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Outcome of Patients on Second Line of Antiretroviral Therapy in Dakar

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Abstract

Context: In resource-limited countries, late start of antiretroviral treatment, lack of compliance and limited access to viral load testing are all factors that contribute to the increase in the number of second-line patients. Despite this situation, treatment options remain limited in our countries. The objectives of this study were to describe the characteristics of patients and to evaluate the outcome of HIV-1 infected patients undergoing second-line ARV treatment.

Methods: Retrospective cohort study conducted at the Department of Infectious and Tropical Diseases (SMIT) of the National University Hospital Centre (CHNU) of Fann in Dakar. HIV-1 infected patients on second-line ARV treatment between January 1, 2008 and December 31, 2016 were included. The data was collected from the medical records and analysed with the Info version 7 software.

Results: In our study, we included 135 patients. The median time to switch from the first to the second line of antiretroviral treatment was 3 years [2.5-5.5]. The average age was 41.7 ± 10.4 years at the start of the second ARV treatment line. The sex ratio (F/H) was 1.4. At the start of ART, 107 (79.3%) were classified as WHO stage 3 and 4 whereas this proportion was 21.5% at the time of the change of treatment. Including the second line, the median CD4+ T cell count was 122/mm^3 (48-223) and after 12 months of treatment, the increase in CD4+ count was on average 208 cells/mm^3. When switching to a different antiretroviral treatment, viral load was available in one third of the cases (31.8%) and the median rate was 79 900[17773-21000000] copies/ml. The most commonly used second line protocols were TDF+3TC+LPV/r (35.6%) followed by ABC+DDI+LPV/r (18.5%). Regarding the patients' outcomes, 13 (9.6%) died and the rate of patients lost to follow-up was 23% after a median follow-up time of 3 years (1-4.5). The median duration of second-line follow-up was 4 years (1.5-6).

Conclusion: Upon initiation of the second-line, few patients had clinical failure. However, the change in treatment remains late because the CD4+ rate was low. Treatment progress is satisfactory on average due to the high rate of lost to follow-up patients. Active research of patients should be strengthened in order to improve the second-line patient monitoring.

Keywords: Second line; Antiretroviral; Therapy; Dakar

Introduction

According to projections, the number of people on second-line of antiretroviral treatment (ART) is expected to increase by 2030 to 0.8-4.6 million (6.6-19.6%) in sub-Saharan Africa [1]. Therapeutic non-compliance is one of the main reasons for the emergence of resistant viruses [2,3]. In Africa, several factors influence compliance to antiretroviral treatment: adverse socio-economic conditions, stock-outs, drug toxicities, co-morbidities and stigmatization [4,5]. A sub-optimal compliance level of less than 90% is the cause of therapeutic failure defined in resource-limited countries by "a detectable viral load higher than 1000 copies/ml persistently after at least six months of taking ARV" [6]. Viral load measurement is the gold standard for monitoring the effectiveness of ARV treatment and diagnosing therapeutic failure. However, in resource-limited countries, for a long time the change of treatment was based on the occurrence of opportunistic infections and/or a decrease in the rate of TCD4+ lymphocytes [7-9]. These results in delayed treatment change associated with the accumulation of resistance mutations with cross-resistance to other molecules that may compromise the efficacy of subsequent therapeutic options [2]. In resource-limited countries, WHO recommends in the second line the combination of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a ritonavir potentiated protease inhibitors (PIs) [6]. Several clinical trials have been conducted on the efficacy of second-line antiretroviral therapy [10-12]. However, few observational studies have been conducted on the profile and survival of second-line patients in West Africa. Nevertheless, these data are important in our countries where the therapeutic arsenal remains limited until now. The objectives of this study are to describe the characteristics of patients and to evaluate the outcome of HIV-1 infected patients under second-line ARV treatment.

Methodology

Study framework

Our study was carried out at the Department of Infectious and Tropical Diseases (SMIT) of the National University Hospital Centre (CHNU) of Fann in Dakar. It is the first HIV care facility in Senegal since 1997. The average number of consultations with People living with HIV/AIDS (PLWHA) is 2500 patients per year and 300 patients are hospitalized. Patients are monitored on a quarterly basis. Antiretroviral drugs are provided by a pharmacist. Medical records are computerized, and appointments are managed using software. Immuno-virological screening is provided free of charge at the laboratory within the facility. The control of biological parameters (hemoglobin levels, transaminases, cholesterol, creatinine, blood sugar) is at the patient's expense.

