most common infection (91.2%) and was discovered in 59.1% of cases during an opportunistic infection. At their first medical examination 54.6% of patients were at 3 and 4 clinical stages, according to the WHO classification. The average Body Mass Index (BMI) was 20.5 kg/m² (IQR 18 - 23) and 29.3% had a BMI < 18.5.

The pre-therapeutic biological assessment showed 7.1% of severe anaemia (hb < 8 g/dl); 10% of kidney insufficiency (creatinine clearance < 60 ml/m²). The median number of T-CD4 lymphocytes at the initiation of the ART was 186 cells/μl (IQR 95 - 268) and 6.4% of the patients had more than 350 cells/μl.

The median time limit between the first medical visit and the initiation of the ART was estimated to 44.0 days (IQR 21 - 206) and the median duration of the treatment was 20.0 months (IQR 9 - 35). The current medication consisted in the association of two nucleoside reverse transcriptase inhibitors (NRTIs) with a non-nucleoside reverse transcriptase inhibitor (NNRTI). The most common Anti Retroviral regimens prescribed included AZT + 3TC + EFV (40.7%), AZT + 3TC + NVP (31.4%).

3.2. Cohort Follow-Up and Survival Progression

During the follow-up, we lost 218 patients (9.7%). Among males we lost of follow-up 4.3% of cases and among females we noted 4.8% of lost of follow-up. Around 104 (4.6%) were transferred to different health centres. Among males, 8.9% were transferred and among females 10% were transferred ($p = 0.44$). 230 deaths representing 10.3% were registered. Among males we Registered 15.4% of deaths and among females, 8.2% of

Table 1. Basic characteristics of HIV infected patients in the cohort taking ART at the Bobo-Dioulasso day hospital between 2008 and 2011.

Characteristics	Male (n = 636)	Female (n = 1607)	Total (n = 2243)
Age (years)			
≤25	11 (1.7)	128 (8.0)	139 (6.2)
26 - 35	112 (17.6)	660 (41.0)	772 (34.4)
36 - 45	282 (44.4)	546 (34.0)	828 (36.9)
46 - 55	164 (25.8)	230 (14.3)	394 (17.6)
>55	67 (10.5)	43 (2.7)	110 (4.9)
Missing data	0 (0.0)	0 (0.0)	0(0.0)
Marital Status			
Single	111 (17.5)	321 (20.0)	432 (19.3)
Married	456 (71.7)	762 (47.4)	1218 (54.3)
Widow	52 (8.2)	397 (24.7)	449 (20.0)
Divorced	16 (2.5)	127 (7.9)	143 (6.4)
Missing data	1 (0.1)	0 (0.0)	1 (0.0)
Education level			
None	260 (40.9)	780 (48.5)	1040 (46.4)
Primary school	158 (24.8)	454 (28.3)	612 (27.3)
Secondary and higher school	216 (34.0)	372 (23.2)	588 (26.2)
Missing data	2 (0.3)	1(0.0)	3 (0.1)
Occupation			
Unemployed	50 (7.9)	1248 (77.7)	1298 (57.9)
Farmer	117 (18.4)	14 (0.9)	131 (5.8)
Trader	95 (14.9)	118 (7.3)	213 (9.5)
Civil servant	263 (41.4)	117 (7.3)	380 (16.9)
Other	111 (17.4)	110 (6.9)	221 (9.9)
Missing data	0 (0.0)	0 (0.0)	0 (0.0)
AIDS screening circumstances			
Voluntary screening	219 (34.4)	587 (36.5)	806 (35.9)
Clinical suspicion	414 (65.1)	912 (56.7)	1326 (59.1)
PTME	0 (0.0)	102 (6.4)	102 (4.6)
Missing data	3 (0.5)	6 (0.4)	9 (0.4)
BMI at the first visit (kg/m²)			
BMI ≥ 18.5	417 (65.6)	1169 (72.7)	1586 (70.7)
BMI < 18.5	219 (34.4)	438 (27.3)	657 (29.3)
Missing data	0 (0.0)	0 (0.0)	0 (0.0)

