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Immunovirological Discordance and Associated Factors among People Living with HIV under Antiretroviral Treatment at Hôpital de Jour de Donka, Guinea

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Abstract

The antiretroviral treatment (ART) has significantly reduced the number of new HIV/AIDS infections and related deaths. However, cases of immunovirological discordance (IVD) are found in various locations. The objective of this study was to determine the profile of People living with HIV (PLHIV) with IVD and to identify associated factors. We conducted a cross-sectional study based on the records of PLHIV under ART for at least 6 months, followed at Hôpital de Jour Donka from 2015 to 2017, and having both viral load (CV) and CD4+ T-cell count. Prevalence of IVD was 34.57%, with 23.87% for immunological discordance (ID) and 10.7% for virological discordance (VD). Females were predominant (66.26%), and male gender influenced IVD with a statistically significant difference (p = 0.006) and was associated with VD (p = 0.007). The average age was 38.77 ± 11.30 years. PLHIV were classified at WHO stages 3 and 4 (86.01%). The median initial haemoglobin level was 11.5 g/L [3.2 - 12]. The mean initial CD4+ T-cell count was 272.84 cells/mm^3 ± 201.6. The median initial viral load (VL) was 147,337 copies/mL [1092 - 31,675,000]. The initial CD4+ T-cell count < 200 cells/mm^3

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was associated with IVD with a statistically significant difference (p = 0.0009) and correlated with ID (p = 0.000). Prurigo was associated with IVD with a statistically significant difference (p = 0.003). Cerebral toxoplasmosis was not associated with IVD but was associated with ID (p = 0.04). This study allowed us to describe the profile of PLHIV with IVD. The main associated factors were male gender, initial CD4+ T-cell count < 200 cells/mm^3, toxoplasmosis, prurigo, and herpes zoster.

Keywords

HIV, Antiretroviral Treatment (ART), Immunovirological Discordance, Donka, Guinea

1. Introduction

The initiation of antiretroviral treatment (ART) in people living with HIV (PLHIV) inhibits viral replication and promotes immune restoration, thus limiting the occurrence of major opportunistic infections, the selection of resistant viruses, and the risk of morbidity and mortality [1] [2].

However, some HIV-infected patients under highly active antiretroviral therapy (HAART) may experience immunovirological discordance (IVD), defined either by a significant increase in lymphocyte levels without virological success or by a CD4+ T-cell count below 200 cells/mm^3 despite an undetectable plasma viral load [3] [4] [5]. This phenomenon may be associated with an increase in morbidity and mortality [6] [7].

IVD has been described in certain studies that have highlighted various factors that may promote its occurrence during ART. These factors are related to late diagnosis, low CD4+ T-cell count at initiation, advanced age, and male gender [8] [9] [10]. In addition, other biological and clinical factors such as immune activation [11], the number of CD4+ T-cells at the initiation of treatment [12], co-infection, poor adherence [13], and the treatment regimen [2] [7] [14] have been associated with the occurrence of IVD.

Studying the phenomenon of IVD and understanding its determinants should help optimize the use of ART in resource-limited countries where the number of patients at advanced stages of HIV infection is still significant [2] [12].

The objective of this study was to describe the profile of PLHIV under ART who experience IVD and to identify its associated factors at Hôpital de Jour Donka.

2. Materials and Methods

2.1. Study Design, Patients, Samples and Recruitment

We conducted a cross-sectional study on PLHIV followed at Hôpital de Jour of Donka from January 1, 2015, to December 31, 2017. We recruited patients in-

fected with HIV-1 under ART regardless of the treatment line for at least 6 months, with a CD4+ T-cell count at the initiation of ART, and whose records contained both CD4+ T-cell count and viral load (VL). The IVD was defined either by a significant increase in CD4+ T-cell count > 200 cells/mm^3 without virological success (Virological discordance (VD)) or by a CD4+ T-cell count <200 cells/mm^3 despite an undetectable plasma VL (Immunological Dissociation (ID)) [15]. The variables included sociodemographic data such as age, sex, and medical history. Bioclinical data such as WHO clinical stage, body mass index (BMI), haematological and biochemical parameters; CD4+ T-cell count, VL, and treatment-related information.