Data collection and statistical analysis

Data were extracted from the databases at the Department of Infectious and Tropical Diseases (SMIT). Patient's medical records and treatment registers were reviewed to complete missing information. We collected data on socio-demographic aspects (age, sex, marital status), clinical characteristics (circumstances surrounding linkage to care, presence of other opportunistic infections, WHO stage of disease (1 to 4), body mass index (BMI), hospitalization), biological values results (hemoglobin, CD4 cell count, HIV viral load), therapeutics aspects (date of start of ART of first line and second line, First-line and second line regimens) and outcomes (patient who are still under follow-up, death, lost to follow up and transfer to another clinical). Categorical variables were described by number and frequency in each class and quantitative variables by mean and standard deviation or median and interquartile interval. Data was entered and analyzed using Epi-info 3.7.1 software. All characteristics of the first and second line antiretroviral therapies have been specified.

Results

A total of 238 patients were on treatment protocols including protease inhibitors. The reasons for non-inclusion were as follow: 48 patients included in clinical trials, 12 cases of HIV2, 48 patients with primary protease inhibitors.

In our study, we included 135 patients. The median time to switch from the first to the second line of antiretroviral treatment was 3 years [2.5-5.5]. It was less than 5 years in 65.9% of cases.

Epidemiological and clinical characteristics

At baseline, the average age was 37.8 ± 10.3 years and more than three-quarters of patients (76%) were between 31 and 55 years of age. The median age was 41.5 years at the time of the second line. There was a female predominance (58.5%) with a sex ratio (F/M) of 1.4. Almost half of the patients were married (48.8%) and 22.4% were widowed. Information on the occupation was available in 103 patients (76.3%). More than a third of the patients worked in the informal sector (38.8%) and 22.4% of the cases were unemployed.

The circumstances for HIV testing were dominated by the management of opportunistic infections (89%). Oral candidiasis (43%) followed by chronic diarrhea (33.3%) and tuberculosis (33.3%) were the most common diseases. At the start of ART, among the 135 patients, 107 (79.3%) were classified as WHO stage 3 and 4 whereas this proportion was 21.5% at the start of the second line. Only one-third (34.2%) of the patients had opportunistic infections at the start of the second line and 12% of the cases had been hospitalized.

At baseline, the average BMI was 18.5 ± 3.9 kg/m^2 and more than half (53.8%) of the patients were undernourished (BMI<18.5 kg/m^2) compared to 37.5% in the second line. Evaluation of the weight difference between the first and second line was available in 82 patients (61.0%). Weight loss was observed in 25 patients (30.5%). It averaged 8.5 ± 8.0 kg.

Immunological and virological aspects

At baseline, the median CD4+ T cell count at J0 was 97/mm^3 [20-167] with outliers of 1 and 381/mm^3. The average hemoglobin level was 9.9 ± 1.9 g/dl. When the second line was included, the median CD4+ T cell count was 122/mm^3 [48-223]. Twelve months after the start of the treatment, the median CD4+ T lymphocytes count increased to 297/mm^3 [172-432]. The increase in CD4+ T lymphocytes averaged 208 cells/mm^3. The average hemoglobin level was 10.4 ± 1.9 g/dl and after one year of treatment with PI, it was 11.7 ± 1.9 g/dl.

At the start of the second line, viral load assay was only available for 43 patients (31.8%). The median viral load rate was 79 900 [17773-21000000] copies/ml. Out of 48 patients, 34 (70.8%) had an undetectable viral load (<50 copies/ml) at one year of second-line treatment.

Therapeutic and evolutionary aspects

The most prescribed first-line protocols were AZT+3TC+EFV (34.1%) followed by AZT+3TC+NVP (26.5%). The three most commonly used second line protocols were: TDF+3TC+LPV/r (35.6%), ABC+DDI+LPV/r (18.5%) and AZT+3TC+LPV/r (14.8%).

