Scientific Research Publishing

Advances in Infectious Diseases, 2019, 9, 226-237
http://www.scirp.org/journal/aid
ISSN Online: 2164-2656
ISSN Print: 2164-2648

Prevalence and Factors Associated with Virologic Failure among People Living with HIV (PLHIV) Monitored in a Decentralized Health Care Facility

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How to cite this paper: Ba, S., Ba, N.D., Sembene, L., Dia, H., Coulibaly, M., Ndiaye, J.L., Dia, N.M. and Ndour, C.T. (2019) Prevalence and Factors Associated with Virologic Failure among People Living with HIV (PLHIV) Monitored in a Decentralized Health Care Facility. *Advances in Infectious Diseases*, **9**, 226-237.
https://doi.org/10.4236/aid.2019.93016

Received: June 17, 2019
Accepted: August 26, 2019
Published: August 29, 2019

Abstract

Introduction: In Senegal, the decentralization of Health Care Centers has contributed significantly to the intensification of antiretroviral treatment. However, Care providers are still facing the treatment optimizing challenge. **Objectives:** To determine the prevalence of virologic failures of PLHIV monitored in a decentralized Health care center and to determine associated factors. **Patients and Methods:** This is a cross-sectional descriptive and analytical study of PLHIV, aged 18 years and over, on first-line treatment, monitored onsite from February 1st to December 31st, 2018. A data collection form was completed from medical records (clinical, immuno-virologic and evolutionary). Any VL > 1000 cp/ml after 6 months of antiretroviral therapy (ART) was considered as virologic failure. Data were captured and analysed using the EPI INFO 2002software. Chi-square test and the Fisher test were used to compare the proportions; a value of $p \leq 0.05$ was considered significant. **Results:** 331 patients were treated with HIV-1 profile in 89% of cases. A proportion of 55% was married and 97% came from rural areas. 80% were either not or poorly educated. The median of age was 44 ± 11 years with a F/M ratio of 3.4. At baseline, 56% were symptomatic at stage 3 or 4 of WHO. They had severe immunosuppression with a median CD4 count of 217 ± 187 cells/mm^3, the viral load was detectable in half of the patients with a median VL of 97,000 cp/ml ± 70,569. The antiretroviral regimen combined 2 NRTIs with 1 NNRTI in 88% of cases. The median of follow-up was estimated at 60

± 43 months. The prevalence of virologic failure was 19%. This prevalence was associated with age less than 25 years (p = 0.04), late diagnosis (CD4 at baseline less than 200 cel/mm^3 (p = 0.002), stage 3 or 4 WHO (p = 0.04) High viral load greater than 10,000 (p = 0.04) at baseline. **Conclusion:** These results suggest making the new therapeutic classes accessible for first-line treatment.

Keywords

ART, Virologic Failure, Associated Factors

1. Introduction

The advent of triple antiretroviral therapy has revolutionized the management of HIV infection by providing lasting suppression of viral replication. This led to a drastic reduction in HIV-related morbidity and mortality, a clear improvement in expectation and quality of life at the individual level, a decrease in the incidence of the disease in regions with good treatment coverage at the community level [1] [2] [3].

There is solid evidence that the increasing improvement of the quality in HIV treatment will save the lives of millions of people, protect them from the risk of infection and save financial resources, in view to eradicate the AIDS epidemic [4] [5].

The Senegalese Antiretroviral Drug Access Initiative (ISAARV) has been initiated since 1998. It followed the various WHO recommendations for antiretroviral treatment (ART). Decentralization, which began in the 2000s, has led to a significant increase in the number of PLHIV on ART. The number of patients under ART increased from 1855 in 2004 to 23202 in 2017 with a proportion of 62% living in rural areas [6] [7]. However, despite all efforts to intensify treatment, practitioners still face some challenges within the management of HIV infection including under-optimization of ART due to the fact that coverage of viral infection is still low on the one hand [7] but also the relatively high prevalence of therapeutic failures [8] [9] [10]. Also, there are few studies on the evaluation of ART in patients treated in a decentralized setting in Senegal [9] [10] [11].

Our study is, therefore, carried out in this context, in one of the largest decentralized health care facilities. The objective of the study was to study the prevalence of virologic failure of first-line antiretroviral therapy for PLHIV treated at the Roi Baudouin public health care center and to determine the associated factors.

