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RESEARCH ARTICLE

Survival and Prognostic Factors of Patients Infected with Human Immunodeficiency Virus at Point G Teaching Hospital, Bamako, Mali

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Abstract

Objective: This study determined the survival rate and prognostic factors of death in hospitalized HIV-infected patients under receiving antiretroviral treatment (ART) at Point G Teaching Hospital, the largest referral facility in Bamako, Mali.

Methods: We conducted a retrospective analysis of data from 474 HIV patients hospitalized at the Infectious Diseases Ward (IDW) of the Point G Teaching Hospital from 2007 to 2016. We used Kaplan-Meier statistical methods and Cox regression model for the data analyses.

Results: Of the 474 patients included into this study, 64.76% (307/474) were censored and 35.23% (167/474) died with an incidence rate of 2. 12 deaths per 100 person-months. The overall survival median of patients was (39 months; 95% CI, 29 to 57 months). However, 42.3% (95% CI 34.6-50) had an overall survival of 60 months. Predictors of mortality among HIV infected persons included WHO classification stage IV (aHR, 1.54; 95% CI, 1.13 to 2. 1), the rate of CD4 <200 cell/mm^3 (aHR, 1.86; 95% CI, 1.12 to 3.04), tuberculosis (aHR, 1.55; 95% CI, 1 .01 to 2.38), Progressive Multifocal Leukoencephalopathy (PML) (aHR, 8.18; 95% CI, 1.96 to 34.06), septicemia (aHR, 1.71; 95% CI, 1.18 to 2.47), Kaposi's disease (aHR, 1.80; 95% CI, 1.01 to 3.23) and regular use of at least two stimulants (aHR, 1.76; 95% CI, 1.15 to 2.66) .

Conclusion: Advanced stage of HIV infection on admission reduced survival of HIV infected hospitalized persons in Mali. Structures adapted for early detection and treatment of HIV infection, opportunistic infections and establishment of a reanimation unit within the infectious diseases ward would better reduce mortality and increase survival of HIV infected patients in Mali.

Keywords: HIV; Survival; Mortality; Prognostic Factors; Mali.

Introduction

Despite significant progress in the fight against Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS), this pandemic continues to be a major global public health problem. In 2018, according to the United Nations Program on HIV/AIDS (UNAIDS), 79 million (61.3 million – 102.3 million) people have become infected with HIV since the start of the epidemic and 37.9 million (32.7 million – 44.0 million) people globally were living with HIV in 2018 [1]. AIDS-related illnesses remain major causes of death worldwide; 37.1 million [26.2 million–52.3 million] people have died from AIDS-related illnesses since the start of the epidemic, including 770 000 (570 000–1.1 million) in 2018 [1]. With unequal geographical distribution, Africa remains the most affected continent. In West and Central Africa, 5 million (4 million – 6.3 million) people were living with HIV in 2018 [1].

Since the detection of the first HIV / AIDS case in Mali, the government has made the fight against HIV/AIDS a health priority. [2]. Since 2001, the Malian Initiative for Access to Antiretrovirals (MIAARV) was instituted and the treatment of HIV / AIDS became free in the country in 2004 [2]. According to the latest Demographic and Health Survey (DHS-V) in 2013, the prevalence of HIV in Mali is 1.1% (varying from 0.6% to 1.8%). However, it's a focal epidemic with higher prevalence groups being female sex workers (24.2%), men who have sex with men (13.7%) and injection drugs' users (5%) as compared to national prevalence [3, 4].

Despite this low national prevalence, the important number of treatment centers and free antiretroviral treatment (ARTs), the Infectious Diseases Ward at the Point G Teaching Hospital in Bamako, records more and more cases at the AIDS stage, with high lethality (43.7%) [5]. Inadequate diagnosis and management of opportunistic infections are probably responsible for the high hospital mortality of HIV and AIDS in our context, it was important to carry out this study with the following objectives: i) to determine the survival of the patients and ii) to determine the prognostic factors associated to death of HIV-infected patients hospitalized in the Infectious Diseases Ward (IDW) at Point G Teaching Hospital.

Patients and Methods

Study Design, Site and Period

We conducted a retrospective cohort study from 2007 to 2016 on HIV positive patients aged 15 years and above, under highly active antiretroviral therapy (HAART) hospitalized in the Infectious Diseases Ward of Point G Teaching of Bamako, Mali. This Ward is the only specialized and the third reference in Mali for infectious and tropical diseases with a capacity of about 300 hospitalizations per year according to the ward 2015 annual report. A medical record was established for each hospitalized patient with socio-demographic, clinical and biological characteristics. After patients' discharge, information from their follow-up visits were mentioned in their medical records. Medical records were entered into an Excel sheet. HIV positive patients' information were extracted from this Excel file to make this study database.

Study Population

The study population was made of HIV-positive patients receiving ART and hospitalized for care at Point G Teaching Hospital from 2007 to 2016. These patients were referred from several health care structures over the country. We included only patients whose medical records had details related to the main study variables.

