First Antiretroviral Therapy Changes in People Living with HIV in Senegal: Incidence, Causes and Predictive Factors

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Abstract

Introduction: In resource-limited countries, the number of available antiretroviral (ARV) drugs is relatively limited. Hence, caregivers face some caution and constraints in the changes of ARV treatment (ART) in people living with HIV (PLHIV). Our objective was to calculate the incidence, to describe the main causes and to identify the predictive factors of the first change of ARV treatment in Senegal.

Methods: We conducted a retrospective cohort study on 331 HIV infected patients who initiated ART in 2009-2011 and followed until March 2012. The incidence was estimated using Kaplan-Meier method. The causes have been grouped into five categories. The identification of predictive factors was done using a Cox proportional hazards model.

Results: At inclusion, mean age, IMC and CD4 cell count were 41 years (interquartile range (IQR)=35-48), 18 kg/m² (IQR=15.6-21.5) and 92 cells/μl (IQR=31-200), respectively.

After an average ART duration of 11.4 months, 65 patients had experienced at least one treatment change resulting in an overall incidence rate of 10.5/100 person-years (95% CI=8.4-12.6). ARVs drug intolerance was the main cause of change in treatment (41/65) followed by therapeutic failures (5 cases) and pregnancy (three cases). The independent predictors of first ART treatment change were female sex (hazard ratio (HR)=1.85; IC 95%=1.07-3.19), underweight (HR=2.20, IC 95%=1.24-3.88) and HIV-1 or HIV-dual infection (HR=3.57, IC 95%=1.11-11.46).

Conclusion: In this cohort, the incidence of the first ART treatment change was low. It was more frequent in women, underweight patients and HIV-1 infected patients. The main cause was ARV intolerance. A better pre-therapeutic evaluation, the availability of ARVs compatible with pregnancy and anti-tuberculosis treatment appear to be relevant in this population.

Keywords: HIV; Anti-retroviral therapy; Substitution treatment

Introduction

In December 2016, 19.5 million people were receiving antiretroviral therapy (ART) worldwide [1]: an unprecedented number that resulted from increasing access to ART in resource-limited countries (RLC).

Despite these advances, HIV is still managed at two speeds: at least 25 ARV drugs from six therapeutic classes have been approved and are available in rich countries while poor countries have to cope with essentially a dozen of ARV drugs of the first three therapeutic classes.

More specifically, in Senegal, the number of people living with HIV (PLHIV) on ART was 18375 in December 2015 [2]. It was 13716 in December 2016 [3] and eleven ARVs were available there at that time. These were seven nucleoside reverse transcriptase inhibitors (NRTIs): Zidovudine (AZT), Lamivudine (3TC), Emtricitabine (FTC), Didanosine (ddI), Tenofovir (TDF), Abacavir (ABC); Stavudine (d4T); two non-nucleoside reverse transcriptase inhibitors (NNRTIs): Nevirapine (NVP), Efavirenz (EFV) and two protease inhibitors (PI): ritonavir-boosted Lopinavir (LTV/r) and ritonavir-boosted Atazanavir (ATV/r). First-line therapeutic combinations where in accordance with 2013 WHO guidelines [4]. Fixed dose combinations were preferred. Those available were: AZT+3TC, TDF+3TC, TDF+FTC, TDF+FTC+EFV. This limited number of ARVs imposed constraints on the initiation of ART and especially on the management of ART changes in PLHIV. The objective of this study was to assess the overall incidence of the first ART change in this population and their causes; as well as the predictive factors for the first ART change.

Methods

We conducted a retrospective cohort study on the population of PLHIV followed at the Department of Infectious Diseases/Regional Research and Training Center on HIV and Associated Diseases, Fann’s University Hospital Center, Dakar, Senegal(SMIT/CRCF). This study included PLHIV who had started ART between January 1, 2009 and December 31, 2011. The first-line ART eligibility criteria were consistent with the 2010 WHO recommendations for ART initiation [5]. After ART initiation, follow-up visits were carried out at D15, M1, M2, M3, M6, M12 and M18 thereafter.