Of the 135 patients included, 13 (9.6%) died after a median time to second line of 2 years [1.5-2.5]. The rate of people lost to follow-up was 23% after a median delay of 3 years [1-4.5]. Most patients (56.3%) are still being treated. The median follow-up times were respectively with the 1st line and with the 2nd line of antiretroviral treatment of 10 years (7.0-11.5) and 5 years [3-7].

Discussion

The objective of this study was to assess the characteristics and outcome of patients receiving second-line antiretroviral treatment at a reference centre in Senegal. Analysis of the epidemiological aspects reveals that they are most often young female subjects. The median age at the inclusion of the second line was 41.5 years. Similar results are reported in different studies. Osinusi-Adekanmbi in Nigeria [13] observed a median age of 35 years and in the SECOND-LINE clinical trial [14] it was 38.5 years. We notice that these treatment changes occur in relatively young patients after a relatively short median time (median time: 3 years) after the start of ART.

This leads us to emphasize the importance of strengthening adherence and patient education when initiating the second line because the availability of third line molecules is still limited in most of our countries. Several studies have examined the relationship between socio-economic conditions and adherence to antiretroviral therapy [15-17]. In our study, 38.8% of the patients worked in the informal sector and 22.4% were unemployed. A meta-analysis that

included 28 studies and 8743 people living with HIV found that there was an association between employment and adherence to treatment (OR: 1.27; 1.04-1.55) and this was particularly important in low-income countries (OR: 1.85; 1.58-2.18) [16]. Yet, a more recent systematic review concluded that most studies do not find a link between socio-economic factors (income, education, employment status) and adherence to antiretroviral therapy [17].

The detection of HIV infection at an advanced stage of the disease remains to this day a frequent situation in our countries, particularly in hospitals. Most patients (89%) included were detected following the treatment of opportunistic infections or diseases. However, we found that at the start of the second line, patients were in a better clinical condition. Only 34.2% of the patients had opportunistic infections.

The prevalence of under nutrition was also lower by 37.1% compared to 53.8% at the start of ART. And, weight loss was noticed in 30.5% of patients. All these data support the start of the second line of treatment before clinical failure occurs. However, the results of the immunological assessment show a state of severe immunosuppression in most of our patients at the time of treatment change. Indeed, the median CD4+ T cell count was 122 cells/mm^3 (48-223). This was observed in both observational and clinical studies.

In the multicentre survey published by Médecins sans frontiéres [18] on their experience with the second line of ART T in resource-limited countries, the median CD4+ rate was 99 cells/mm^3. In the «2 LADY» clinical trial, it was 187 cells/mm^3 [10]. Due to reagent stock shortages, only one third (31.8%) of our patients performed a viral load test during the transition to the second line of treatment. The decision to change treatment was based on the occurrence of opportunistic infections or a decrease in CD4+ T cell count.

However, we hope that the situation will improve with the development in recent years of quantitative point-of-care (POC) HIV viral load assay [19]. The use of the Gen-Xpert platform has been validated in several studies and by WHO with a sensitivity of 94% and a specificity of 99% for the detection of virologic failure (>1,000 copies/mL) [20,21].

The median viral load rate of 79,900 copies/ml observed in our series is higher than those reported in clinical trials in resource-limited countries. It varied around 19,000 copies/ml [11,14,22]. High viral load during first-line treatment failure is a strong determinant of second-line effectiveness because it is more often associated with an accumulation of resistance mutations [11].

Therefore, in most clinical trials, efficacy results are stratified on viral load level (<100,000 copies/ml and>100,000 copies/ml). Häggblom et al observed that the median time to onset of second line failure was 3.43 years in patients with detectable viral load compared to 4.53 years in patients without viral failure at change [23]. These results show yet again the importance of an early switch in treatment in the event of treatment failure, but also the importance of close monitoring after the initiation of the second line, especially when the switch was done late, as it was the case for most of our patients (Table 1).

The systematic review published in 2017 by Kanters et al. confirms that the combination of two nucleoside reverse transcriptase inhibitors plus lopinavir/ritonavir remains the second-line protocol of choice [24] and was prescribed in our cohort in 78.8% of patients. However, in addition to atazanir/ritonavir, dolutegravir is one of the alternatives proposed in second line in the last update of WHO's recommendations of antiretroviral regimens [25].