Sampling

We used Power and Sample Size software, version 3.1.2 by Dupont & Plummer to calculate the sample size [6]. To obtain the optimal sample size, we constituted two groups of patients according to the WHO classification (WHO stage IV patients and those at stages II or III). We identified WHO stage IV as the most commonly associated to HIV/AIDS-related deaths over the 108 months follow-up period from 2007 to 2016. Thus, with the following assumptions (a level of bilateral significance of 5%, a power of 80%, a ratio of

unexposed/exposed subjects of 3:2, a median survival in unexposed people estimated at 48 months and a hazard ratio (HR) of 1.5 to be detected), the minimum size required during the 108 months follow-up of this study was 186 patients in WHO stage IV and 279 patients in stages II or III. After adding 5% as the correcting factor for contingency change in exposure, the total sample size was 474 (195 WHO Stage IV patients and 279 patients in Stage II or III). Of a total of 1,237 HIV-infected patients 'records from the Infectious Diseases Ward during the study period, we prepared in advance two lists (a list of 556 patients at stage IV and a second of 681 patients at stages II or III). We used "ALEA.ENTRE. BORNES" command from Excel 2013 to randomly select the required sample size in each group.

Independent and dependent variables

The primary variable was the time interval in months to censoring. Patients under ART were followed up to the date of death, lost to follow up, transfer or completion of the study. Patients lost to follow up or transferred at the end of the study period were censored; so, they were alive during the period of follow-up. We considered patients who escaped during their hospitalization or who never visited after their discharge from hospital as lost to follow-up. We carried out a random right censoring of type I with duration really observed. We calculated survival time in months using the time between the date of ART initiation and the date of the event (death) or date of censoring. We calculated survival time in months using the time between the date of ART initiation and the date of the event (death) or date of censoring. Measured predictive variables were socio-demographic (age, sex, marital status, residence, stimulant use, salary occupation), clinical (weight, medical history, organic disorders, opportunistic infection, WHO stage of AIDS) and therapeutic regimen.

Data analysis

We performed data analysis with R software (version 3.5.1) using the "Library survival". We used Kaplan Meier's method to determine overall patient survival. Overall mortality rates by period of follow-up were determined based on follow up duration and the number of deaths. Log rank statistical test and bivariate Cox analysis were applied to compare patients' survival according to socio-demographic, clinical, biological factors, and opportunistic infections. We built a Cox model to identify statistically significant prognostic factors. For this modeling, we introduced all factors that were statically significant with a $p < 0.05$ in the bivariate analysis and then used the "backward" method to find a final model. We considered the lowest "Akaïke" criterion (AIC) and model fit over time to retain the final model [7].

Ethical Considerations

The ethical clearance was obtained from the medical committee of Point G Teaching Hospital. Data were collected anonymously and confidentially.

Results

Study population Characteristics

During the survey period, we followed 2 631 patients in the IDW. Among them, 47% (1 237/2 631) were infected by HIV. Among these HIV infected patients, we included 38.31% (474/1 237) in this study (figure 1). Women were more frequent in the study sample than men (266/208) with a sex-ratio of 1.27. Adults represented more than half of the study patients (53.37%) in the age group 31 to 45 years with a median age of 38 years (range: 17 to 80 years). The median age of the patients included was 38 years (range: 17 to 80 years) and 53.37% (253/474) were aged between 31 to 45 years (Table 1). In our cohort, 59.5% (282/474) of the patients were married, 79.7% (378/474) resided in an urban area and 66% (313/474) had a monthly paid position. Relative to lifestyle, 35.7% (165/474) of the patients regularly used a stimulant and 20% (95/474) consumed at least two stimulants. Few patients had a medical history: high blood pressure (HBP) 6.8% (32/474), diabetes 1.3% (6/474), peptic ulcer disease 7% (33/474) and tuberculosis 5.9% (28/474)