2. Patients and Methods

This is a cross-sectional, descriptive and analytical study of PLHIV, treated at the Department of Internal Medicine and Dermatology of Roi Baudouin Hospital located in the outskirts of Dakar. This hospital is one of the first health care facilities dedicated to the treatment of adults infected with HIV within the implementation of the decentralization program. The study focuses on patients

treated onsite from February 1st to December 31st 2018. Subjects included in this study were all aged 18 and over, on first-line ART for more than 6 months and have received at least one viral load after ART monitoring during the period. Patients treated with triple therapy who did not perform any viral load and/or VL is not available were not included.

Virologic failure was defined as any viral load greater than 1000 copies/ml after at least 6 months of ART.

Data were collected using pre-established questionnaires from the medical records and were used to collect the following data: socio-demographic (age, sex, marital status, occupation, source), clinical (HIV profile, Initial Body Mass Index (BMI), WHO stage, gateway to HIV care), para-clinical (CD4 count, viral load (VL), hemoglobulin, creatinine), therapeutic (Antiretroviral regimens), evolutionary (therapeutic failure). All data were captured and analysed using Excel and EPI INFO 2002 software. Descriptive frequency and average statistics techniques were used. Bivariate analysis was performed by comparing the qualitative characteristics of patients regarding the occurrence of virologic failure using the Chi-square test or the exact Fischer test in accordance with their applicability condition. A p-value below 0.05 was considered statistically significant.

For ethical considerations: An anonymous database was created from patients medical and social records. No information was available to identify the patients included in this study. The database remains a property of the Roi Baudouin Health Center. The study was authorized by the Institutional Head.

3. Results

3.1. Epidemiological Aspects

A total of 331 patients data was collected. A clear female predominance was noted with a F/M sex ratio of 3.4. The median of age was 44 ± 11 years. Patients mostly came from the rural area in 97.6% of the cases. More than 3/4 of patients had low levels of education with 50.2% without school education and 30.2% having stopped at the primary school level. 17.2% reached secondary school level 2.4% had a higher education level. More than half (56%) of the targeted population was married. 21.7% were widowed, 15.3% divorced and 7% single. In 36.2% of the cases, patients were unemployed. The proportion of traders was 27.2% and tailors were 14.5% of the cases.

3.2. Clinical and Paraclinical Aspects

89.4% of patients were infected with HIV-1 7% with HIV-2 and 3.6% were co-infected with HIV-1 and HIV-2 dually.

At baseline, 56% of patients were symptomatic, 35% were classified as WHO stage 4 and 21.5% at stage 3. 18.1% were at stage 2 and 25.4% at stage 1. The median body mass index (BMI) at the time of the initial examination was 19.36 ± 4.4 kg/m^2. 43% had a BMI less than 18.5 kg/m^2, 45% of the target had a BMI between 18.5 and 25 kg/m^2. A BMI greater than 25 kg/m^2 was noted in 12% pa-

tients. Opportunistic infections were present in 316 patients. These infections were dominated by digestive disorders in 28% of cases. Cutaneous mucosal diseases followed (25%), Pulmonary diseases were present in 5% of cases.

Immunosuppression was generally severe at baseline with a median CD4 + T cell count of 217 ± 187 cells/mm^3. About half (47%) had a CD4 < 200 cells/mm^3, 28% had a cell count between 200 and 350 cells/mm^3, 13% had a rate between 350 and 500 cells/mm^3, and only 11% had a CD4 count > 500 cell/mm^3.

With regards to biological status, 168 patients benefited from a viral load (VL) assessment at baseline. 44% of the target (165 patients) had a detectable viral load with a median VL of 97,000 ± 70,569 copies/ml of blood. The median of creatinine level was 8 ± 5.6 mg/l. Transaminases and blood glucose had normal values. Slight anemia was noted with a median haemoglobin (Hb) value of 11 g/dl ± 1.9. 71% had anemia with Hb value < 12 g/dl and 7% severe anemia with Hb < 8 g/dl. HBsAg was investigated in 98 patients (30%) and 5% of PLHIV were diagnosed positive (Table 1).

Table 1. Socio-demographic, clinical and paraclinical characteristics of patients at baseline.