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Received July 05, 2017; Accepted July 11, 2017; Published July 18, 2017

Citation: Diouf A, Youbong Tj, Dieye Fl, Ciss Vmp, Cisse-Diallo Vmp, et al. (2017) First Antiretroviral Therapy Changes in People Living with HIV in Senegal: Incidence, Causes and Predictive Factors. J AIDS Clin Res 8: 709. doi: 10.4172/2155-6113.1000709

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M6 and then every three months. Routine clinical and biological data (age, sex, occupation, marital status, weight, height, clinical stage, HIV serotype, cell blood count, transaminases, serum creatinine, CD4 cell count, plasma viral load) were collected from the medical records of the PLHIV. Data on changes in ART and their causes were collected from medical records and prescriptions classified at the pharmacy.

The data were entered on an Excel database and analyzed using the Stata software version 14. The event of interest was the first change in ART regardless its cause and the random variable studied was the exposure time to the first ART that was defined as the period between the initiation of the first line ART and the date of the first ART change (for any reason) for patients who had a change in treatment prior to March 16, 2012. For patients who didn’t experience an ART change, the data were censored at the date of death or date of last visit. The incidence was estimated using the Kaplan-Meier method. The causes of the first ART changes were grouped into different categories: intolerance, therapeutic failure, ARV stock out, intercurrent disease, desire for pregnancy or ongoing pregnancy. For each category, the overall incidence was measured; as well as the incidence during the first semester of ART and beyond. The identification of predictive factors of change in treatment (any cause) was performed using a Cox proportional hazard model with fixed co-variables: age, body mass index (BMI), WHO clinical stage, HIV serotype, hemoglobin level, CD4 cell count, transaminases, creatinine.

**Results**

**Study population**

At ART initiation, the patients’ ages ranged from 16 years to 70 years old (median=41 years). The majority of these patients (61%, 95% CI=55.6-66.2) were female. An important proportion was infected with HIV-1 (283=85.5%; 95% CI=81.2-88.9). Thirty-four were infected with HIV-2 (34=10.3%, 95% CI=7.3-14.0), while fourteen (4.2%; 95% CI=7.3-14.0) were dually-infected with HIV-1 and HIV-2 (HIV-D). Almost 80% of these patients had advanced or severe symptoms, including 39.7% (95% CI=34.2-45.4) at WHO stage 4. More than half of the patients had a BMI=18.5 kg/m$^2$ and 34.8% (95% CI=29.7-40.3) had less than 50 CD4/µl (Table 1). The delay between the knowledge of HIV positive status and the first visit in the clinic was specified in 218 patients, ranging from 0 to 2050 days with an average of 38 days (standard deviation (SD)=148) The average time between the first visit and ART initiation was 31 days (SD=163).

The different first line ART regimens are presented in Table 2. Five patients were receiving 3 NRTIs while two other patients (one infected with HIV-2 and one dually infected) were receiving two NRTIs and one NNRTI; although HIV-2 is naturally resistant to NNRTIs.

At the endpoint date, the average follow-up duration was 11.4 months (SD=10.8 months). A total of 226 (68.7%) patients were still being followed, 23 (7%) were transferred, 37 (11.2%) were reported lost to follow-up and 43 (13.1%) were deceased.

**Overall incidence of first ART change**

After an average duration of ART of 11.4 months, 65 patients had at least one change in treatment: 19.6% of the population (95% CI=15.4-23.9). During the 38 months follow-up, the overall incidence rate was 10.5/100 PY (95% CI=8.4-12.6). The incidence rate decreased with follow-up duration. It was 30/100 PY during the first semester (95% CI=21.4-38.6) and 8.7/100 PY beyond (95% CI=5.7-11.6); P<0.001. In the first year and the second year of follow-up, incidence rates were 22.1/100 PY (95% CI=16.8-27.3) and 10.9/100 PY (95% CI=4.6-17.2), respectively.

The cumulative incidence was 22.8% after one year of treatment (95% CI=18.2-27.3), 34.8% after two years (95% CI=29.7-39.9) and 38.7% after three years (95% CI=33.5-44.0). The increase was more significant during the first months of follow-up (Figure 1).