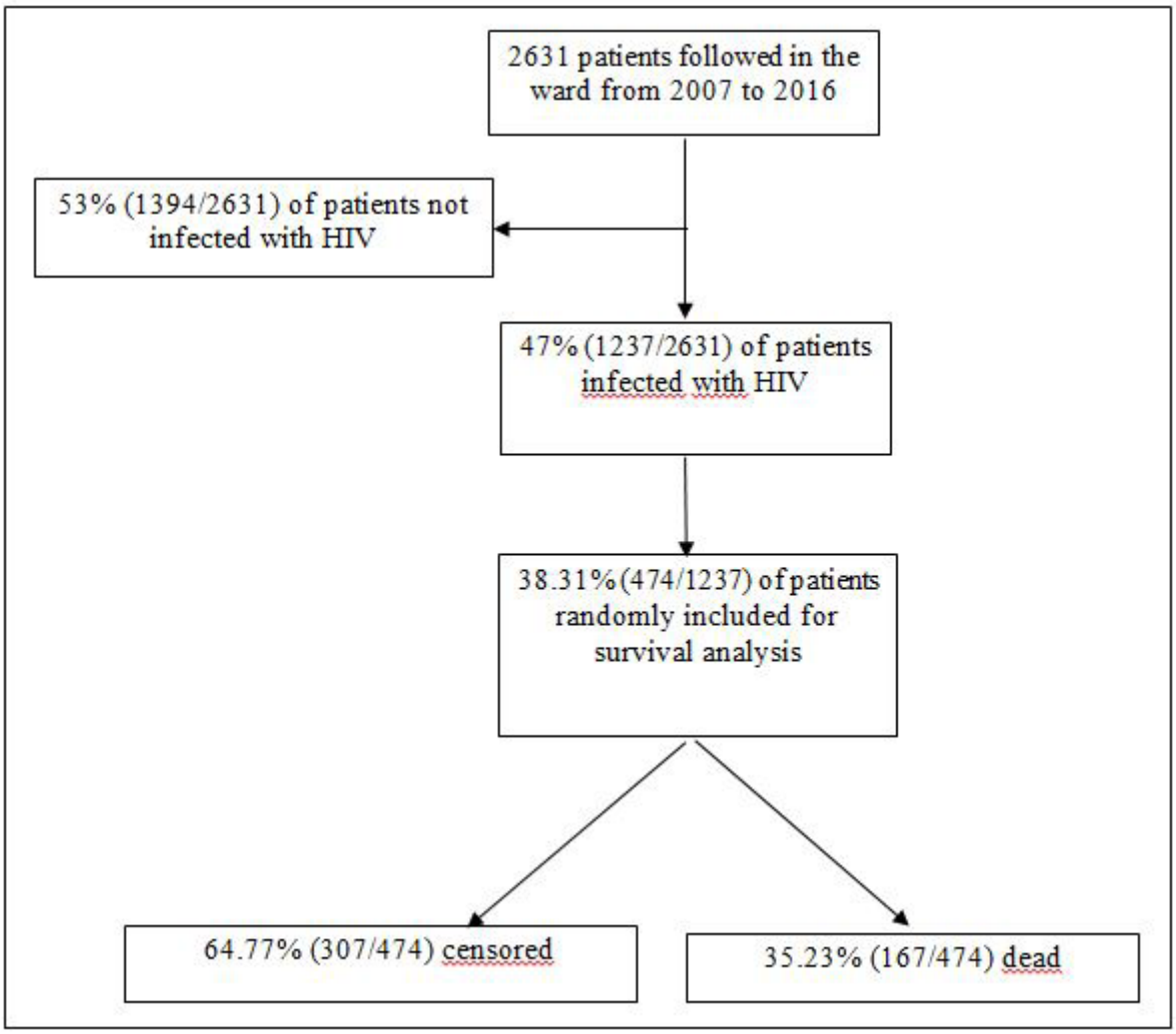

Figure 1: Participants' flow chart

	Patients followed N = 474	Lost follow up n (%)	Transferred n (%)	Dead n (%)	Median survival (month) (95% CI)	Test of log-rank (p)
Personal characteristics						
Sex						
Male	208 (43.88)	6 (6.88)	2 (0.96)	85 (40.9)	24 (15 - 40)	0.004
Female	266 (56.12)	7 (6.63)	4 (1.50)	82 (30.8)	57 (37 - 97)	
Age group						
15-30 years	110 (23.21)	4 (3.64)	2 (1.82)	32 (29.1)	44 (32 - 66)	0.42
31-45 years	253 (53.37)	6 (2.37)	4 (1.58)	98 (38.7)	34 (25 - 40)	
above 45	111 (23.42)	3 (2.70)	0 (0)	37 (33.3)	64 (31 - 80)	
Occupation						
Monthly renumeration	313 (66.03)	11(3.51)	3 (0.96)	119 (38)	32 (24 - 53)	0.14
No monthly renumeration	161 (33.97)	2 (1.24)	3 (1.86)	48 (29.8)	46 (33 - 80)	
Marital status						
Married	282 (59.49)	8 (2.84)	3 (1.06)	102 (36.2)	37 (29 - 45)	0.59
Divorced / Widowed	68 (14.35)	2 (2.94)	1 (1.47)	20 (29.4)	62 (44 - 71)	
Single	124 (26.16)	3 (2.42)	2 (1.61)	45 (36.3)	33 (29 - 46)	

	Patients followed N = 474	Lost follow up n (%)	Transferred n (%)	Dead n (%)	Median survival (month) (95% CI)	Test of log-rank (p)
Residence						
Urban	378 (79.75)	7 (1.85)	5 (1.32)	142 (37.2)	34 (25 - 53)	
Peri urban	74 (15.61)	5 (6.76)	0 (0)	19 (25.7)	62	0.38
Rural	22 (4.64)	1 (4.55)	1 (4.55)	6 (27.3)	46	
Number of stimulants consumed						
No stimulant	210 (44.30)	8 (3.81)	2 (0.95)	62 (29.5)	57 (26 - 85)	0.05
1 stimulant	169 (35.65)	5 (2.96)	4 (2.37)	69 (40.8)	44 (27 - 64)	
At least 2 stimulants	95 (20.04)	0 (0)	0 (0)	36 (37.9)	25 (11 - 39)	
Continued						
Medical background						
Hypertension						
Yes	32 (6.75)	3 (3.13)	0 (0)	7 7 (21.9)	-- -	0.24
No	442 (93.25)	12 (2.71)	6 (1.36)	160 (36.2)	37 (25 - 57)	
Diabetes						
Yes	6 (1.27)	0 (0)	0 (0)	3 (50)	46 (10 - 46)	0.84
No	468 (98.73)	13 (2.78)	6 (1.28)	164 (35)	37 (32 - 45)	
Peptic ulcer						
Yes	33 (6.96)	2 (6.06)	0 (0)	12 (36.4)	34 (27 - 34)	0.87
No	441 (93.04)	11 (2.49)	6 (1.36)	155 (35.1)	39 (29 - 57)	
Tuberculosis						
Yes	28 (5.91)	1 (3.57)	0 (0)	11 (39.3)	41 (18 - 41)	0.70
No	446 (94.09)	12 (2.69)	6 (1.35)	156 (35)	37 (27 - 57)	
Biological parameters						
Weight (kg)						
50 and over	105 (22.15)	3 (2.86)	1 (0.95)	30 (28.6)	46 (29 - 85)	0.26
Less than 50	369 (77.85)	10 (2.71)	5 (1.36)	137 (37.1)	36 (26 - 53)	
CD4 count (Unit / mm3)						
500 and more	12 (2.53)	1 (8.33)	0 (0)	2 (16.7)	-	0.009
200 - 499	73 (15.40)	1 (1.37)	0 (0)	16 (21.9)	-	
Less than 200	389 (82.07)	11 (2.83)	6 (1.54)	149 (37.1)	33 (25 - 44)	
Type of HIV						
HIV 1 only	445 (93.88)	12 (2.70)	6 (1.35)	158 (35.5)	39 (31 - 57)	
HIV 2 only	16 (3.38)	1 (6.25)	0 (0)	5 (31.2)	-	0.99
HIV 1 + VIH 2 associated	13 (2.74)	0 (0)	0 (0)	4 (30.8)	24 (7 - 24)	
Therapeutic regimen						
L0	5 (1.05)	1 (20.00)	0 (0)	1 (20)	67 (33 - 84)	
L1	396 (83.54)	9 (2.27)	4 (1.01)	144 (36.4)	33 (23 - 46)	0.05
L2	73 (15.40)	3 (4.11)	2 (2.74)	22 (30.1)	53 (31 - 66)	
WHO stage						
II - III	279 (58.86)	10 (3.58)	5 (1.79)	84 (30.1)	46 (37 - 77)	0.002
IV	195 (41.14)	3 (1.54)	1 (0.51)	83 (42.6)	24 (10 - 44)	

