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Comparing Treatment Outcomes of Antiretroviral Therapy in HIV-1 and HIV-2 Infected Patients, in Bamako, Mali

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Abstract

Background—HIV-2 leads to a less-severe disease than HIV-1 but is known to be resistant to Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs). We goaled to evaluate the clinical and biological outcomes of HIV-1 and HIV-2 infected-patients under Antiretroviral Therapy (ART) that do not include NNRTIs.

Methods—This is a case-control study of 100 participants (half in each group) to measure the frequency of clinical and biological adverse effects, and disease outcome at 6 and 12 months of treatment (M6 and M12) We included.

Results—Opportunistic infections were more frequent in HIV-1 infected patients with 82% when compared to HIV-2, 68%. However, the prevalence of treatment adverse events was slightly higher in HIV-2 infected patients. The average increase of CD4 cell count at M6 of treatment was 139.93 and 159.41 cells/mm3, for HIV-2 and HIV-1 groups respectively, and at 153 and 217 cells/mm3, at M12 for HIV-2 and HIV-1 respectively. A total of nine HIV-2 and six HIV-1 deaths were reported during the study

Conclusion—This study has shown that ART regimens that do not include NNRTIs are effective equally in the treatment of HIV-1 and HIV-2 infections. Nevertheless, we recommend regular and continuous laboratory monitoring for all HIV treated patients.

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Authors Contributions

Oumar AA, Dao S, Kane A, Cissoko Y and Maiga M wrote the research protocol. Kane A, Cisse M, Konate I, Maiga M, Dembélé JP collected the data. Murphy R, Dao S and Maiga M supervised the research study. Yombi JC and Cissoko Y analyzed and interpreted the results of the study. Oumar AA, Maiga M, Dao S, Seydi M, Cissoko Y, Konate I and Yombi JC wrote the manuscript. All authors have approved the final version of the manuscript.

Keywords

ART; Adverse Effects Taxonomy Topics; HIV-1; HIV-2; Mali

Introduction

HIV infection is a major public health issue in most tropical countries, particularly in sub-Saharan Africa.1 In 2016, UNAIDS estimated nearly 36.7 million people living with HIV/AIDS worldwide, 25.8 million of whom in sub-Saharan Africa [1]. In Mali, according to the Demographic and Health Survey (DHS-V) conducted in 2012, the overall prevalence of HIV is 1.1% of the general population [2]. The seroprevalence of HIV-2 infection was at 0.2% in the general population [3]. HIV-2 is currently endemic to West Africa only, although cases were reported in the 1980s in India and Europe [4,5]. The first cases of HIV-2 were discovered in West Africa (in Senegal and Guinea-Bissau) in 1986.6 HIV-2 differs mainly from HIV-1 by its envelope proteins. The weak pathogenicity of HIV-2 compared to HIV-1 is now well-established and is expressed by a relatively lower viral loads usually found in HIV-2 infections [7], which results in longer incubation time and lower transmission rates of both sexual and mother-to-child routes [7]. Compared with those infected with HIV-1, patients infected with HIV-2 have slower disease progression and lower plasma viral loads.8 However, just as HIV1, HIV-2 can also lead to AIDS. The West African regions affected by HIV-2 infections have usually low accessibility to antiretroviral therapy, which makes data on the outcomes of antiretroviral therapy from HIV-2 infected patients very rare. The natural resistance of this virus to Non-Nucleotide Reverse Transcriptase Inhibitors (NNRTIs) and to fusion inhibitors restricts their use as option in treatment regimens [4,9]. Also, the decreased susceptibility of HIV-2 to certain protease inhibitors, namely Nelfinavir, Amprenavir and Atazanavir [10–12], only adds to the therapeutic restrictions associated with HIV-2 infections. Recently, Peterson et al. found similar treatment efficacy of an integrase inhibitor (raltegravir) for the two types of infections [13]. However, another recent study found that HIV-2 strains isolated from infected patients in Mali and Belgium had two major mutations of resistance for raltegravir.5 In this project, we evaluated the outcomes of treatment of HIV-2 and HIV-1 infected patients in Bamako, using a case-control study design to record adverse effects and treatment effectiveness during ART.