WHO classification			
Stage 1	112 (17.6)	393 (24.5)	505 (22.5)
Stage 2	135 (21.2)	405 (25.2)	540 (24.1)
Stage 3	294 (46.2)	648 (40.3)	942 (44.0)
Stage 4	90 (14.2)	147 (9.1)	237 (10.6)
Missing data	5 (0.8)	14 (0.9)	19 (0.8)
Type of HIV			
HIV1	562 (88.4)	1484 (92.4)	2046 (91.2)
HIV2	23 (3.6)	33 (2.0)	56 (2.5)
HIV1 + 2	51 (8.0)	90 (5.6)	141 (6.3)
Missing data	0 (0.0)	0 (0.0)	0 (0.0)
Haemoglobin rate (g/dl)			
Haemoglobin ≥ 8	548 (86.2)	1370 (85.2)	1918 (85.5)
Haemoglobin < 8	42 (6.6)	117 (7.3)	159 (7.1)
Missing data	46 (7.2)	120 (7.5)	116 (7.4)
Creatinine clearance (ml/m²)			
<60	66 (10.4)	153 (9.5)	219 (9.8)
60 - 89	258 (40.6)	586 (36.5)	844 (37.6)
≥90	258 (40.6)	721 (44.9)	979 (43.6)
Missing data	54 (8.5)	147 (9.1)	201 (9.0)
Initial CD4 (number/μl)			
<200/μl	393 (61.8)	793 (49.3)	1186 (52.9)
200 - 350/μl	211 (33.2)	654 (40.7)	865 (38.5)
>350/μl	18 (2.8)	125 (7.8)	143 (6.4)
Missing data	14 (2.2)	35 (2.2)	49 (2.2)
Therapeutics			
Time limit between the first examination and the initiation of the ART (day), median (IQR)	35 (18; 174)	47 (21; 220)	44 (21; 206)
2NRTI + 1NNRTI	541 (85.1)	1340 (83.4)	1881(83.8)
2NRTI + 1PI	93 (14.6)	263 (16.4)	356 (15.9)
3NRTI	2 (0.3)	4 (0.2)	6 (0.3)

Categorical variables are expressed as number (% total); continuous variables are expressed as median (interquartile range).

deaths ($p < 10^{-3}$) and 1691 cases were still in the active cohort, representing 75.4%. There were 230 deaths for a total of 4282 persons-years (5.4 deaths for 100 persons-years 95% CI: 4.8 - 6.3). Most deaths, 156 out of 230, representing 68.1% occurred during the first six months following the ART initiation. Survival probability after 6

months, 1 year and 2 years was 92.6%, 91% and 88.9% respectively.

3.3. Mortality Predictors

During the univariate analysis, socio-demographic factors associated to death included age and male gender. Death risks were two times higher in men ($p < 10^{-3}$) than women (**Figure 1**) and 3.8 times higher among patients more than 55 years old ($p = 0.002$).

AIDS clinical suspicion at screening ($p < 10^{-3}$), severe malnutrition with a BMI $< 18.5 \text{ kg/m}^2$ ($p < 10^{-3}$), WHO 3 and 4 stages ($p < 10^{-3}$) at the initiation of the antiretroviral treatment were the clinical factors associated to death.

Biological characteristics such as HIV-2 infection, poor TCD4 lymphocytes ($< 200/\mu\text{l}$), severe anaemia (hb $< 8 \text{ g/dl}$), creatinine clearance $< 60 \text{ ml/m}^2$ were significantly associated with death (**Table 2**).

The median time limit between the first medical visit and the starting of the ART among dead patients was comparable to that of living patients, that is, 18 versus 17 days $p = 0.6$.

At the multivariate analysis the following characteristics at the initiation of the ART were independently associated with death: male gender, BMI $< 18.5 \text{ kg/m}^2$, WHO stage 3 and 4, HIV-2, T-CD4 lymphocytes $< 200/\mu\text{l}$, haemoglobin rate $< 8 \text{ g/dl}$ and Creatinine clearance $< 60 \text{ ml/m}^2$ (**Table 2**).

4. Discussion

Our study provides for the first time both mortality rates and death risk factors among patients on ART in a cohort involving many participants in a governmental health centre in Burkina Faso and in West Africa. Longitudinal studies in West Africa were carried out either in governmental health centres or among few participants. In our retrospective cohort, we found a mortality rate of 5.4 deaths for 100 persons-years. Most death cases representing 68.1% occurred during the first six months following ART and there were 218 lost of follow-up representing 9.7%. It is highly recommended that patients adhere to their treatment and follow-up visits to achieve treatment efficacy. Several studies have demonstrated that mortality in southern countries during the first six months of ART initiation is higher than in northern countries with higher number of the patients lost of follow-up [6,7,9].