	Patients followed N = 474	Lost follow up n (%)	Transferred n (%)	Dead n (%)	Median survival (month) (95% CI)	Test of log-rank (p)
System Disorders						
Nervous system disorders						
Yes	95 (20.04)	3 (3.16)	0 (0)	37 (38.9)	29 (15 - 64)	0.38
No	379 (79.96)	10 (2.64)	6 (1.58)	130 (34.3)	44 (32 - 62)	
Respiratory / ENT disorders						
Yes	147 (31.01)	2 (1.36)	3 (2.04)	46 (31.3)	41 (24 - 97)	0.57
No	327 (68.99)	11 (3.36)	3 (0.92)	121 (37)	34 (27 - 57)	
Digestive disorders						
Yes	61 (12.87)	3 (4.92)	2 (3.28)	16 (26.2)	33 (27 - 40)	0.03
No	413 (87.13)	10 (2.42)	4 (0.97)	151 (36.6)	62 (57 - 80)	
Cardiovascular disorders						
Yes	16 (3.38)	0 (0)	0 (0)	9 (56.2)	66 (3 - 67)	0.33
No	458 (96.62)	13 (2.84)	6 (1.31)	158 ((34.5)	37 (29 - 55)	
Skin and mucous membrane disorders						
Yes	21 (4.43)	0 (0)	1 (4.76)	3 (14.3)	-	0.09
No	453 (95.57)	13 (2.87)	5 (1.10)	164 (36.2)	37 (29 - 55)	
Blood-oncological disorders						
Yes	18 (3.80)	0 (0)	0 (0)	7 (38.9)	18 (13 - 46)	0.83
No	456 (96.20)	13 (2.85)	6 (1.32)	160 (35.1)	39 (31-57)	
Urogenital disorders						
Yes	16 (3.38)	1 (6.25)	0 (0)	3 (18.8)	123 (31 - 123)	0.09
No	458 (96.62)	12 (2.62)	6 (1.31)	164 (35.2)	37 (27 - 55)	
Septecemia						
Yes	82 (17.30)	4 (4.88)	0 (0)	43 (52.4)	24 (9 - 33)	0.0008
No	392 (82.70)	9 (2.30)	6 (1.53)	124 (31.6)	46 (36 - 66)	

Table 1: Patient survival according to socio-demographic, clinical and biological factors

Overall mortality and follow-up time interval	Mortality rate per100 people years (CI 95%)
Overall mortality rate	16. 94 (16.25 - 17.63)
Mortality rate by follow-up time interval	
0 to 1 year	21. 24 (9.69 - 32.79)
0 to 2 years	16. 50 (8.70 - 24.31)
0 to 5 years	8. 95 (5.63 - 12.26)
0 to more than 5 years	2. 36 (1.03 - 3.70)