Methods

This is a case-control study of a 4-year follow-up period, that took place at the HIV/AIDS “Center of Listening, of Care, Animation and Council” (CESAC) of Bamako. CESAC is one of the largest centers taking care of people living with HIV (PLHIV) in Mali. The center uses a computerized routine information gathering system since 2005. We used SPSS version 12.0 software to analyze the data. Demographic (age, sex), clinical and immunological characteristics (weight, clinical stage, CD4 cell counts, duration of HIV infection and disease outcome, opportunistic infections, ART regimens) were collected.

1. Ethical Aspects

Authorization was requested from the CESAC management team and was accepted by the Director. The Ethics Committee of the Faculty of Medicine, Pharmacy and Dentistry of Bamako also approved the study. A coded number was assigned to each participant to ensure confidentiality.

2. Groups Definitions

This case-control study included two sex-matched groups (Table I):

Group 1: All patients aged 18 years old or more, HIV-2 infected and treated for the 1st line ART regimens consisting of two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and a Protease Inhibitor (PI) for at least 6 months continuously without any interruption.

Group 2: All patients aged 18 years old or more, infected with HIV-1 and treated with second-line ART treatment (2 NRTIs + 1 PI), for at least 6 months of treatment, were included.

The two groups were matched by age range and sex.

3. ART regimen

The different regimens used in the two groups are summarized in Table II. The stavudine + lamivudine + indinavir /ritonavir regimen was the most commonly used in both groups (Table 2).

4. Outcome Measures

The treatment response was assessed based on clinical outcome (weight gained, onset of opportunistic infections) and immunological improvement (CD4 cell count) at month-6 (M6) and month-12 (M12) of ART. Tolerance was assessed based on clinical adverse effects and biological disorders. Assessment of HIV-2 plasma viral load was not routinely performed in Bamako.

5. Statistical Analysis

The data were entered and analyzed with SPSS software version 16.0. The relative risk was calculated for the various parameters. Comparisons of means were performed using the Student’s test and $p \leq 0.05$ was considered statistically significant.

Results

A total of 3,850 patients on ART during the study period were evaluated, and the first 100 patients that met our inclusion criteria were enrolled, with 50 HIV-1 and 50 HIV-2 cases. The demographic, clinical and immunological characteristics are summarized in Table I. There was no statistically significant difference in age, sex, clinical stage and CD4 count at inclusion (Table I).

The most commons clinical adverse effects were: diarrhea, nausea, vomiting, anorexia, skin reactions, headache, dysphagia, dizziness, insomnia, joint pain, nephritic colic and

lipodystrophy. The most commons biological disorders were: hepatic cytolysis, amylasemia, total cholesterol, hyperglycemia, hypertriglyceridaemia, anemia, neutropenia, hypereosinophilia, thrombocytopenia.

1. Clinical Response/Outcome

Clinically, weight gained in the first six months was similar in both groups, but a significant difference (higher) at M9 (p= 0.02) and M12 (p = 0.01) was observed in HIV-2 infected patients. During follow-ups, opportunistic infections occurred in 68% of HIV-2 infected patients and 82% HIV-1 infected patients (Table III).

The prevalence of treatment-related side effects was comparable in the two groups with Relative Risk (RR) of 1.7 at M6 and RR of 2.2 at M12 (44% versus 20%). However, clinical lipodystrophy only occurred in 2% of HIV-1 infected patients. The mortality was also comparable in the two groups. There were 18% deaths in HIV-2 infected patients and 12% in HIV-1 infected patients with an RR of 1.5 (0.57–3.90).

2. Immunological Response

The nadir CD4 cells/mm3 was 122 (67–258) for HIV-1 versus 151 (49–298) for HIV-2 (p = 0.27). There was a steady but not significant increase in CD4 cell counts in one or the other group at all stages of the treatment, with an average CD4 cells gained of 139.93 and 159.41 cells/mm3, respectively for HIV-2 and HIV-1 at M6 (p = 0.00001). However, the CD4 cells gained was not significantly different at M12 between the two groups (p = 0.16).

