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Factors Associated with Adverse Therapeutic Outcomes in People Living with HIV (PLHIV) Monitored in Roi Baudouin Health Care Center, Dakar, Senegal

Selly Ba[1,2*], Ndeye Diama Ba[3], Lamanatou Sembene[3], Thierno Souleymane Baal Anne[2], Habibatou Dia[3], Jean Louis Ndiaye[1], Ndeye Mery Dia Badiane[4], Cheikh Tidiane Ndour[5]

[1]Doctoral School of Thies University, Thies, Senegal
[2]Intrahealth International, Dakar, Senegal
[3]Roi Baudouin Hospital, Dakar, Senegal
[4]Department of Health, Gaston Berger University, Saint Louis, Senegal
[5]AIDS Department/Ministry of Health, Dakar, Senegal
Email: *sellyba2003@yahoo.fr

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Abstract

Background: Optimizing antiretroviral therapy is an essential step to reach the 90 - 90 - 90 targets. Despite tremendous progress made for antiretroviral treatment (ART) to be accessible in countries with limited resources, health care providers continue to face challenges due to the under-optimization of ART due to therapeutic failures and poor retention. **Objectives:** To determine the prevalence of adverse therapeutic outcomes in a decentralized health care center and to determine associated factors. **Patients and Methods:** This is a cross-sectional descriptive and analytical study targeting PLHIV, aged 18 years and over, on first line antiretroviral treatment (ART), monitored onsite from February 1st to December 31st, 2018. A data collection form was completed from medical records (clinical, immuno-virological, therapeutic and evolutionary). Data were also collected from interviews with patients for additional socio-demographic information including the level of HIV knowledge. Data were captured and analyzed using EPI 2002 and R software. Proportions were compared using the chi -square and Fisher tests and logistic regression. A value of $p < 0.05$ was considered significant. **Results**: 331 patients were enrolled with HIV-1 profile in 89% of the cases. A proportion of 55% was married and 98% came from the rural area. 80% were either not or poorly educated. The median of age was 44 ± 11 years with a F/M ratio of 3.5. 30% that had not shared their HIV status, and more than half had a low knowledge of HIV transmission. At baseline, 56% were symp-

tomatic at WHO stage 3 or 4. 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 viral load (VL) of 97,000 ± 70,569 cp/ml. The antiretroviral regimens combined 2 nucleoside reverse transcriptase inhibitor (NRTI) with 1 no nucleoside reverse transcriptase inhibitor (NNRTI) in 88% of the cases. The median duration of follow-up was estimated at 60 ± 43 months. The prevalence of adverse therapeutic outcomes was 36% (119 patients). The proportion of virological failure was 19%, lost follow up was 20% and the mortality was 4%. The adverse therapeutic outcomes were associated with the age less than 25 years (p = 0.007) and with a late diagnosis (CD4 T cells at baseline less than 200 cell/mm^3, p = 0.02). **Conclusion**: These results suggest the need to make new therapeutic classes available for first-line treatment and to promote actions improving retention in care.

Keywords

Antiretroviral Treatment, Adverse Therapeutic Outcomes, Associated Factors

1. Introduction

Thirty-seven (37.9 million) people live with HIV/AIDS worldwide, according to the estimates of the United Nations Programme on HIV/AIDS (UNAIDS) in 2018 [1]. The great majority of HIV-infected patients live in resource-poor countries. Sub-Saharan Africa is paying a heavy burden with 25.6 million people infected, more than two-thirds (69.4%) of cases. The advent of antiretroviral treatment (ART) has revolutionized the management of HIV infection by enabling lasting suppression of viral replication. This led to a drastic reduction in HIV-related morbidity and mortality, a significant improvement in life expectancy and quality of life at individual level, a reduction in the incidence of the disease in regions with good treatment coverage at community level [1] [2] [3].