Table 2: Overall mortality rate per patient follow-up time interval

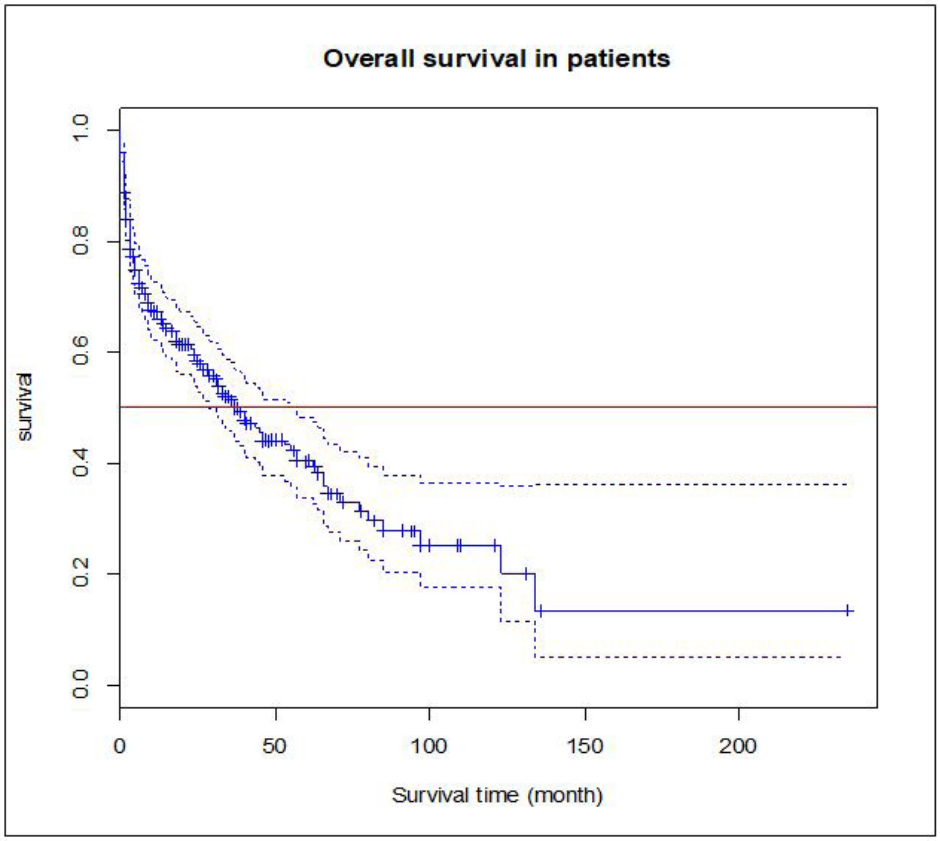

Figure 2: Overall patients' survival (Kaplan-Meier analysis)

(Table 1). Almost all patients 93.9% (445/474) were infected with the only HIV-1 serotype. The first-line therapeutic regimen (L1) composed by two Nucleoside reverse transcriptase inhibitors (2 NRTIs) associated with one Non-Neucleoside reverse transcriptase inhibitors (1 NNRTI) has represented 83.5% (396/474). Co-infection (HIV 1 and HIV 2) was present with 2.73% (13/474). At the last time point, the median patient body weight was 40 kg (range: 17 to 80 kg) and 82.06% (389/474) had a CD4 of less than 200 cell/mm^3 with a median CD4 at 50 cell/mm^3 (range: 1 to 824 cell/mm^3). The clinical status of enrolled HIV/AIDS patients was very advanced: 41.1% (195/474) were at stage IV according to WHO classification, 50% (237/474) were in category B3 and 34.6% (164/474) in the category C3 according the CDC classification. The most frequent disorders were respiratory and otorhinolaryngological 31.01% (147/474), neurological 20.04% (95/474), septicemia 17.29% (82/474) and digestive 12.86% (61/474). Tuberculosis was the most frequent opportunistic infection in patients with 15.61% (74/474) followed by cerebral toxoplasmosis with 10.97% (52/474), Kaposi's disease with 6.32 (30/474) and esophageal candidiasis with 6.11 (29/474) (Table 1).

Patients' Survival

We followed the study cohort for 986 person-years with an overall mortality rate of 16.94 per 100 person-years (95% CI, 16.25 to 17.63). This mortality rate was higher the first year after initiation of the ART (21.24 per 100 person-years; 95% CI, 9.69 to 32.79) (Table 2). Overall patient survival was 68.3% (95% CI, 63.2 to 73.3) at 12 months of follow-up, 42.3% (95% CI, 34.6 to 50) at 60 months of follow-up and 31% (CI95%, 21.1 to 40.8) at 96 months of follow-up. A total, we noted 35.23% (167/474) deaths with an overall median survival of 39 months (95% CI, 29 to 57 months) (figure 2). The frequency of loss to follow up was low with 4,2% (13/307). However, patient's median survival varied significantly according to certain factors. The median survival was statistically shorter in males than females (24 months, 95% CI, 15 to 40 months) versus (57 months, 95% CI, 37 to 97 months) with (log-rank test, p=0.004). Patients at stage IV according to the WHO classification survived less than those at stage II and III (24 months, 95% CI, 10 to 44 months) versus (46 months, 95% CI, 37 to 77 months) with, (log-rank test, p=0.002). Death occurred earlier in patients with septicemia (24 months, 95% CI, 9 to 33 months) versus patients unreached (46 months, 95% CI, 36 to 66 months) with (log-rank test, p=0.0008), in patients with Kaposi's disease (5 months, 95% CI, 3 to 29 months) than patients unreached (40 months, 95% CI,

33 to 53 months) with (log-rank test, p=0.02), in patients with Progressive Multifocal Leukoencephalopathy (4 months) than those unreached (39 months, 95% CI, 31 to 57 months) with (log-rank test, p=0.01) and in patients with digestive disorders (33 months, 95% CI, 27 to 40 months) than those without digestive disorders (62 months, 95% CI, 57 to 80 months) with (log-rank test, p=0.03) (Table 1, 3).

Prognostic Factors (Cox Model)

This study using a multivariate Cox analysis allowed to identify many factors of poor prognosis among the patients followed for HIV infection in the Infectious Diseases Ward of the Point G Teaching Hospital of Bamako. These predictors were essentially related to the clinical condition of the patient. This is stage IV of the WHO classification (aHR, 1.54; 95% CI, 1.1 to 2. 1), CD4 count < 200 cell /mm^3 (aHR, 1.86; 95% CI, 1.12 to 3.04), tuberculosis (aHR, 1.55; 95% CI, 1.01 to 2.38), PML (aHR, 8.18; 95% CI, 1.96 to 34.06), septicemia (aHR, 1.71; 95% CI, 1.18 to 2.47) and Kaposi's disease (aHR, 1.80; 95% CI, 1.01 to 3.23). We also identified the regular consumption of at least two stimulants, a patient's behavior, as a factor of poor prognosis (aHR, 1.76; 95% CI, 1.15 to 2.66) (Table 4).