VARIABLES	NUMBERS (n = 331)	PERCENTAGE
Gender		
Male	257	77.6%
Female	74	22.4%
Median Age (years) (Standard Deviation: Std Dev)	44 ± 11	
Provenance		
Rural areas	323	97.6%
Urban areas	8	2.4%
Level of Education		
No School education	166	50.2%
Primary level	100	30.2%
Secondary level	57	17.2%
Higher level	8	2.4%
Profile		
HIV-1	296	89.4%
HIV-2	23	7%
HIV-1 and 2	12	3.6%
Median BMI (kg/m^2) (Std Dev)	19.36 ± 4.4	
WHO Stage		
Stage 1	84	25.4%
Stage 2	60	18.1%
Stage 3	116	35%
Stage 4	71	21.5%
Median CD4 (cell/mm^3) (Std Dev)	217 ± 187	
Median VL in cp/ml (n = 165) (Std Dev)	97,000 ± 70,569	
Median Creatinine (mg/l) (Std Dev)	8 ± 5.6	
Median Hemoglobin (g/dl) (Std Dev)	11 ± 1.9	

3.3. Therapeutic Aspects

The antiretroviral regimen combined 2 nucleoside reverse transcriptase inhibitor (NRTI) with 1 no-nucleoside reverse transcriptase inhibitor (NNRTI) in 88% of cases; 36 patients (9%) benefited 2NRTI and 1 protease inhibitor (PI) based regimen. A treatment combining 3 NRTI was instituted in 2 patients. The most represented combinations were AZT/3TC/EFV (113 patients) and TDF/3TC or FTC/EFV (113 patients) followed by AZT/3TC/NVP (51 patients). For HIV-2 infected patients at baseline, only Indinavir was available at the beginning of ISAARV, showing that 9 of the patients had to receive this molecule before being put under LPV/r (Table 2).

3.4. Evolutionary Aspects

The mean duration of follow-up was 60 months ± 43. Compliance was rated as good in 90% of cases. The prevalence of treatment failure was 19% (62 patients). The time to onset of virologic failure was at M12 (Month 12) in 40% of cases, 19% of virologic failures occurred at M24 follow-up and 27% at M36. The virologic failure involved 57 patients with NNRTI and 5 patients with PI. The prevalence of virologic failure was higher in younger patients < 25 years of age (35% versus 18%) $p = 0.04$, but also in those with severe immunosuppression with CD4 < 200 cell/mm^3 (25% versus 13%) $p = 0.002$. Virologic failure was also associated with advanced-stage disease (WHO stage 3 or stage 4) at baseline (30% versus 14%) $p = 0.04$ and high viral load at ART initiation (21% versus 7%) $p = 0.002$. However, the association was not significant between treatment failure and sex ($p = 0.47$) and level of education ($p = 0.48$) (Table 3).

Table 2. Distribution of patients according to the initial therapy.

INITIAL THERAPY	NUMBER	PERCENTAGE
AZT/3TC/EFV	113	34%
AZT/3TC/NVP	54	16%
TDF/3TC/EFV	62	19%
TDF/3TC/NVP	9	3%
TDF/FTC/EFV	51	15%
D4T/3TC/EFV	3	1%
D4T/3TC/NVP	1	0.3%
AZT/3TC/LPVr	21	6%
TDF/3TC/LPVr	5	1.5%
TDF/FTC/LPVr	1	0.3%
AZT/3TC/IND	7	2%
D4T/3TC/IND	2	0.6%
AZT/3TC/ABC	2	0.6%
Total	331	100%

Table 3. Factors associated with virologic failure.

VARIABLES	NUMBER	VIROLOGIC FAILURE n (%)		P value
		Yes	No	
Age				
Age < 25 years	17	6 (35)	11 (65)	0.04
Age ≥ 25 years	314	56 (18)	258 (82)	
Gender				
Female	257	48 (19)	209 (81)	0.47
Male	74	14 (19)	60 (81)	
Education				
Weak	266	50 (19)	216 (81)	0.48
High	65	12 (22)	53 (78)	
Anemia				
Hb < 12 g/dl	225	44 (19)	181 (81)	0.10
Hb ≥ 12 g/dl	89	12 (13)	77 (87)	
WHO				
Stage 1 or 2	144	21 (14)	123 (86)	0.04
Stage 3 or 4	187	41 (30)	146 (70)	
CD4 Count				
CD4 < 200 cel/mm^3	154	39 (25)	115 (75)	0.002
CD4 ≥ 200 cel/mm^3	176	23 (13)	153 (87)	
CV IN				
CV < 10,000	27	02 (07)	25 (93)	0.04
CV ≥ 10,000	141	30 (21)	111 (79)	

4. Discussion

Like the entire international community, Senegal is committed to eliminating the HIV epidemic by 2030 through the 90-90-90 intermediate objectives. Achieving these ambitious goals requires the intensification of antiretroviral therapy. Decentralization of treatment has greatly contributed to the optimization of ART in Senegal. Roi Baudouin Hospital, located in the outskirts of Dakar, is one of the largest decentralized health care facility dedicated to antiretroviral therapy.