There is compelling evidence that scaling up the quality of HIV treatment will quickly save the lives of millions of people, protect them from the risk of infection and save financial resources in view to eradicate the HIV/AIDS epidemic [4] [5] [6]. Thus, these scientific evidences have greatly influenced the WHO guidelines regarding the introduction of antiretroviral treatment (ART). These guidelines have evolved significantly from 2006 to 2015 and have certainly motivated the WHO (World Health Organisation) recommendations of 2015, which suggest the test and treat of all PLHIV, regardless of their level of CD4 count [7]. These new recommendations are in line with the ambitious objectives of the UNAIDS aiming at eliminating the epidemic of HIV AIDS by 2030 through 90 - 90 - 90 intermediate objectives. These objectives ambition to get 90% of people living with HIV to be screened, 90% of them on ART, and finally to make the viral load undetectable in 90% of PLHIV under treatment [8] [9].

Senegal adopted this new approach in 2016 under the TATARSEN concept "Test All, Treat All and Retain" [10]. In Senegal, the Senegalese initiative for

access to antiretrovirals ARV (ISAARV) has been initiated since 1998. It followed the various WHO recommendations for antiretroviral therapy. Decentralization, which started in the 2000s, has led to a significant increase in the number of PLHIV on ART. The number of patients on ART has increased from 1.855 in 2004 to 23.202 in 2017 and 62% lived in rural areas [10] [11]. However, despite all efforts to scale up treatment, health care practitioners still face some challenges within the management of HIV infection, including under-optimization of ART.

This under-optimization of antiretroviral treatment is due in mainly to the high prevalence of treatment failures despite the variety of antiretrovirals (ARVs) on the market [12] [13], but also to the low retention of treatment due to exit of PLHIV from the regular monitoring circuits [14].

Our study is therefore carried out in this context in one of the biggest decentralized health care facility. Its purpose was to study the prevalence of adverse therapeutic outcomes in PLHIV monitored at Roi Baudouin Health care center and to determine associated factors.

2. Patients and Methods

Our study was conducted at the Unit of Internal Medicine and Dermatology of Roi Baudoin health care center based in the outskirts of Dakar. This hospital is one of the first health care facilities dedicated to the treatment of adults infected with HIV in the context of decentralization. This is a cross-sectional and analytical study on PLHIV monitored onsite during from February 1st to December 31st, 2018. Subjects included in the study were aged 18 years and over, on first line ART for more than 6 months, having received at least one viral load after starting ART and followed during that period. Patients treated with triple therapy who did not perform any viral load (VL) and/or VL unavailable were not included.

Operational definitions:

Virological failure has been defined as any viral load greater than 1000 copies/ml after at least 6 months of treatment.

Antiretroviral therapy attrition is the proportion of patients under treatment and not transferred who died or were lost follow-up at 12, 24 or 36 months.

Patients lost follow-up LFUP: Any patient who has not shown up to the health care center to collect their ARVs for three months after the last appointment and from whom the health center has no news.

Adverse therapeutic outcomes were defined as the proportion of patients put on treatment who are either in virological failure or in attrition.

Data were collected using pre-established questionnaires filled out from medical records and from interview with patients for additional information.

Lost to follow up and deceased patients were identified from the Excel file and medical records. The Lost to follow up were sought by telephone reminder.

Those who were found were subjected to the same interview form after obtention of their informed consent. The data collected related to the socio-demographic status (age, sex, marital status, profession, provenance), clinical data (HIV profile, initial Body Mass Index (BMI), Initial WHO stage, gateway to HIV care), para-clinical data (CD4 count, viral load, Hemoglobin, creatinine), therapeutic data (ART regimens), evolutionary data (virological failure, LFUP, death, success). All data were entered and analyzed using Excel, EPI INFO 2002 and R software. Descriptive statistics of frequency and average were used. Bivariate analysis was used by comparing the qualitative characteristics of the patients regarding the occurrence of adverse therapeutic events (virological failure or attrition) using the Chi-square test or the exact Fischer test in accordance with their applicability condition.

The influence of the independent variables on dependent variables (Treatment outcome) was assessed using a multivariate logistic regression analysis.