3. Clinical Tolerance

Adverse events at M6 were greater in HIV-2 patients with 58% versus 34% in HIV-1 infected patients (P= 0.02). These events were mainly diarrhea, nausea and vomiting observed at M6 in both HIV-2 and HIV-1 (Table III). However, these clinical adverse effects persisted at M12 with 44% for HIV-2 patients and only 20% for HIV-1 infected patients (P=0.018). The events included diarrhea and nausea in HIV-2 infected patients, whereas in HIV-1 patients, the clinical adverse effects were dominated by pruritus skin reactions and dizziness (Table III). The mean serum creatinine level was 87.2 ± 27.0 μmol/L for the two groups, the mean hemoglobin was 11.6 ± 1.5 g/dL and the mean ALT was 17.6 ± 13.1 U/L (Table I). There was no significance difference in mean serum creatinine levels between HIV-2 and HIV-1 infected patients (93.4± 17.0 μmol/L versus 81.9 ± 11.2 μmol/L) (p = 0.02) at month 12. The mean ALT for HIV-2 was 18.6 ± 14.6 IU/L versus 16.6 ± 11.4 IU/L for HIV-1 (P = 0.43) at month 12. There was no difference between the mean hemoglobin between the two groups: HIV-2 (11.4 ± 1.9 g/dl) versus HIV-1 (11.9 ± 0.8 g/dl), (p = 0.07) at month 12 (Table I).

4. Discussion

Our study, in Mali, showed an efficacy of ART regimens without NNRTIs that was similar in HIV-1 and HIV-2 infected patients. However, opportunistic infections were higher in HIV-1 group compared to HIV-2 patients. Adverse effects were more common in HIV-2 infected patients at M6 and M12. Adverse effects were mostly due to 3TC+D4T+IDV/r (lamivudine + stavudine + indinavir/ritonavir) regimen, which is the most prescribed regimen with 78%

of observed events by M6, and 81% events by M12. However, there was no statistical difference in mortality between the two groups during treatment (P= 0.57). Also, there was no difference between HIV-2 and HIV-1 groups for advanced disease stage, weight-gained and opportunistic infections occurrence. This could be explained by the fact that HIV-1 infected patients were followed-up on treatment for long time, because they were already on second-line regimens when enrolled in our study. Overall, the prevalence of treatment-related adverse events slightly higher in HIV-2 infected patients. Only one case of clinical lipodystrophy occurred in an HIV1 infected patient. This may be due to the relative short follow-up time during our study (one year). The prevalence of opportunistic infections occurring during treatment was not statistically different between the two groups. However, slightly more opportunistic infections occurred with HIV-1 compared to HIV-2, which could be explained by HIV-1 being more pathogenically aggressive with higher viral loads seen with patients. Candidiasis with 63.1% occurrence was the most predominant opportunistic infection. The other pathologies seen were rare with a total frequency of less than 20%.

The mortality under treatment was also slightly higher in the HIV-2 group (18%) compared to HIV-1 group (12%) but was not statistically significant (P = 0.57). Similar mortality rate has been reported elsewhere in the literature, in Senegal and Gambia.14–16

The mean number of CD4 cells increased at M6 of ART and was +72 cells/μl (41–140). Overall, among HIV-2 patients whose started ART and had available viral load (VL) results, 10 to 39% was undetectable at baseline. Nevertheless, among patients who initiated a PI-free regimen, one in six (17%) had an undetectable VL at baseline.

Most patients were treated with regimens containing 2 NRTIs associated with 1 PI. In general, there was an increase in CD4 levels in most patients and in both groups. The PI the most used in our study site was indinavir/ritonavir (IDV/r). Its good efficacy has been well recognized [11,12]. The number of patients under lopinavir was low in our cohort; however, a study conducted in Paris reported a great clinical response to HIV-2 infections [17]. On the other hand, regimens that include nelfinavir or amprenavir, as well as the combinations of three nucleotide analogues of the reverse transcriptase have not proven to be effective. For example, saquinavir-ritonavir-based regimens have shown conflicting results from different studies [10,18,19]. The decrease in sensitivity to certain PIs, coupled with a much higher prevalence of mutations conferring multi-resistance to nucleotide analogues of reverse transcriptase versus HIV-1,10,15 limits the treatment options for HIV-2 alone or HIV-1/2 co-infections [14,15]. This highlights the need to make available drugs like indinavir, lopinavir-ritonavir, darunavir and tenofovir, in HIV-2 affected countries.