The mortality rate, 5.4 deaths for 100 persons-years that we found out was low compared to common rates in resources-limited countries [10]. In a meta-analysis concerning resources-limited countries like Asia, Africa, Central and South America, mortality rates varied between 2.6% and 29.7%. The lowest rate was recorded in

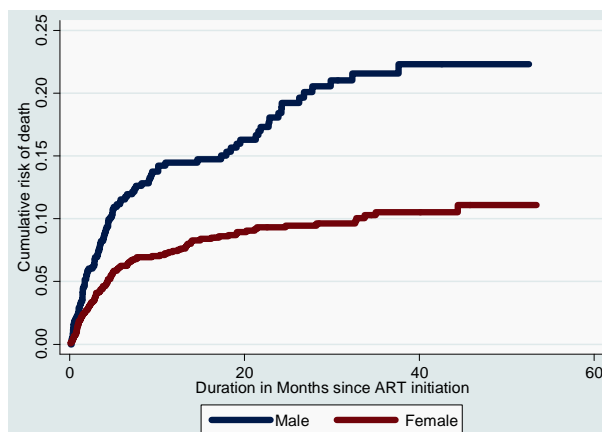


Figure 1. Risks and death curve according to gender among the HIV infected patients cohort on antiretroviral treatment at the Bobo-Dioulasso day hospital between 2008 and 2012.

a multi-regional South American cohort and the highest in sub Saharan Africa [10]. In Dakar, Senegal, on 404 adult patients from the antiretroviral treatment access initiative, the mortality rate was 12.5 deaths for 100 persons-years in the first year and decreased to 6.6 for 100 persons-years in the second year [11]. In Ivory Coast, on 10,211 adult patients taking part in the Aconda Programme, a non-governmental programme for the access to ART, the mortality rate for a period of 18 months was 11.2%, the proportion of lost to follow-up was 13.6% and 85% for the survival probability with no consideration of the rate of CD4 lymphocytes [12]. In Yaounde, Cameroon, on 315 patients, a 9% mortality rate and 21.2 for 100 persons-years mortality were noted [13]. In Ethiopia, among a cohort of 1540 patients, the mortality rate varied from 15.4 for 100 persons-years in the South [14], to 2.03 (95% CI 1.64 - 2.51) for 100 persons-years in the East [15]. However, lower mortality rates among patients on ART are often recorded in northern countries [7].

Mortality among patients on ART in countries with poor resources is often due to opportunistic infections and immune reconstitution inflammatory syndrome [10, 16,17].

In our study, patients started ART mostly at an advanced immune-depression stage due to late screening. For most patients, HIV screening was initiated on the basis of a clinical suspicion. Therefore, it was not a real screening. Patients who have discovered their HIV infection following a clinical suspicion have almost more than two times risks to die than those who have been screened when their infection was asymptomatic. This advanced immune-depression with WHO 3 and 4 stages, weak T-CD4 lymphocytes rates, low haemoglobin rate and a BMI less than 18.5 kg/m^2 at the initiation of ART were often reported in African cohort [6,7,11,12,14,18,19] and in other southern countries [10,20-23]. Late screening

Table 2. Factors associated with death among an HIV infected patients cohort on ART at the Bobo-Dioulasso day hospital between 2008 and 2012.

Independent predictors	RR [CI 95%]	P	Adjusted RR [CI 95%]	P
Gender				
Female	1	-	1	-
Male	1.98 [1.52 - 2.56]	<10 ⁻³	1.75 [1.30 - 2.36]	10 ⁻³
Age (years)				
≤25	1	-	1	-
26 - 35	1.83 [0.84 - 3.98]	0.13	1.54 [0.70 - 3.39]	0.28
36 - 45	1.53 [0.70 - 3.34]	0.28	1.07 [0.48 - 2.37]	0.87
46 - 55	2.72 [1.24 - 5.96]	0.01	1.78 [0.79 - 4.02]	0.16
>55	3.80 [1.62 - 8.89]	2.10 ⁻³	1.60 [0.64 - 3.96]	0.31
Marital status				
Unmarried	1	-		
Married	0.86 [0.66 - 1.12]	0.26		
Level of education				
None	1	-		
Primary school	0.78 [0.56 - 1.07]	0.13		
Secondary and above	0.91 [0.67 - 1.25]	0.56		
Occupation				
Unemployed	1	-		
Working	1.15 [0.89 - 1.49]	0.29		
BMI (kg/m²)				
≥18.5	1	-	1	-
<18.5	3.96 [3.05 - 5.16]	<10 ⁻³	2.04 [1.48 - 2.82]	<10 ⁻³
WHO classification				
Stage 1 & 2	1	-	1	-
Stage 3 & 4	2.65 [1.97 - 3.56]	<10 ⁻³	1.56 [1.13 - 2.19]	8.10 ⁻³
Type of HIV				
HIV1 & HIV 1 + 2	1	-	1	-
HIV2	2.30 [1.27 - 4.07]	6.10 ⁻³	2.39 [1.28 - 4.49]	6.10 ⁻³
Haemoglobin rate (g/dl)				
≥8	1	-	1	-
<8	4.21 [3.02 - 5.87]	<10 ⁻³	2.26 [1.57 - 3.25]	<10 ⁻³
Creatinine clearance (ml/m²)				
≥90	1	-	1	-
60 - 89	1.50 [1.09 - 2.07]	0.01	0.97 [0.68 - 1.39]	0.88
<60	5.30 [3.74 - 7.46]	<10 ⁻³	2.40 [1.59 - 3.63]	<10 ⁻³
Initial CD4 (nb/μl)				
≥200	1	-	1	-
<200	3.11 [2.27 - 4.25]	10 ⁻³	2.30 [1.62 - 3.23]	<10 ⁻³