All variables with $p \leq 0.25$ were retained in the initial multivariate model. The other models were designed using the step-by-step approach, gradually removing the variables that do not provide enough information to the model.

The robustness (adequacy) of the final model was assessed using the test by Hosmer and Lemeshow. The final model was selected using the Akaike Information Criteria (AIC), which is a Parsimony Index. A value of $p < 0.05$ was considered significant in the final model.

For ethical considerations: An anonymous database was established from the medical and social records of patients. No information was available to identify the patients included in this study. For the interview with patient, the informed and express consent of the patients was sought. The database remains the property of Roi Baudoin Health care center. The study was authorized by the director and by the medical committee of the health care center.

3. Results

Socio demographic aspects

A total of 331 patients data were collected. A clear female predominance was noted with a F/M sex ratio of 3.5. The median age was 44 ± 11 years. They came from the rural area in 98% of cases. Almost a third (28.5%) had not shared HIV status. More than three-quarters of the patients were poorly educated with 50% without school education and 30% who stopped at primary school level, 17% reached secondary education level and 2% had a higher education level. The level of HIV knowledge was low, 35% of the target did not know the means of protection against HIV infection, 57.3% had a low knowledge of the means of HIV transmission. The mother-to-child transmission was the least known, unknown by 65% of the target. More than Half of the target was married, the widowed represented 22%, the divorced were 15% and 7% were single. 42% of cases were unemployed. Traders represented 31% of cases and tailors were 17% of cases (**Table 1**).

Table 1. Epidemiological characteristics of patients.

VARIABLES	NUMBERS (n = 331)	PERCENTAGE
Gender		
Female	257	89%
Male	74	11%
Median Age (years) (Standard Deviation: Std Dev)	44 ± 11	
Shared status (n = 274)		
Yes	196	71.5%
No	78	28.5%
Level of knowledge HIV modes of transmission (n = 274)		
Good	117	42.7%
Poor	157	57.3%
Level of knowledge HIV modes of transmission (n = 274)		
Good	178	65%
Poor	96	35%
Level of knowledge HIV mother to child transmission (MTCT) (n = 274)		
Good	96	35%
Poor	178	65%
Provenance		
Rural area	323	97.6%
Urban area	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%
Marital status		
Single	23	7%
Married	185	56%
Divorced	51	15%
Widowed	72	22%
Profession (n = 288)		
No profession	120	42%
Traders	90	31%
Tailors	48	17%
Others	30	10%

Clinical aspects

89.4% of patients were infected with HIV-1, 7% with HIV-2 and 3.6% with HIV-1 and HIV-2 dually. At baseline, 56% of patients were symptomatic, classified in WHO stage 4 (35%), stage 3 (21.5%). 18% were in stage 2 and 25% in 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% of the patients. Opportunistic infections were present in 316 patients. These infections were dominated by digestive disorders in 28% of the cases, cutaneous-mucosal affections in 25%, pulmonary diseases were present in 5% of cases.

Paraclinical aspects

Immunosuppression was generally severe at baseline with a median T cell CD4 count of 217 ± 187 cells/mm^3. About half (47%) had a CD4 count < 200 cells/mm^3, 28% had a count between 200 and 350 cells/mm^3, 13% had a rate between 350 and 500 and only 12% had CD4 count > 500 cells/mm^3.

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

Therapeutic aspects

The antiretroviral regimen combined 2 nucleoside reverse transcriptase inhibitor (NRTI) with 1 no nucleoside reverse transcriptase inhibitor (NNRTI) in 88% of the cases, 37 patients (11%) benefited 2NRTI and 1 protease inhibitor PI based regimen. A treatment combining 3 NRTI was instituted in 2 patients (Table 2).