2.2. Ethics Statement and Procedure

This study was performed in the Day hospital at Donka University Hospital in Conakry (Guinea). In this study, all the Immunological and virological assays were performed in the Laboratore de Bioloogie moleculaire Nestor Bangoura/Helene Labrousse de l'Hôpital de Jour de Donka in Conakry. Sample collection and monitoring were done in collaboration with the clinicians in Conakry. The protocol was approved by the Research Committee of the University Gamal Abdel Nasser (Conakry, Guinea) and performed following the Declaration of Helsinki.

2.3. Viral Load Detection and CD4+ T-Cell Counting

- Viral load testing: The measurement of plasma HIV RNA viral load was performed using Generic HIV Viral Load kit (Biocentric®, France), developed by Agence Nationale de Recherches sur le Sida et les hépatites (ANRS). This is an in vitro nucleic acid amplification test that allows for the detection and amplification of HIV-1 RNA in human plasma specimens. Additionally, the Abbott m2000 RealTime System (Abbott Molecular Inc., USA) was employed using the Abbott RealTime HIV-1 assay kit, which facilitates the detection and amplification of HIV-1 RNA. These tests were conducted following the manufacturers' recommendations.
- Lymphocyte TCD4+ counting: flow cytometry using the BD FACSCount™ machine was used for the counting of CD4+ T lymphocytes with the BD FACSCount™ CD4 reagents (Becton, Dickinson and Company BD Biosciences, San Jose, USA). These reagents are used to enumerate the absolute counts of CD4 T lymphocytes and determine the percentage of lymphocytes that are CD4 T lymphocytes in unlysed whole blood (CD4 counts and CD4 percentages). Its content CD4 PE/CD14 PE-Cy™5/CD15-PE-Cy5, fluorescent nuclear dye, and reference beads; reagent tube caps; fixative solution. The assay has been performed according to the manufacturer consideration.

2.4. Data Collection and Statistical Analysis

Clinical and paraclinical data were collected in patient folders using a pre-established

data processing form.

The data were entered into a mask of the Epi-info software version 7.2, then exported to Excel and analyzed using the R software. The Chi-square test and Fisher's exact test were used for comparing proportions or estimating the association between variables when the conditions for use were met. Quantitative variables were compared using the Student's t-test. Multivariate logistic regression analysis was used to analyse factors associated with immunovirological dissociation. The significance level was set at a p-value less than 0.05.

3. Results

During this study, we collected patient data over a follow-up period of 3 years from January 1, 2015, to December 31, 2017. Out of 1515 records, we selected 243 patient records that met the inclusion criteria (Figure 1). The median age was 38 [IQR: 30 - 46]. Females were predominant with a ratio of 0.5. Polygamous couples were the most represented (56.67%) (Table 1). The overall prevalence of IVD was 34.57% [IQR: 28.60 - 40.91], which was further classified into ID (23.87%) [IQR: 20.07 - 27.22] and VD (10.7%) [IQR: 7.33 - 14.52].

Most of our patients were classified in WHO stages 3 and 4 (86.01%) and had a normal BMI (56.79%). Among opportunistic infections, oesophageal candidiasis was the most prevalent (42.8%), followed by prurigo (23.7%). The analysis of factors associated with IVD was conducted based on various parameters (Table 2). According to gender, IVD showed a statistically significant difference ($p = 0.002$), and it was associated with VD ($p = 0.006$). Alcohol consumption influenced VD with a statistically significant difference ($p = 0.04$). Clinically, a history of tuberculosis, cerebral toxoplasmosis, and prurigo were correlated with IVD, with respective statistically significant differences of $p = 0.01$, $p = 0.04$, and $p = 0.000$. Herpes zoster was correlated with VD with a statistically significant difference of $p = 0.03$.