Clinical adverse reactions, mainly digestive disorders, have been reported during antiretroviral therapy, with 58% in HIV-2 patients versus only 34% in HIV-1 patients at M6. These were mainly diarrhea, nausea and vomiting in both HIV-2 and HIV-1. These clinical adverse effects persisted at M12 with 44% of HIV-2 patients versus 20% of HIV-1 patients. The 3TC + D4T + IDV/r regimen had the highest reporting rate with 78% by M6 and 81% by M12. But we also found that the 3TC + TDF + LPV/r (lamivudine + tenofovir + lopinavir/ritonavir) and 3TC + ZDV + AB (lamivudine + zidovudine + abacavir) regimens

were the best tolerated in our patients. The biological effects associated were lipid disorders, but there was no significant difference between the groups at M6 and M12.

Limitations: few limitations were noted including the study design that was a retrospective case-control study of one center only, which therefore reflects that center patient management experience and conditions. Another limitation is related to some missing biological data, such as the HIV-2 viral load, which was not an available option to patients. Nevertheless, this study is one of the few on the treatment outcomes of HIV-2 treated patients.

Conclusion

The ART administered to HIV-2 infected patients in Mali were effective, tolerated and accepted despite few noted adverse effects by M6 and M12, such as diarrhea, neuropathy, vomiting and headache. These adverse effects were mainly related to stavudine containing regimens and older PIs such as indinavir. However, limited therapeutic options were available for HIV-2 infected patients. Therefore, there is still a need for new and safe ART regimens for this special group of HIV patients.

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Table 1:

Characteristics of the Study Population.

Characteristics	HIV-2	HIV-1	P value
Male (n)	13	13	
Female (n)	37	37	0.59
Age mean	39.64	36.66	0.176
Clinical Stage: World Health Organization's Classification			
Stage I	4	4	
Stage II	22	23	0.52
Stage III	24	21	
Stage IV	0	2	
CD4 count Mean (cells/mm^3)	165.7	233.5	0.1
Nadir CD4 (cellules/mm3)	151 (49–298)	122 (67–258)	0.27
Creatinine	93.4	81.9	0.22
Hemoglobin	11.36	11.91	0.07
Alanine Aminotransferase	18.66	16.6	0.33

Table 2:

Therapeutic Regimens Received By HIV-1 And 2 Infected Patients.

Regimens	HIV-2 N=50	HIV-1 N=50	P value
lamivudine+stavudine+indinavir/ritonavir	35 (70%)	32 (64%)	0.67
lamivudine+stavudine+lopinavir/ritonavir	5 (10%)	5 (10%)	0.74
lamivudine+tenofovir+indinavir/ritonavir	2 (4%)	3 (6%)	*
lamivudine+tenofovir+lopinavir/ritonavir	1 (2%)	3 (6%)	*
lamivudine+zidovudine+abacavir	2 (4%)	1 (2%)	*
lamivudine+zidovudine+lopinavir/ritonavir	5 (10%)	6 (12%)	0.75

* n is less than 5

Table 3:

Relative Risks Treatment Outcomes in HIV-1 and HIV-2 infected Patients

Description		HIV-2	HIV-1	RR	IC	P value
Opportunistic infections	**Yes**	34	41	1.2	0.96–1.51	0.165
	No	16	9			
Adverse Effects at Month-6	**Yes**	29	17	1.7	1.08–2.65	0.027
	No	21	33			
Adverse Effects at Month-12	**Yes**	22	10	2.2	1.16–4.15	0.018
	No	28	40			
Prognostic	**Alive**	41	44	1.5	0.57–3.90	0.57
	Dead	9	6			