Evolutionary aspects

The median duration of follow-up was 60 ± 43 months. Compliance was judged satisfactory in 90% of the cases. During the study period, the treatment outcome was not favorable in 34% of the target. This unfavorable development was a type of virological failure (36%) and attrition to care (24%). The time for virological failure to occur was Month 12 in 40% of cases, 19% of virological failures occurred at Month 24 follow-up and 27% at Month 36 follow-up. Non-retention was 20.5% LFUP and 4.2% death. The time for onset of lost to follow up was at Month 12 (21.5%), Month 24 (21.5%) and Month 36 (15%); the mortality was 4.2% including 2 Deaths at Month 12 and 3Deaths at Month 24. The search for patients lost to follow up made it possible to find 25 patients out of 68 (36%). The reasons evoked by these found patients lost to follow up were financial difficulties (36%) travel (36%), clinical improvement (20%).

Table 2. Clinical, paraclinical and therapeutical characteristics of patients.

VARIABLES	NUMBERS (n = 331)	PERCENTAGE
Profile		
HIV 1	*296*	89.4%
HIV 2	*23*	7%
HIV 1 and 2	12	3.6%
Median BMI (kg/m²) (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/mm³) (Std Dev)	217 ± 187	
CD4		
<200	155	47%
200 - 349	93	28%
350 - 499	43	13%
>500	40	12%
Median VL in cp/ml (n = 165) (Std Dev)	97.000 ± 70.759	
Median Creatinine (mg/l) (Std Dev)	8 ± 5.6	
Antigenemia HBS (n = 98)		
Positive	05	5%
Negative	93	95%
Median Hemoglobin (g/dl) (Std Dev)	11 ± 1.9	
Therapeutic protocols		
2NRTI/1NNRTI	292	88%
2NRTI/1PI	37	11%
3NRTI	2	1%

Factors associated with adverse therapeutic outcomes

In bivariate analysis, the generally unfavorable therapeutic outcome was greater in the young subject under 25 years (64% versus 34%) p = 0.007, but also in those who had a severe immunosuppression with a CD4 count < 200 cell/mm^3 (41% versus 30%) p = 0.02, low financial income (monthly income below 100.000 CFA francs) (31% versus 21%) p = 0.05, male sex (43% versus 34%) p = 0.07, the low level of knowledge on mother-to-child transmission (MTCT) (33% versus 18%) p = 0.01.

In the final logistic regression model, only the three variables age, T cells CD4 and level of knowledge of MTCT were retained, the results of the final model showed that age less than 25 years (p = 0.01) and severe immunosuppression (p = 0.006) were significantly associated with the adverse outcome (Table 3).

Table 3. Factors associated with adverse therapeutic outcomes.

VARIABLES	Bivariate model				Multivariate model			
	OR	IC95%		P value	OR	IC 95%		P value
Age < 25 years	3.49	1.25	9.71	0.007	4.11	1.33	3.36	0.01
Gender: Male	1.49	0.88	2.56	0.07				
Low financial income < 100,000 per month	1.81	0.86	3.81	0.05				
Low level of MTCT knowledge	2.1	1.10	4.33	0.01	1.712	0.908	3.35	0.10
CD4 COUNT < 200 cells/mm^3	1.61	1.02	2.52	0.02	2.25	1.26	4.07	0.006

4. Discussion

Scaling up antiretroviral therapy is essential to achieving the elimination goals of HIV. In Senegal, the implementation of decentralized Health care center for PLHIV has resulted in a significant increase in the number of patients on antiretroviral therapy [11]. However, there is still the challenge of optimizing antiretroviral therapy with high prevalence of treatment failure and also attrition on ARVs. Within that framework, research into the determinants of therapeutic outcomes (leaving the treatment circuit and therapeutic failures in patients on ARVs) is nowadays crucial in order to inform programmatic decisions and to help healthcare providers in targeting interventions.