**Causes of ART changes**

In the population studied and during the follow-up period, 65 incident changes in ART were observed. The majority (41) was attributed to intolerance to ARVs, 32 of which occurred during the first

| Characteristics | N     | Median (IQR) or % |
|-----------------|-------|------------------|
| Age (years)     | 329   | 41 (35-48)       |
| <45             | 208   | 63.2             |
| Sex             | 331   |                  |
| Male            | 129   | 39.0             |
| BMI (kg/m$^2$)  | 238   | 18 (15.6-21.5)   |
| <18.5           | 126   | 52.9             |
| 18.5 ≤ IMC<25   | 86    | 36.1             |
| ≥ 25            | 26    | 10.9             |
| HIV serotype    | 331   |                  |
| HIV-1           | 283   | 85.5             |
| HIV-2           | 34    | 10.3             |
| HIV-Dual        | 14    | 4.2              |
| WHO clinical stage | 295  |                |
| Stage 1 or 2    | 63    | 21.4             |
| Stage 3 or 4    | 232   | 78.6             |
| Haemoglobin level (g/dL) | 299 | 10 (8.2-11.4) |
| ≤ 11            | 210   | 70.2             |
| Creatinin level (mg/L) | 269 | 9.1 (7-11)      |
| >15             | 15    | 5.6              |
| ALAT (IU/L)     | 272   | 24 (16-39)       |
| >100            | 7     | 2.6              |
| CD4 cell count (cells/µL) | 313 | 92 (31-200)    |
| <200            | 234   | 74.8             |

*Interquartile range

| Characteristics | N    |
|-----------------|------|
| HIV serotype    |      |
| HIV-1           | 178  |
| HIV-2           | 42   |
| HIV-Dual        | 102  |
| N               | 322  |
| %               | 100  |

| ART regimens       | HIV-1 | HIV-2 | HIV-Dual |
|--------------------|-------|-------|----------|
| AZT+TDC+EFV        | 111   | 1     | 1        |
| AZT+TDC+NVP        | 53    | 0     | 0        |
| TDF+TDC+EFV        | 77    | 0     | 0        |
| TDF+TDC+NVP        | 26    | 0     | 0        |
| D4T+TDC+EFV        | 5     | 0     | 0        |
| D4T+TDC+NVP        | 7     | 0     | 0        |
| AZT+TDC+LPV/r      | 2     | 23    | 9        |
| TDF+TDC+LPV/r      | 0     | 7     | 1        |
| D4T+TDC+LPV/r      | 0     | 2     | 0        |
| AZT+TDC+ABC        | 0     | 1     | 2        |
| AZT+TDC+TDF        | 1     | 0     | 0        |
| TDF+TDC+ABC        | 0     | 0     | 1        |
| ABC+TDC+EFV        | 1     | 0     | 0        |
| Total              | 283   | 34    | 14       |

*3TC or FTC

| Characteristics | N     |
|-----------------|------|
| HIV-1           | 178  |
| HIV-2           | 42   |
| HIV-Dual        | 102  |
| %               | 100  |
semester and 9 after six months of follow-up. Five incident changes were attributed to therapeutic failures and they were all recorded after the first semester of follow-up. Only one change by ARV stock out was notified after six months. The other most frequent causes were the discovery of an ongoing pregnancy or the desire for pregnancy (three cases), the initiation of an anti-tuberculosis treatment (two cases) and the discovery of a positive HBs antigen (two cases). The most frequently discontinued ARV drugs were AZT, d4T, NVP and EFV.

The incidence of changes in treatment by ARV intolerance was 24.4/100 PY (95% CI=16.5-32.3) during the first semester of follow-up and 3.5/100 PY (95% CI=1.3-5.7) after the first semester; p<0.05. Changes related to therapeutic failure did not occur during the first semester and the incidence was 2.3/100 PY after six months of treatment (95% CI=0.3-4.2).

Predictive factors of the first ART change

The Cox regression models are presented in Table 3.

In univariable analysis and, at a 20% significance level, the risk of change in treatment was higher in women, HIV-1 and HIV-D infected patients (versus HIV-2), underweight patients, those with a low CD4 cell count (<200/μl) and those with a low hemoglobin level (<11 g/dl).