and advanced immune-depression on ART initiation are the major causes for early mortality of patients taking ART among cohorts in countries with poor resources.

Throughout the survey we found out that men were nearly two times more exposed to death risks than women. A strong relationship between male gender and mortality when taking ART was reported in other African cohorts [11,24,25]. In our centre, there was no significant difference between men and women lost to follow up. In Kenya, a survey demonstrated that the rate of men in follow up programmes is lower than that of women [26]. Besides, men have a bad observance of the ART [27]. However, a survey in China showed that death risk on ART is higher when the patient does not regularly have medical visits and that women do not regularly attend checkups as men [28].

Through our results, death risk was higher among HIV-2 infected patients compared to HIV-1 and HIV-1 + 2 infected patients in a multivariate analysis. A study conducted in Ouagadougou, Burkina Faso shows that similar results are reported in non-governmental centres treating HIV infected patients [29]. In this study among patients with advanced immune-depression, there is a higher mortality rate and a lower immune restoration among HIV-2 patients compared to HIV-1 patients.

In one hand, results on immunity restoration were discovered in Gambia [30] and Ivory Coast [12]. On the other hand, in the Gambian survey mortality was higher among HIV-1 patients compared to HIV-2 and HIV-1 + 2 patients [30]. In the study carried out in Ivory Coast, there is no statistical difference in the mortality rate regarding the type of HIV [12]. In a prospective cohort survey conducted in Guinea Bissau between 1990 and 2007, 223 HIV-1 infected patients participated in the study. Those with a HIV-2 infection in addition to HIV-1 presented a slow progression towards AIDS and had a higher TCD4 lymphocytes rate [31].

We also noticed that 9.8% of patients in our cohort had a creatinine clearance $< 60 \text{ ml/m}^2$ at the ART initiation. In Zambia, a survey came out to the same proportions. Similarly, the authors of the study found a very close relation between the high rate of creatinine at ART initiation and death occurrence [32]. However, it is demonstrated that in countries with poor resources, where there are not always etiologic investigations in case of high creatinine, the initiation of ART improved patients' kidney function [33]. Factors associated to kidney impairment among HIV infected patients initiating ART combine diabetes, high blood pressure, heart diseases, traditional treatment and HIV-related factors such as low TCD4 lymphocytes, high viral load, WHO stage III and IV, and low BMI [34,35]. Nowadays according to WHO recommendations [36] tenofovir is widely used in Africa,

so there are many problems with patients suffering from a kidney insufficiency when starting an ART. Though it is very efficient and well tolerated [36-38], tenofovir worsens existing kidney lesions among African cohorts [39-41].

Finally, in our study, age and level of education were not considered as risk factors. In Ethiopia, patients with a primary school education level have higher death risks than uneducated ones [14].

Our study has weaknesses: the Bobo-Dioulasso day hospital is a national reference teaching hospital with an experienced team. It provides free services including biological assessment and most opportunistic infection treatments. Our results are not representing the situation in the overall country, especially the HIV care in remote health districts where there are few practitioners and people have limited resources. However, a survey done by DWB-Holland tries to show that mortality in both vertical and integrated programmes is similar [42]. Because of the retrospective aspect of our study, data collection and the quality of some information have limitations. Some data are also missing and some factors such as viral load, opportunistic infections, death causes, and observance assessment were not taken into account. Finally, the number of those lost to follow up and the fact that we have no information on them could be a factor which does not make for the true assessment of mortality rates.

5. Conclusion

In our cohort, the mortality rate was 5.4 deaths per 100 person-years. Male gender, BMI $< 18.5 \text{ kg/m}^2$, WHO stages 3 and 4, the number of T-CD4 lymphocytes $< 200/\mu\text{l}$, hemoglobin rate $< 8 \text{ g/dl}$, creatinine $\geq 120 \mu\text{mol/l}$ were factors independently associated with death. This study provides for the first time, mortality rates and death risk factors for patients on ART in a cohort with a large number of participants in a government centre in Burkina Faso and West Africa. It emphasizes once again the need for screening and early initiation of ART.

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