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Survival among Dually Infected HIV Patients Compared to HIV-1 Mono-Infected Patients Receiving ART in Senegal: A Twelve-Year Cohort Study

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Abbreviations

HIV-2s: Human Immune Deficiency Virus type 2 single; HIV-1s: Human Immune Deficiency Virus type 1 single; HIV-D: Human Immune Deficiency Virus Dual; ART: Antiretroviral Therapy; ARV: Antiretroviral; NRTI: Nucleoside-Reverse Transcriptase Inhibitors; NNRTI: Non-Nucleoside-Reverse Transcriptase Inhibitor; PI: Protease Inhibitor; BMI: Body Mass Index; CDC: Center for Diseases Control and Prevention; IQR: Interquartile Range; PY: Person-Years; HR: Hazard Ratio

Background

In West Africa, HIV-2 single infection (HIV-2s) and HIV-1 + HIV-2 dual infection (HIV-D) remain endemic but their morbidity is progressively decreasing [1-4]. Among HIV-D infected patients receiving antiretroviral therapy (ART), data on mortality are very scarce [5-8]. The purpose of this analysis was to compare survival of HIV-D infected with that of HIV-1 singly infected (HIV-1s) patients over twelve years of follow up after ART initiation.

Methods

A total of 403 HIV infected patients (10 HIV-D infected and 393 HIV-1s infected) who initiated ART in Senegal between 1998 and 2002 were included in a prospective cohort and followed until June 2010. Initial ART regimens combined two nucleoside-reverse transcriptase inhibitors (NRTI) plus either one non-nucleoside-reverse transcriptase inhibitor (NNRTI) or one protease inhibitor (PI). Clinical and biological assessments were performed at ART initiation and every semester thereafter. The data was censored at the date of the most recent visit and the survival function estimated by the Kaplan-Meier method. Cox proportional hazards models were used to identify risk factors of death among the baseline characteristics of the patients (age, sex, hemoglobin level, body mass index (BMI), CDC Stage, viral hepatitis B or C co-infection, HIV type, CD4 cell counts, HIV viral load, co-trimoxazole prophylaxis, ART regimen). Stata version 12.1 was used for analyses. The Senegalese national ethics committee approved this study and every participant signed an informed consent form after receiving a complete information sheet.

Table 1: Baseline characteristics of patients by HIV serotype.

Characteristics	HIV-D N = 10	HIV-1s N = 393	p-value
Age (years)			< 0.001
Mean (SD)[a]	49.5 (4.6)	37.8 (8.9)	
> 40	100.0	38.7	
Sex (%)			0.048
Male	80	44.5	
Female	20	54.5	
BMI (kg/m²)			0.625
Mean (SD)	19.9 (2.2)	20.4 (3.6)	
< 18.5	10.0	30.8	
CDC Stage (%)			0.720
A/B	30.0	45.0	
C	70.0	55.0	
Hemoglobin level (g/dL)			0.199
Mean (SD)	11.5 (2.1)	10.7 (1.8)	
< 10	30.0	33.6	
CD4 cell counts (cells/µL)			
Mean (SD)	173.2 (123.6)	148.0 (120.2)	0.534
< 200	55.6	69.6	
HIV-1 viral load (log copies/mL)			< 0.001
Mean (SD)	3.8 (1.1)	5.0 (0.8)	
Coinfection HBV or HCV (%)	37.5	23.5	0.402
Cotrimoxazole prophylaxis (%)	90.0	78.4	0.696
PI based regimen (%)	70.0	41.2	0.102

[a]Standard deviation

Results

Among the 403 patients, 220 were female. At baseline, median age was 37 years; interquartile range (IQR) = 31-43; 223 patients (55.3%) were at CDC stage C. The median values of BMI, hemoglobin level and CD4 cell counts were 19.9 kg/m² (IQR = 17.9-22.4), 10.7 g/dl (IQR = 9.3-12.0) and 127 cells/µl (IQR = 53-217), respectively. A total