After adjustment on eventual confounders, the independent predictors of the first ART change were female sex, underweight, HIV-1 and HIV-D infection. Female patients had a risk of ART change nearly twice higher than that of male patients (HR=1.85, 95%CI=1.07-3.19). Underweight patients were more than twice at risk for ART change than those with a BMI ≥ 18.5 kg/m² (HR=2.20, 95%CI=1.24-3.88). Compared with HIV-2 infected patients, HIV-1 and HIV-D-infected patients were at much greater risk of ART change (HR=3.57, 95%CI=1.11-11.46).

Discussion

After 38 months of follow-up, the overall incidence of ART change was 10.5/100 P-Y. These changes were mainly attributed to poor tolerance of ARVs, therapeutic failures, desire of or ongoing pregnancy, initiation of anti-tuberculosis treatment, discovery of a positive HBs antigen or, more rarely, ARV stock out. Independent risk factors for the first ART change in this population were female sex, underweight, HIV-1 and HIV-D infections (comparing HIV-2 infection).

Our study took place at the SMIT/CRCF, which is a reference center that is supposed to ensure quality monitoring of PLHIV with good record keeping. It looked at the occurrence of changes in ART. The advantage of a longitudinal study is that it is possible to identify risk factors or predictive factors that underlie these changes after ARV initiation. The data of our study were collected through two sources: medical records were confronted with prescriptions in order to have comprehensive data on treatment changes in our cohort.

Our study was retrospective and, as a result, it has limitations on accessibility and completeness of medical records: therefore, important co-variables such as adherence, preparation of patients for ART were not included in our analysis. Neither was the viral load included, as this variable was only available for a very small proportion of patients at inclusion. The duration of follow-up was relatively short and the number of events low after the first semester.

The characteristics of our cohort (advanced age, low BMI, advanced clinical stage and low CD4 cell count) suggest a deep immunosuppression. Similar characteristics were observed in most of the cohorts studied in the RLC [6,7].

The incidence rates previously reported in West Africa are higher than those observed in our cohort. In Côte d’Ivoire, an overall treatment change incidence of 20.7/100 PY has been reported for a median duration of 16.9 months [8]. In Mali, the incidence rate of ART changes was 16.2/100 PY for a median duration of 15 months [9]. Similarly, a study in Kenya, found an incidence of 18.6/100 PY for a median duration of 10.7 months [10].
The lower incidence in our cohort could be explained by the use of less toxic first-line regimens such as TDF than in previous studies. In our study, nearly 40% of patients receiving TDF were at first-line treatment compared to 4.2% who received d4T. The first-line regimens used in the above studies contained little or no TDF. They were mainly based on AZT, d4T and NVP. Given the toxicity profiles of these different ARVs and the role of ARV side effects in treatment changes, the lower incidence observed in our cohort seems relevant. Another explanation could be the empirical application by clinicians of a strategy of "saving ARV molecules" but there is no evidence to suggest a different application in Senegal.

In the literature, ARV side effects are the main cause of the changes in treatment [11-15]. These results are consistent with those found in our study. Similarly, the causes of change in treatment observed in our cohort are in accordance with those reported in Côte d’Ivoire [8]: ARV intolerance was the main cause of treatment changes with an incidence rate of 12.4/100 PY and over one third of these changes were due to pregnancy and tuberculosis.

In Mali, the study rather focused on line-of-treatment changes and reported a second-line incidence of 3.3/100 PY [9]: a low incidence consistent with the one of our study and other data from developing countries [5,10,16-20]. The mechanisms of "economy of molecules" can be put forward as an explanation but also the routine non-suppression of the viral load, non-adherence to ART and side effects.

It is nevertheless recognized that in West Africa, female PLHIV are more adherent to treatment and follow-up, and therefore with a greater likelihood of benefiting from a change in ART. Malnutrition is often associated with metabolic disorders that may be contra-indications of ARVs or factors contributing to their toxicity; the absence of systematic blood-biochemical evaluation may explain the greater frequency of ART changes in this case. The therapeutic arsenic is more limited for patients infected with HIV-2 which is naturally resistant to NNRTIs. There are fewer opportunities for change in this population; resulting in lower frequency.