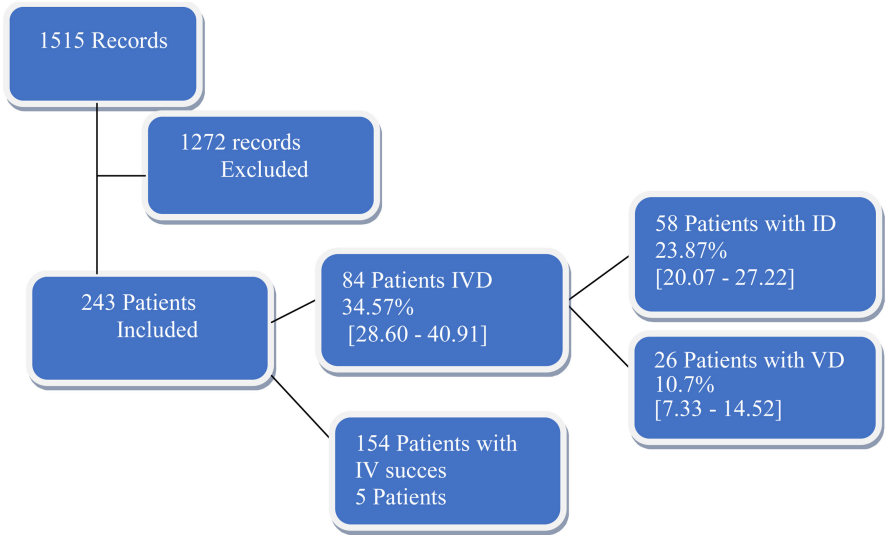

Figure 1. Flowchart of patients who started the ART during the study period.

Table 1. Caracteristics of the study population.

Variables	Overall	Patient whithout IVD n = 159	Patient with IVD n = 84	*p-value*
Gender				
Male	82 (33.74)	43 (27.04)	39 (46.43)	**0.002***
Female	161 (66.26)	116 (72.96)	45 (53.57)	
ratio	0.51			
Age range (years)				
16 - 35	107 (44.03)	74 (69.16)	33 (30.84)	0.28*
36 - 71	136 (55.97)	85 (62.50)	51 (37.50)	
Median Age [IQR]	38 [30 - 46]	37 [16 - 68]	39.5 [20 - 71]	0.3*
Alcool comsumption				
Yes	40 (16.46)	24 (15.09)	16 (19.05)	0.4*
NO	203 (83.54)	135 (84.91)	68 (80.95)	
tabacco consumption				
Yes	35 (14.40)	22 (13.84)	3 (15.48)	0.73*
NO	208 (85.60)	137 (86.16)	71 (84.52)	
Patient whit hypertension				
Yes	12 (4.94)	9 (5.73)	3 (3.57)	0.46*
NO	231 (95.06)	148 (94.27)	81 (96.43)	
CD4+ T-cells at initiation of ART				0.001**
≤200	106 (43.62)	43 (27%)	63 (75%)	
201 - 499	104 (42.8)	85 (53%)	19 (23%)	
≥500	33 (13.58)	31 (19%)	2 (2.4%)	
ARV regimen				
TDF + 3TC + EFV	234 (96.31)	155 (97.48)	82 (97.61)	0.95**
AZT + 3TC + EFV	3 (1.23)	2 (1.26)	01 (1.19)	0.96*
AZT + 3TC + NEV	3 (1.23)	3 (1.89)	01 (1.19)	0.69*
TDF + 3TC + Lp/r	2 (0.82)	1 (0.6%)	1 (1.2%)	0.64*
AZT + 3TC + Lp/r	1 (0.41)	0 (0%)	1 (1.2%)	0.3*
Viral Load at Initiation				
VL under 1000 cp/mL)	0	0 (0%)	0 (0%)	0.9*
VL upper 1000 cp/mL	48	18 (100%)	30 (100%)	

*Fisher's exact test; **Pearson's Chi-squared test.