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of 169 patients (41.9%) were receiving PI based tritherapy. Among HIV-D infected patients, initial ART regimens combined 2 NRTI + either indinavir (seven patients) or one NNRTI (three patients). At baseline, HIV-D infected patients were more likely to be male (80% vs. 44.5%; P = 0.048); they had a higher mean age (49.5 vs. 37.8 years; P < 0.0001) and lower mean viral load (3.8 vs. 5.0 log copies/ml; P < 0.001) compared to HIV-1s infected patients (Table 1). As of June 30th 2010, mean follow up duration was 81.8 months (IC95% = 77.4-86.2); it was longer for HIV-1s (82.5 months; IC95% = 78.1-86.9) than for HIV-D patients (54.3 months; IC95% = 15.4-93.1); p = 0.05. A total of 126 deaths (31.3%) and 38 lost to follow up (9.4%) were notified resulting in a retention rate of 59.3%. During 2246.2 person-years (PY) of exposure time, overall mortality rate was 4.0/100 PY (95% CI = 3.5-4.5). Mortality rate decreased progressively from 13.2/100 PY (95% CI = 9.9-16.6) during the first year to 1.9/100 PY (95% CI = 0.3-2.8) after five years of ART. The mortality rate was 6.9/100 PY among HIV-D infected patients (95% CI = 4.8-9.1) versus 3.9/100 PY (95% CI = 3.4-4.4) among HIV-1s infected patients; log rank test: p = 0.001. Seven out of ten HIV-D patients died including two of three HIV-D patients who were receiving 2 NRTI + 1 NNRTI. HIV-D infection was a risk factor for death (adjusted hazard ratio (HR) = 4.6; 95% CI = 2.0-10.6) as well as hemoglobin level < 10 g/dl (adjusted HR = 1.5; 95% CI = 1.0-2.2), BMI < 18.5 kg/m^2 (adjusted HR = 1.5; 95% CI = 1.-2.2) and CD4 cell counts < 200 cells/µl (adjusted HR = 2.2; 95% CI = 1.3-3.7) at baseline.

Discussion

In this study, we found that HIV-D infected patients had a lower survival than HIV-1s infected patients receiving ART. The characteristics that might contribute to increased mortality among HIV-D infected patients were predominant male sex and advanced age [9] but their effects were controlled in multivariate analysis. Another factor was the use of suboptimal ART regimens. An adequate ART regimen for HIV-D infected people must include ARV drugs that are simultaneously active against HIV-1 and HIV-2. This condition excludes all the NNRTI, the fusion inhibitor and several PI [10]. In our cohort, at baseline, three HIV-D infected patients were receiving 2 NRTI + 1 NNRTI although HIV-2 is naturally resistant to the NNRTI. Such suboptimal regimens were common in other West African cohorts [8,11-13] but might not impact treatment outcomes in the short term [11]. The several studies that compared outcomes of ART in HIV-D infected and HIV-1s infected patients reported discordant results. Two previous studies conducted in Burkina Faso found a lower survival among HIV-D infected patients. The first one reported a crude HR of 1.27 (95% CI = 0.84-1.94) and the second one an adjusted HR of 1.26 (95% CI = 0.76-2.07) [6,8]. In Mumbai, India, over a three-year period, the risk of death was 50% among HIV-D infected patients versus 9% among HIV-1s infected patients [7]. However, in Ivory Coast no difference was found: HR = 0.91 (95% CI = 0.59-1.40) [5]. In these previous studies, the mean duration of ART was less than three years: this may explain their inability to detect a statistically significant difference in mortality although some reported poorer immunologic outcomes in HIV-D infected patients [5,7,12]. Other explanations are related to the limitations in the management of ART for such patients. There is a lack of adequate monitoring tools for HIV-2s infection: CD4 cell counts, viral load and drug resistance tests are not as clearly understood as for HIV-1s infection [14-20]; resistance selection appears earlier than in HIV-1s infection [10]; and the definition of therapeutic failure still remains unclear [20-23]. Hence, the suboptimal outcomes of ART in HIV-2 infected individuals are established [24,25]. Moreover, in resource-limited settings, the therapeutic options for HIV-2s infection and HIV-D infection are very limited, and the second line regimens do not automatically include a new class of ARV drug. These problems will mainly impact the long-term outcomes.

To our knowledge, this is the first prospective cohort study to compare differences in mortality between HIV-D infected and HIV-1s infected patients under ART for such a long period. These differences may be explained, at least, in parts, by the insufficiencies in the management of ART for HIV-D infected individuals. However, these results must be interpreted with caution due to the limited sample size. Further research using adequate management of HIV-D infection is necessary to confirm whether HIV-2 co-infection is a risk factor for death among HIV-1 infected patients under ART. West African cohorts' collaboration can contribute to elucidate this question.

Ethics Approval and Consent to Participate

This study was approved by the "Conseil National d'Éthique pour la Rechercheen Santé" (CNERS). Before inclusion, every participant received complete information on the study and signed an informed consent form.

Availability of Data and Materials

For this manuscript, the data will not be shared due to the ownership rules. These data are under the responsibility of three agencies: « Conseil National de Lutte contre le Sida » (CNLS), « Agence Nationale de Recherches sur le Sida et les hépatites virales » et Institut de Recherche pour le Développement « IRD ».

Competing Interests

The authors declare that they have no competing interests.

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Author's Contribution

Assane Diouf and Amandine Cournil conceived the work.

Assane Diouf and Sabrina Eymard-Duvernay coordinated data collection and quality control.

Assane Diouf, Amandine Cournil and Sabrina Eymard-Duvernay did the data analysis and interpretation.

Assane Diouf drafted the manuscript.

Amandine Cournil, Sabrina Eymard-Duvernay and Louise Fortes-Deguenonvo revised the consecutive drafts.

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