Tuberculosis						
Yes	74 (15.61)	2 (2.70)	1 (1.35)	29 (39.2)	37 (4 - 66)	0.15
No	400 (84.39)	11 (2.75)	5 (1.25)	138 (34.5)	40 (32 - 55)	
Esophageal candidiasis						
Yes	29 (6.12)	0 (0)	1 (3.45)	7 (24.1)	-	0.84
No	445 (93.88)	13 (2.92)	5 (1.12)	160 (36)	37 (29 - 55)	
Kaposi's disease						
Yes	30 (6.33)	0 (0)	2 (6.67)	13 (43.3)	5 (3 - 29)	0.02
No	444 (93.67)	13 (2.93)	4 (0.90)	154 (34.7)	40 (33 - 53)	
Cerebral toxoplasmosis						
Yes	52 (10.97)	0 (0)	0 (0)	19 (36.5)	19 (15 - 34)	0.72
No	422 (89.03)	13 (3.08)	6 (1.42)	148 (35.1)	40 (33 - 53)	
Isosporiosis						
Yes	3 (0.63)	0 (0)	0 (0)	0 (0)	-	0.21
No	471 (99.37)	13 (2.76)	6 (1.27)	148 (35.5)	37 (29 - 55)	
Meningeal cryptococcosis						
Yes	9 (1.90)	1 (11.11)	0 (0)	3 (33.3)	-	0.66
No	465 (98.10)	12 (2.58)	6 (1.29)	164 (35.3)	37 (29 - 57)	
Lymphoma						
Yes	3 (0.63)	0 (0)	0 (0)	2 (66.7)	8	0.05
No	471 (99.37)	13 (2.76)	6 (1.27)	165 (35)	39 (31 - 57)	
Continued						
Progressive Multifocal Leukoencephalopathy						
Yes	2 (0.42)	0 (0)	0 (0)	2 (100)	4	0.01
No	472 (99.58)	13 (2.75)	6 (1.27)	165 (35)	39 (31 - 57)	
Cervical tumor						
Yes	1 (0.21)	0 (0)	0 (0)	0 (0)	-	0.61
No	473 (99.79)	13 (2.75)	6 (1.27)	167 (35.3)	39 (29 - 57)	

Table 3: Survival of patients according to opportunistic infections

Prognostic factors	Bivariate HR, (95% CI)	p-value	Multivariate aHR , (95% CI)	p-value
WHO stade				
II and III	1 (ref.)		1 (ref.)	
IV	1.61 (1.19 - 2.19)	0.002	1.54 (1.13 - 2.1)	0.006
CD4 count (unit / mm^3)				
<200	1 (ref.)		1 (ref.)	
≥ 200	2.07 (1.27 - 3.38)	0.004	1.85 (1.12 - 3.04)	0.01
Tuberculosis				
No	1 (ref.)		1 (ref.)	
Yes	1.34 (0.9 - 2)	0.15	1.55 (1.01 - 2.38)	0.04
Progressive Multifocal Leukoencephalopathy				
No	1 (ref.)		1 (ref.)	
Yes	4.96 (1.22 - 20.13)	0.02	8.18 (1.96 - 34.06)	0.004
Septicemia				
No	1 (ref.)		1 (ref.)	
Yes	1.8 (1.27 - 2.54)	<0.001	1.71 (1.18 - 2.47)	0.004
Kaposi's disease				
No	1 (ref.)	0.02	1 (ref.)	
Yes	1.91 (1.08– 3.27)		1.8 (1.01 - 3.23)	0.04
Number of stimulants consumed				
No stimulant	1 (ref.)		1 (ref.)	
1 stimulant	1.29 (0.91 - 1.82)	0.14	1.51 (1.06 - 2.15)	0.02
At least 2 stimulants	1.63 (1.08 - 2.46)	0.02	1.75 (1.15 - 2.66)	0.009

Table 4: Patient's associated prognostic factors (Cox model)

Discussion

In this first study on prognosis of hospitalized HIV patients in a low prevalence country, we found an overall mortality of 16.94 per 100 person-years and an overall survival probability of 42.3% at 60 months follow-up. We identified several factors of poor prognosis related to the clinical or biological status.

Characteristics of the Population

This study showed that HIV management is an important component of the infectious diseases Ward activities with 47.01% of the hospitalizations over the study period. It found that HIV mostly affects young adults and women in the capital city of the country with a sex ratio (female / male) of 1.27 and a median age of 38 years. More than half of the patients in this cohort were married and lived in urban areas. These results are in accordance with the trends observed in the last Demographic and Health Survey (DHS) in Mali where HIV prevalence in the general population aged 35-39 was 1.4% compared to 1.1% in the total population aged 15-49 years [3]. This DHS also showed that HIV prevalence was 1.3% among women and 0.8% among men with a prevalence of 1.9% in urban areas 1.9% versus 0.9% in rural areas [3]. HIV Prevalence among women separated from their partner (2.0%) was higher than among women in union (1.4%), as well as among singles (1.2%) [3]. More than half 55.69% (264/474) of the participants in our study consumed at least one stimulant. A cohort in Ethiopia described the use of stimulant by HIV-infected patients in 40.85% of patients [8]. HIV-1 only remains the predominant serotype with 93.88% (445/474) of the patients in our cohort; this reflects the trend of the HIV epidemic in Mali where subtype 1 is largely predominant [3]. A multicenter antiretroviral treatment surveillance

study conducted in 2010 reported this prevalence of HIV-1 in West Africa [9]. Like most cohorts' patients in Africa, our patients were on the combined 2 NRTIs and 1 NNRTI therapeutic regimen [10-12].