Our study is one among the first to suggest the evaluation of the optimization of ART through virological failure in PLHIV monitored in this hospital to determine associated factors. It included 331 patients monitored from February to December 2018.

Epidemiologically, a female predominance was found in our series with a sex ratio of 3.4. This confirms the feminization of the epidemic due to the vulnerability of women in Sub-Saharan Africa [12] [13] [14] [15]. This feminization of HIV infection may be explained by the fact that women are more subject to ex-

tensive screening due to systematic recommendation of HIV testing during pregnancy [16].

The median age in our series was 44; like what was found in Togo [17]; meanwhile, it is much higher than the results found in Burkina Faso [18]. The low level of school education in our series is comparable to the findings in Mozambique [19].

Clinically, our study revealed that most of patients requesting treatment were at an advanced stage of the disease with opportunistic infections. This late recourse to treatment is a common issue within the monitoring of HIV infection in several African countries [20] [21] [22].

At paraclinical level, the low level of CD4 lymphocytes counts also justified the late detection of HIV infection [12] [18] [22].

With regards to treatment, the classic association of 2NRTI and 1NNRTI was the standard in our study in 89% of cases. This choice is consistent with WHO recommendations [23] and is based primarily on cost but also on the need to maintain generic LPV/r stocks for second-line treatment of HIV-1 infection in resource-limited countries.

Virologically, viral load quantification was used to evaluate the antiretroviral response [23] and a virological failure prevalence of 19% was determined. This prevalence was lower than those in the subregion, namely in Togo [17], Burkina Faso [18] and Cameroon [14]. On the other hand, a smaller prevalence has been described in Ethiopia [24], Nigeria [25], South Africa [26] and Uganda [27] with a prevalence of 14.7%, 13.7%, 13.7% and 11.3%, respectively.

In our series, failure was not associated with sex, unlike in Burkina [18], Tanzania [28] and Uganda [29]. This difference in vulnerability could be explained by a pharmacological difference based on sex [30] but also the low hospitalization of men [18].

However, our study has shown an association between virologic failure and young age. This is a confirmation of what was found in several studies [12] [24] [31] [32].

Several factors were associated with failure in adolescents. In addition to poor compliance [10] [24] and long exposure [33], the inadequacy of galenic forms has also been reported [34]. It is, therefore, necessary to strengthen therapeutic education sessions for better adherence of adolescents but also to conduct studies aiming at clarifying the biological causes of high rates of virologic failure in young subjects [12].

Likewise, as described in several studies [18] [19] [24] [35], virologic failure in our series was associated with late monitoring. This suggests a constant advocacy among treatment providers for the early initiation of ART, which have proven to be effective both individually and collectively [4] [5]. This advocacy aims at encouraging screening as initiated by health care providers. If followed carefully, it will help avoid missed opportunities for screening, especially in countries with concentrated epidemics and where screening mainly targets most at-risk groups.

We could not document the mutations of resistance associated with therapeutic failures, like in the study of Dioura [9]. This is a limitation in our study and can be explained by the limited accessibility to these tests only performed in HIV treatment reference centers. Thus, it would be relevant to conduct an epidemiological surveillance of resistance by performing genotyping tests to justify the choice of effective molecules for the treatment of HIV infection. However, special attention should be paid to our study. In fact, the sub-optimal therapeutic response addressed in our study with a high prevalence of virologic failure is an appeal to urgently make available new high-barrier therapeutic classes namely integrase inhibitors to improve the quality of first-line ART in HIV-infected patients. Moreover, the efficacy of integrase inhibitors as first-line treatment compared to NRTI and PI has been described in several studies [36] [37] [38] [39]. This led to the recommendations formulated by WHO and UNAIDS to support the use of Dolutegravir-based protocols as first-line treatment in HIV-infected patients [40] [41]. Applying these new recommendations in Senegal could help optimize ART and monitor treatment failures effectively [42].

5. Conclusion

Our study is one among the first conducted in a decentralized setting. It showed a virological failure prevalence of 19%. This prevalence was associated with young age, but also with late diagnosis. The results of our study suggest making available the genotyping tests in decentralized setting to better adapt the second-line therapeutic choices. Thus, it is urgent to make the integrase inhibitors with a strong genetic barrier available in Senegal to improve the quality of HIV infection monitoring. Implementing these measures is crucial for achieving the UNAIDS 90-90-90 goals.

Acknowledgements

Thanks to Mr. Jean Nguessan for the English translation of the article.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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