According to paraclinical aspect, VD was correlated with the haemoglobin level with a statistically significant difference (p = 0.003); the initial CD4+ T-cell count ≤ 200 influenced IVD and ID with a statistically significant difference (p <

0.0001). According to therapeutic aspect, second-line treatment with the combination AZT+3TC+Lp/r was correlated with VD with a statistically significant difference (p = 0.004).

We observed on multivariate analysis (Table 3) that, the factor associated with IVD after adjusting for independent variables were: male gender with OR = 3.1 [1.38 - 6.6], p = 0.006; an initial CD4+ T-cell count ≤ 200 with OR = 5.97 [2.08 - 17.01], p = 0.0009; and prurigo with OR = 3.38 [1.5 - 7.62], p = 0.003. The variables associated with ID were: cerebral toxoplasmosis with OR = 6.03 [1.07 - 33.99], p = 0.04, and an initial CD4+ T-cell count ≤ 200 with OR = 5.09 [2.15 - 12.48], p = 0.000. Only male gender was associated with VD, OR = 13.91 [2.05 - 94.02], p = 0.00.

Table 2. Multivariate of the: associated factors to IVD.

Associated factors	DIV		
	OR	CI 95%	*p-value*
Gender (M/F)	3.01	[1.38 - 6.6]	**0.006**
Age > 35 years	1.69	[0.81 - 3.54]	0.16
BMI < 18.5	1.56	[0.6 - 3.58]	0.0287
Tuberculosis	0.65	[0.18 - 2.28]	0.5
Cerebral toxoplasmosis	6.02	[0.64 - 55.98]	0.14
CD4+ T-cell < 200	5.97	[2.08 - 17.1]	**0.0009**
Prurigo	3.38	[1.5 - 7.62]	**0.003**

Table 3. Multivariate analysis of the associate factors to ID and VD.

Associated factors	immunological discordance			virological discordance		
	OR	IC 95%	*p-value*	OR	IC 95%	*p-value*
Gender (M/F)	-	-		13.91	[2.05 - 94.02]	**0.007**
Age > 35 year	1.56	[0.7 - 3.08]	0.19	1.46	[0.23 - 8.97]	0.68
BMI < 18.5	-	-		0.87	[0.15 - 5.04]	0.87
Cerebral toxoplasmosis	6.03	[1.07 - 33.99]	**0.04**	-	-	-
Oesophageal candidiasis	0.58	[0.28 - 1.8]	0.13	2.08	[0.37 - 11.57]	0.39
Tuberculosis	2.32	[0.8 - 6.73]	0.11	-	-	-
Kaposi's diseases	3.03	[0.4 - 20.10]	0.24	-	-	
Hepatis B virus	-	-	-	2.95	[0.39 - 22.45]	0.29
Prurigo	-	-	-	3.8	[0.82 - 17.62]	0.08
CD4+ T-cell < 200	5.09	[2.15 - 12.48]	**0.000**	6.67	[0.3 - 145.83]	0.23

4. Discussion

From January 1, 2015, to December 31, 2017, we conducted a cross-sectional study with the objective of describing the profile of PLHIV experiencing IVD and determining associated factors. The limitation of this study was the small size of the included patients. Two explanations can be provided. Firstly, this work is a cross-sectional study using data collected previously, and secondly, due to the prioritization of VL testing, the CD4 count is reserved for patients in the advanced stage of WHO.

We selected 243 patient records that met the inclusion criteria. All the experiments were performed at Laboratoire de Biologie moléculaire Nestor Bangoura/Helene Labrousse de l'Hôpital de Jour de Donka.

We observed an overall prevalence of IVD of 34.57%. A similar rate was found by Anude CJ *et al*. in Nigeria, who reported a prevalence of 33% [8]. However, Ka D *et al*. in Senegal, Cassoti J *et al*. in Brazil, and Ouedraogo SM *et al*. in Burkina Faso reported lower prevalence ranging from 4% to 19.3% [12] [13] [16].