Our study is one of the first carried out in the era of TATARSEN [10], which aims to assess the determinants of adverse therapeutic outcomes in PLHIV followed at Roi Baudouin Health care center. The study targeted 331 patients followed from February to December 2018, under first-line antiretroviral treatment. In our series, virological failure was defined as any VL greater than 1000 cp/ml. This definition is in accordance with WHO recommendations in countries with limited resources unlike the standards of Northern countries where virological failure is fixed on a VL threshold <50 copies/ml. [15]. Thus, special attention in addition to strengthening therapeutic education must be paid to patients who replicate between 50 and 1000 copies to minimize the occurrence of mutations. This is even more true since a lot of scientific evidence has shown in so-called controlled patients with persistent viral replication, a higher risk of occurrence of therapeutic failure [16] [17] [18] [19]. Virological failure in our series was 19%. This prevalence is like the one described by Boender (20) in countries with limited resources, and lower than those described in the sub-region precisely in Togo [21] and Burkina-Faso [22].

This high prevalence of virological failure in first-line treatment suggests the need to make new treatment classes, namely integrase inhibitors, available to improve the quality of first-line treatment for patients infected with HIV. WHO recommendations [23] suggesting the use of protocols based on Dolutegravir as first-line treatment of the patient infected with HIV are applied in Senegal. This recommendation could help within the optimization of the ART but also the monitoring of therapeutic failures [24].

In addition to therapeutic failure, optimization of ART is hampered by attrition to ARVs. In our series, the prevalence of attrition (death or Lost to follow up) was 24%. The mortality was 4%, comparable on those described in several African countries [25] [26]. This lethality is partly due to the delay in diagnosis which constitutes a problem of the monitoring of the HIV infection in developing countries. Attrition was dominated by a high prevalence of lost to follow up (20%). This prevalence is comparable on those described in India [27], higher than those described in Burkina Faso [28] and South Africa [29].

As described in several studies [30] [31] [32], the main reasons for leaving the treatment circuit, as mentioned by the patients lost to follow up found in our series were travel, geographic accessibility, financial difficulties [30]. Other reasons such as stigma and structural constraints, namely long waiting times, were mentioned in certain studies [32] [33] [34] [35]. These findings therefore suggest the need to develop an economic support program for poor PLHIV in addition to strengthening the social support package. There is also a need to increase decentralized Health care centers to better retain patients in care and to scale up care differentiation to avoid structural causes such as waiting times [30] [33].

In general, the adverse event related to treatment was associated in our series with severe immunosuppression testifying the late diagnosis of HIV infection. This late recourse to care constitutes a monitoring issue with regards to HIV infection in several African countries [36] [37]. This therefore suggests constant advocacy with patients monitoring stakeholders for the early initiation of ART, which have proven to be beneficial at both individual and collective levels [4] [5].

The adverse events relating to treatment was associated with young age in our series. This association corroborates what has been described in several studies [38] [39]. The reasons which are mostly mentioned in the non-optimization of ART in the young subject are the low compliance [40], the long duration of exposure [41], the inadequacy of dosage [42]. Thus, it is necessary to reinforce therapeutic education sessions for better adhesion of adolescents but also to conduct mainly qualitative studies aimed at clarifying the factors of treatment adverse events in young people.

Our study includes some limitations, namely the non-documentation of resistance mutations associated with therapeutic failure. This is due to the limited accessibility of genotyping which is done only in reference laboratories. The prevalence of patients lost to follow up may be overestimated since some of them may have died or may be followed at other health centers. However, despite these limitations, we believe that the results of our study provide an important insight into the factors associated with the adverse therapeutic outcomes (virological failure or attrition) and could inform programmatic decisions aimed at promoting the optimization of ART.

5. Conclusion

Our study evaluated the determinants of adverse therapeutic outcomes treat-

ment in a decentralized health care center. Our results show that the adverse therapeutic outcomes are associated with late diagnosis of HIV infection and with young age. Our study reveals that integrase inhibitors with a strong genetic barrier must urgently be made available in Senegal to optimize antiretroviral treatment, but also to develop programmatic strategies to promote early diagnosis and ART initiation and PLHIV retention in care, which are important pledges to reach the 90 - 90 - 90 targets.

Conflicts of Interest

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

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