Variables	At baseline	At start of second-line regimen
Sex (n %)		
Male	79 (58,5)	-
Female	56 (41,5)	
Age (years)		
Median [IIQ]	37,5 [27–45]	41,5 [30 – 47]
Mean (SD)	37,8 ± 10,3	41,7 ± 10,4
BMI (kg/m2)		
Median [IIQ]	17,6 []	19,4
Mean (SD)	18,5 ± 3,9	19,8 ± 4,7
Undernourished (BMI <18,5kg/m^2)		
Yes	73 (53,8)	51 (37,8)
No	62 (46,2)	84 (62,2)
Entry of care (n %)		
Treatment of opportunistic infections	120 (89,0)	
Voluntary testing	6 (4,4)	-
Family screening	6 (4,4)	
Pregnancy	3 (2,2)	
Clinical stage (WHO)		
1-2	28 (20,7)	106 (78,5)
3-4	107 (79,8)	29 (21,5)
Hospitalization (n, %)		
Yes	-	16 (12)
No		119 (88)
CD4 count % (/mm^3) (N=106)		
Median [IIQ]	97 [20 – 167]	122 [48 – 223]
M12 (second line)	_	297 [172 –432].
Hemoglobin level(g/dl)		
Mean (SD)	9,9 ± 1,9	10,4 ± 1,9
M12 (second line)		11,7 ± 1,9
Viral load (copies/ml) (N=43)		
Median [IIQ]	_	79 900 [17773 –210000]
M12 (<50 copies/ml) (n,%)		34 (70,8)
Antiretroviral therapy (n,%)		
AZT+ 3TC+ EFV/NVP	82 (60,7)	

TDF+3TC+EFV/NVP	25 (18,9)	
D4T+3TC+EFV/NVP	18 (13,6)	
DDI+3TC+EFV/NVP	9 (6,8)	
TDF+3TC/FTC+LPV/r		61 (45,2)
ABC+DDI+LPV/r		25 (18,5)
AZT+3TC+LPV/r		20 (14,8)
TDF+3TC/FTC+ATV/r		9 (6,7)
Outcomes (n,%)		
Follow up		76 (56,3)
Lost to follow-up		31 (23,0)
Transferred		15 (11,1)
Death		13 (9,6)

Table 1: Demographic, clinical, biological characteristics and outcomes of patients at baseline and at start of second line antiretroviral therapy. HIV Cohort 2008 – 2016, Dakar (Senegal).

As for our second-line patients' outcomes, the lethality (9.6%) and the rate of lost to follow-up patients (23%) observed are higher compared to the data in the literature. A study in Nigeria reported a lethality of 6.8% and a percentage of lost to follow-up patients of 8.2% [13]. In South Africa, Murphy [26] also reported a lethality of 6% and a lost to follow-up patients rate of 9%. In our cohort, we believe that the mortality rate was underestimated given the high percentage (23%) of patients who discontinued their treatment. In fact, in Africa, the lethality of lost to follow-up patients varies between 12% and 87% [27]. High viral load, advanced clinical stage, low CD4 counts and suboptimal adherence to therapy were the factors associated with second-line HIV treatment failure in sub-Saharan Africa in the metanalysis published by Edessa et al. [28].

This work is the first cohort study conducted at the Department of Infectious Diseases of the National University Hospital Centre (CHNU) of Fann on the second line patients of ARV treatment. Despite our very interesting results, our study has limitations in terms of the percentage of missing data, particularly for biological and immuno-virologic parameters, and the size of our sample.

Conclusion

Overall, we observed that changes in treatment occurred late and a high rate of lost to follow-up patients was noticed. In order to remedy this situation, it is necessary to make the viral load measurement available by nationwide implementation of the quantitative point-of-care (POC) HIV viral load assay and an alert system with the social service so as to reduce the rate of treatment interruption. The evaluation of the efficacy, safety and outcome of second-line antiretroviral treatment patients by analysing our different cohorts are necessary to better orient our treatment access policies.

Ethical Considerations

The Head of the Department of Infectious Diseases approved this retrospective study. To preserve patient confidentiality, no personal identifiers were used on the data collection form. All data collected was rendered anonymous prior to analysis.

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