The median age of the study population was 38 years [IQR: 30 - 46]. This result was previously reported comparable by Kone F *et al*. in Cote d'Ivoire (35 years) and Cassoti J *et al*. in Brazil (38.5 years) [16]. However, it is lower than that of Massaly A *et al*. (42 years) and Ka D *et al*. (44 years) in Senegal [13] [17]. The age was higher in patients with Virological Dissociation (VD) (39.8 years vs 38.77 years, p = 0.3).

The female gender was predominant in our study (66.26% versus 33.74%) with a sex ratio of 0.51. This observation is consistent with most studies conducted in Africa among PLHIV [12]. However, Tan R *et al*. in the USA found a male predominance (76.2%) [18].

According to the type of IVD, we observed a prevalence of ID equal to 23.87%. This result is higher than those of Massaly A *et al*. (12.7%) in Senegal and Kone F *et al*. in Cote d'Ivoire (5.6%). We observed 10.7% VD. This result was close to that of Massaly A *et al*. in Senegal (11.6%) and lower than that of Kone F *et al*. in Cote d'Ivoire (43.3%) [19]. The difference between these results could be explained by the heterogeneity of study populations, study durations, treatment regimens used, and the duration of treatment.

IVD was predominantly found in female patients (53.57% vs. 46.43%, p = 0.002) in our study. Ouedraogo SM *et al*. in Burkina Faso, Manga NM *et al*., in Senegal also found a female predominance with prevalence ranging from 19.22% to 64.1% [12]. However, Ka D *et al*. in Senegal observed a male predominance of IVD (29.7%) [13]. This female predominance could be explained by the fact that women more frequently attend healthcare services and, on the other hand, constitute a vulnerable group [13].

VD was predominant in male patients (57.69%, p = 0.006). This vulnerability of males to virological failure could be explained by the fact that men undergo HIV testing less frequently and tend to initiate their antiretroviral treatment at a

more advanced stage than women [20].

Tobacco consumption did not influence IVD (p = 0.05), unlike alcohol consumption (p = 0.04). This could be explained by the fact that alcohol exacerbates HIV infection through its action on antiviral medications. Indeed, it becomes an enzymatic inducer in the case of chronic consumption and an enzymatic inhibitor in the case of acute alcoholism [21].

Most of patients had a BMI between 18.5 - 24.99 kg/m^2 (56.79%), and 26.75% were underweight. The median BMI was 20.84 kg/m^2 [IQR: 11.5 - 39.81], a result comparable to that of Ouedraogo SM *et al.* in Burkina Faso, who found a median BMI of 20.5 kg/m^2. IVD was found in patients with a median BMI of 20 kg/m^2 [IQR: 11.72 - 30.21, p = 0.0007] and a BMI of 19.77 kg/m^2 [IQR: 11.7 - 30.21, p = 0.0006]. This could be explained by malnutrition being associated with protein deficiency, where there is a decrease in the function of all lymphoid organs, starting with the thymus [13].

Many of our patients were classified as WHO stage 3 and 4 (86.01%), similar to the findings of Ka D *et al.* in Senegal and Anude CJ *et al.*, and Emeka E *et al.* in Nigeria, who found prevalence ranging from 68.55% to 96% [8] [13]. The delay in diagnosis in low-income countries could explain this difference. Most patients had opportunistic infections at inclusion, dominated by oral candidiasis (42.8%), followed by prurigo (23.73%), herpes zoster (4.83%), and tuberculosis (8.1%). This can be explained by the fact that in sub-Saharan Africa, cutaneous-mucosal infections manifest prominently in PLHIV [22]. Tuberculosis (p = 0.03), cerebral toxoplasmosis (p = 0.04), and prurigo (p = 0.000) were associated with IVD and specifically with ID (p = 0.01, p = 0.04, and p = 0.000). Herpes zoster was associated with VD (p = 0.03). These opportunistic infections should be systematically investigated to prevent complications.