ART changes are more frequent in high-income countries [26]. This reflects the enormous differences in the management of PLHIV’s vis-à-vis poorer countries: a much wider and diversified therapeutic arsenal and routine availability of viral load and genotyping tests provide more latitude and comfort in treatment changes in rich countries.

### Conclusion

Our study looked at the first ART change in a resource-constrained context characterized by a limited therapeutic arsenal and patients at an advanced disease stage. The incidence was low here with the main reason being ARV intolerance.

A better pre-therapeutic evaluation of patients, earlier ART initiation, a more diversified therapeutic arsenal and the availability of ARV drugs compatible with pregnancy and tuberculosis treatment should allow better management of initial ART changes in sub-Saharan Africa.

### Acknowledgement

The authors acknowledge all the people living with HIV who consent to participate to this study, the social workers of SMIT/CRCF (Mariane Ndiaye Berthé, Catherine Fall Sané, Absa Ba and Khady Gassama), the pharmacists of CRCF (Pr Bara Ndiaye, Dr. Mama Basty Koita-Fall, Dr. Mamadou Ndiaye) and the medical secretary of the SMIT/CRCF (Mrs Coumba Gueye Cissé).

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#### Table 3: Cox models identifying the predictive factors for the first ART change.

| Characteristics | Univariable analysis Hazard Ratio (95% CI) | Multivariable analysis Hazard Ratio (95% CI) |
|-----------------|-------------------------------------------|---------------------------------------------|
| Age (years)     | 0.99 (0.97-1.02)                          | -                                          |
| Female sex*     | 1.85 (1.08-3.19)                          | 1.65 (1.07-3.19)                           |
| HIV-1 or HIV-D² | 2.80 (0.88-8.94)                          | 3.57 (1.11-11.46)                         |
| WHO stage 3 or 4 | 1.22 (0.63-2.35)                          |                                             |
| BMI (kg/m²) ≤ 18,5² | 2.06 (1.17-3.62)                          | 2.20 (1.24-3.88)                          |
| CD4 cell count ≤ 200/µL | 1.77 (0.94-3.32)                          | 1.63 (0.86-3.29)                          |
| Haemoglobin level (g/dL) | 0.91 (0.93-1.26)                          | 0.99 (0.88-1.14)                          |
| Creatinin level (mg/L) | 0.99 (0.95-1.13)                          | -                                          |
| Transaminases (IU/L) | 0.99 (0.99-1.01)                          | -                                          |

*reference=male sex, #reference=HIV-2, ²reference=WHO stage 1/2, ³reference=BMI>18.5 kg/m²

The discovery of a positive HBs antigen resulted in an ART change in 2 cases. This finding is consistent with the results of Anlay et al. [7] and Njuguna et al. [21] who found 1 and 8 cases of HBs antigen positivity, respectively, which resulted in ART changes [7,21]. It was only in 2013 that the WHO has recommended the use of TDF+TDF+EFV (HIV-1) or TDF+XTC+LPV/R (HIV-2 and HIV-1+2) as first line ART, explaining the change in treatment in all of these studies [16].

Our study found that the female sex, underweight and HIV serotype were predictive factors for ART change. Studies that addressed risk factors for ART change had significant methodological differences from our own: they were specifically concerned with intolerance of certain ARVs [8,10,22], changes in therapeutic lines [9] or delays in ART changes [23-25]. In Mali, the risk factors for line change were: a change in previous ART, low CD4 cell counts, advanced age and triple therapy with NNRTI in HIV-2 infected patients [9]. In this study, some variables such as HBV serology, HIV-D infection were not taken into account although they are potential confounders.

In India, Chandy et al. [23] used a model based on the Generalized Estimation Equations (GEE) with the change delay as an independent variable. They also considered behavioral data such as stigma, depression, adherence and quality of life. Associated factors were side effects and low CD4 count. Whereas Slama et al. [25] found as associated factors non-suppression of the viral load, non-adherence to ART and side effects.
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