A total 82.07% (389/474) of our patients were admitted with very low lymphocyte rate (less than 200 cells/mm3) and at advanced clinical stage of the disease with 41.14% (195/474) at WHO stage IV. We observed at least one opportunistic infection in 42.82% of the patients. The biological status of our patients was similar to that of other cohorts followed in West Africa where patients were hospitalized with an average CD4 count of 75 cells/mm3 [9]. Fortes DL et al in 2011 in Senegal reported 86% of the patients admitted with a CD4 count of 200 cells/mm3 or less [13]. Previous studies in Africa described 94% of patients at WHO stage III or IV and 89.42% with opportunistic infection [9, 13]. This difference could be explained by an under-diagnosis of opportunistic infections in our context. The diagnosis of most opportunistic infections requires a very high technical platform with specific biological and radiological tools. One case of undiagnosed pneumocystis has recently been described in Pakistan [14].

Probability of Survival and Mortality Rates

In our cohort, an overall mortality of 16.94 per 100 person-years, 95% CI95% (16.25 - 17.63) was recorded with a higher rate in the 1st year after starting antiretroviral treatment [21.24 per 100 person-years, CI95% (9.69 - 32.79)]. The high mortality rate observed in the first 12 months within our hospitalized patients was also observed in other studies even though they were specifically following up cohorts of patients receiving ART but not hospitalized, thus of a different clinical typology". This type of study is different from ours because if patients are not hospitalized, they are usually not in an advanced stage of the disease and should be less susceptible to die. In a retrospective cohort followed in Nepal from 2006 to 2011, the overall mortality was 6.3 per 100 person-years but the mortality during the first three months after initiation of ART was [21.9 per 100 person-years (95% CI 16.6 - 28.8)] [11].

A retrospective cohort from 2007 to 2011in Ethiopia described an overall mortality rate of 5.15 per 100 persons-year (95% CI: 4.73 - 6.37) with 9.8 deaths per 100 persons-year at 12 months of follow-up [15]. A prospective study in a rural area of South Africa with 2,221 participants enrolled from 2003 to 2010 found a lower mortality rate than our study, 11 deaths per 100 person-years (95% CI: 9.7 - 12.5) [16]. Other studies in Tanzania, Malawi and Senegal found mortalities rates respectively 24.2%, 28.6% and 44% [17-18, 13]. Although immunological and virological responses to antiretroviral therapy in sub-Saharan African patients are comparable to those observed in patients treated in high-income countries, early mortality rates in our region have remained very high [8].

In our study, the overall survival probability of HIV/AIDS patients was 68.3%, CI95% (63.2% - 73.3%) at 12 months follow-up, 42.3%, CI95% (34.6% - 50%) at 60 months follow-up and 31%, CI95% (21.1% - 40.8%) at 96 months follow-up. This survival is similar to those of some cohorts followed in Africa such as the one in Addis Ababa where the mean of survival times in months was 41.17 (CI 95%, 39.69 - 42.64) and in Cameroon where the survival probability was 47% at 5 years (CI 95%, 40 to 55%) [12,19]. On the other hand, the probability that our patients would survive was lower than those of patients in two recently followed cohorts in northwestern and southern Ethiopia, 61.4% and 64% respectively after a 72 month follow-up period both cohorts [10,8]. The probability of survival of HIV-infected patients varies considerably from one cohort to another. A meta-analysis of a total of 57 studies including 294,662 participants had estimated the probabilities of survival at 2, 4 and 6 years respectively at 87%, 86% and 78% in patients under HAART versus 48%, 26% and 18% in patients not under HAART [20]. Although evidence of considerable heterogeneity was found in that meta-analysis, the probability of survival in our cohort was lower.

The early mortality and low survival rate among our patients are explained by several parameters, including a late diagnosis of HIV infection, the late initiation of HAART reflecting a very low CD4 count (82.06% < 200 cell/mm^3) and a very advanced clinical stage at enrolment (41.14% in WHO stage IV). This situation of late use of care has already been

described in other studies. Patients with late HIV diagnosis had a higher risk of mortality (aHR = 3.22, 95% CI: 1.17-8.82) than patients with early HIV diagnosis in a retrospective cohort from 2010 to 2015 in northern Ethiopia [21].

Thus, early diagnosis of HIV infection through the development of voluntary testing, timely initiation of antiretroviral treatment and strengthening of HIV care should be implemented in order to reduce early mortality among HIV/AIDS patients. This package of interventions includes screening, treatment and/or prophylaxis for major opportunistic infections, rapid initiation of antiretroviral treatment and increased support for adherence to interventions that are now recommended by WHO [22, 23].