The median initial haemoglobin level was 11.5 g/L [IQR: 3.2 - 12]. Patients with IVD had a median level of 10.8 g/L [IQR: 3.24 - 12.2, p = 0.39]. This result is comparable to the analysis by Ka D *et al.* in Senegal (10.4 g/L, p = 0.834) [13]. However, we found a correlation between the median initial haemoglobin level 511.3 [IQR: 3.2 - 14]) and VD (p = 0.003). The mean CD4+ T-cell count at baseline was 272.84 cells/mm^3 ± 201.6, indicating advanced immunosuppression (200 - 399 cells/mm^3) due to late diagnosis of HIV infection. This result is similar to those of Kayigamba FR *et al.* in Rwanda (240 cells/mm^3 [150 - 295]) [23]. However, Ouedraogo SM *et al.* in Burkina Faso and Ka D *et al.* in Senegal observed lower results, 42 cells/mm^3 [IQR: 12 - 63] and 65 cells/mm^3 [IQR: 2 - 407], respectively [12] [13]. CD4+ T-cell values were associated with IVD for an initial CD4+ T-cell count < 200 cells/mm^3 (p = 0.000). They were also correlated with DI (p = 0.000). This result is comparable to those reported by Pinzone R *et al.* in Italy, Smith CJ *et al.* in England [24] [25]. Severe immunosuppression (CD4+ T-cell count < 200 cells/mm^3) before initiating antiretroviral treatment is a factor favouring a poor immune response.

The median viral load at baseline was 147,337 copies/mL [IQR: 1092 -

31,675,000]. This result is similar to that of Kilaru K *et al*. in the Caribbean, who observed a median viral load at baseline of 122,500 copies/mL [54,125 - 350,000] [26], unlike Grabar S *et al*. in France, who found a median rate of 35,000 copies/mL [27]. This observation could be explained by the fact that in our study, many patients were diagnosed at an advanced stage of immunosuppression.

In our study, 98.77% of patients were on first-line ART, with 96.3% on the therapeutic protocol based on TDF+3TC+EFV. Overall, ARV protocols were not associated with IVD. However, DV was correlated with the AZT+3TC+Lp/r protocol ($p = 0.004$). Moore D *et al*. in Canada also found a correlation between virological dissociation and the use of the AZT+3TC protocol [7].

In multivariate analysis, the following parameters were associated. Male gender, CD4+ T-Cell count (<200 cells/mm^3), Pruritus was associated with IVD. However Cerebral toxoplasmosis was not associated with IVD. In the study conducted by Anude CJ *et al*. in Nigeria, factors associated with immune restoration failure included male gender and age less than 30 years [8]. However, in Senegal, Massaly A *et al*. found that age less than 35 years was the only risk factor associated with IVD [17]. Similarly, Ka D *et al*. observed that age greater than or equal to 43 years, initial CD4 count < 100 cells/mm^3, and male gender were associated with IVD [13]. These results may be explained by the fact that some patients were initiated on ART late with a VL > 100,000 copies/mL, severe immunosuppression (CD4 < 200), which are among the factors influencing the immunovirological response in PLHIV under ART [28].

5. Conclusion

This study allowed us to describe the profile of PLHIV with IVD. The main associated factors were male gender, initial CD4+ T-cell count < 200 cells/mm^3, toxoplasmosis, prurigo, herpes zoster and advanced stage III and IV of WHO. Indeed, a long-term study could help confirm our observations and identify any additional factors. It could also contribute to understanding the impact of IVD on patient survival and the risk of opportunistic infections.

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Authors' Contributions

Contributed to data collection: MSD, DK, CTD, ID, ON, OMD.

Contributed to participant recruitment and evaluation: MSD, DK, CTD, ID, BFD, ASK, MMS, TMT.

Contributed to study design: MSD, DK, MC.

Contributed to data analysis: MSD, DK, CTD, ID, ON, OYK, APK, PK, OMD.

Wrote the paper: MSD, DK, CTD, ID, BFD.

Contributed to editing the paper: All. All authors have read and agreed to the

published version of the manuscript.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. The protocol was approved by the R.C of the University Gamal Abdel Nasser (Conakry, Guinea) and performed following the Declaration of Helsinki.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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