Cox's analysis with this cohort identified several factors of poor prognosis in patients followed for HIV infection in the Infectious Disease Ward of the Point G Teaching Hospital in Mali. Almost all of these risk factors were related to the clinical or biological status of our patients. These are the CD4 rate < 200 cell/mm^3, tuberculosis, WHO stage IV classification, PML, septicemia and Kaposi's disease. Other authors previously described these factors. In Ethiopia, a retrospective study conducted from 2005 to 2010 among 3,012 AIDS patients found that the number of CD4 at initiation of ART ≤ 200 cells/mm^3 is associated to higher mortality (aHR, 5.02; CI95%, 2.03 to 12.39). In another retrospective study also conducted in Ethiopia, authors reported for a cohort of 784 patients, that one of the predictive factors for death was the number of CD4 <50 cell/mm^3 (aHR, 2.70; CI95%, 1.26 to 5.80) [15]. In a cohort of 14,932 HIV-infected patients who started antiretroviral treatment between April 2004 and June 2011 in Johannesburg, South Africa, the observed death rate was 13.3% and the latest follow-up CD4 count was the most powerful predictor of death (<50 vs ≥ 550 cells/mm^3 – Relative Risk (RR): 46.3; 95% CI, 26.8 to 80) [24]. In another large cohort of 16,546 patients followed in Asia, a low CD4 count prior to antiretroviral treatment was a risk factor for high mortality [25]. Tuberculosis, known since the first years of the fight against HIV/AIDS as a common opportunistic infection was found as a risk factor for death in several cohorts in Ethiopia: (aHR, 2.93; CI95%, 2.11 to 4.02), (aHR, 2.30; CI 95%, 1.28 to 4.11), (aHR, 1.82; CI 95%, 1.41 to 3.51) [10, 15, 8]. In two of these studies, WHO stage IV classification was a highly significant predictor of mortality for HIV infected people: (aHR, 7.36; CI95%, 3.17 to 17.12) and (aHR, 24.97; CI95%, 2.75 to 26.45) [15, 8]. In North Africa, a retrospective study of hospitalizations at the Tripoli Medical Centre conducted in 2013 on 227 HIV-infected patients found that sepsis was associated with an increased risk of death (HR: 6.98) [26]. In Brazil, septicemia has been reported as the main risk factor for hospital mortality in HIV-infected patients (aHR, 3.35; CI95%, 1.42 to 7.86) [27]. Since 1994, a multicenter observational cohort study conducted by the *Zidovudine Epidemiology Study Group* on 1,044 patients with AIDS, including 143 Kaposi cases, concluded that Kaposi's sarcoma is a predictor of death (RR: 1.78; CI 95%, 1.26 to 2.52) [28]. A study conducted by the *Uganda Cancer Institute* from 1992 to 2007 on 404 patients with Kaposi's disease showed that stage S1 of Kaposi's disease was a factor associated with death 4 months after diagnosis (HR, 6.4; CI95%, 1.9 to 21.1) and stage T1, 4 to 24 months after diagnosis (HR, 4.0; CI95%, 1.4 to 11.5) [29].

All these factors of poor prognosis require specialized management with an adequate technical platform to reduce mortality. The Infectious Diseases Ward of University Hospital of Point G does not have an Intensive Care Unit (ICU) and qualified intensive care staff. It is therefore necessary to create an ICU in the Ward and train infectious disease specialists in intensive care. In addition to the early initiation of antiretroviral treatment suggested by WHO, there is also a need to intensify screening and early initiation of tuberculosis treatment. Although admission is subsidized, many of our health facilities do not have effective tuberculosis diagnosis tools, including culture and PCR methods (e.g. GenXpert). It is therefore important to provide adequate materials to health facilities to improve the rate of tuberculosis diagnosis to reduce tuberculosis associated mortality in general and specifically among people living with HIV (PLWH).

Another poor prognostic factor identified in this study is related to patient behavior, namely the regular consumption of at least two abusive substances (AHR, 1.76; CI95%, 1.15 to 2.66).

This behavioral factor for abusive substances has been cited by other authors in Ethiopia (HR, 3.72; CI95%, 1.39 to 9.97) [8]. An Australian study described high rates of smoking among PLWHA as a major cause of premature mortality and morbidity [30]. A study in the US concluded that in a context where HIV care is well organized and antiretroviral therapy is free, HIV-infected smokers lose more years of their lives because of smoking than because of HIV [31]. The excess mortality of smokers is tripled, and

the risk of death associated with smoking attributed to the population double that of the baseline population [31]. The different cardiopulmonary morbidities caused by substance abuse associated with immunosuppression reduce the survival of PLWH. Recurrent lung infections are a common cause of morbidity and mortality among PLWH and are exacerbated within smokers even after combined antiretroviral treatment [32]. The different cardiopulmonary morbidities caused by abusive substances associated with immunosuppression reduce the survival of PLWH. Recurrent lung infections are a common cause of morbidity and mortality among PLWH and are exacerbated in smokers even after combined antiretroviral treatment [32]. Although it's difficult to abandon habits, preventive awareness campaigns on the use of abusive substances must be carried out in addition to the implementation of a support framework in our structures for the gradual withdrawal of HIV-infected patients.

Conclusion

Our study shows that patients continue to be hospitalized in Mali at advanced stages of HIV infection with early mortality and reduced survival. The survival rate of HIV/AIDS patients in Mali is 68.3%, CI95% (63.2% - 73.3%) at 12 months follow-up. Poor prognostic factors are CD4 rate < 200 cell/mm3, tuberculosis, WHO stage IV classification, PML, septicemia, Kaposi's disease and regular consumption of at least two abusive substances. Structures adapted for early detection and treatment of HIV infection, opportunistic infections, and establishment of a reanimation unit within the infectious diseases ward would better reduce mortality and increase survival of HIV infected patients in Mali.

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