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Factors Influencing Residual HIV-1 Replication in Patients Treated with Tenofovir, Lamivudine and Dolutegravir at the Al-Nadjma Polyvalent Center in N'Djamena, Chad

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A B S T R A C T

The objective of this study was to determine the factors influencing low-level residual replication in patients infected with HIV-1 treated with TLD followed at the Center Polyvalent AL-Nadjma in N'Djamena, Chad. This was a retrospective and prospective study with an analytical aim which took place at the Polyvalent Al-Nadjma center from April 2022 to December 2023 in the city of N'Djamena. The study began with the interview of 135 patients, 108 of whom signed informed consent to participate in this study. Patients infected with HIV 1 on ART based on the combination of Tenofovir, Lamivudine and Dolutegravir (TLD) for at least 2 years with a load of 999 copies/mL were included. A total of 108 plasmas were collected and analyzed by the RT-PCR technique. The data from the interviews as well as the RT-PCR results were analyzed with R Studio software. 70% (76/108) of the participants were female with a M/F sex ratio of 0.42. The average age of the patients was 40.58 ± 9.58 years. Factors influencing residual replication were related to age with a prevalence of 27.27% of patients in the age group of 40 to 50 years, to initial HIV VL with 18.66% in patients who had an initial VL between 40 – 200 copies/ml and 22.22% in those with a baseline VL between 501 - 999 copies/ml, at prior ART, most patients were on prior ART consisting of (Viraday®). A prevalence of 23.95% of low-level residual viremia was observed in these patients and also non-compliance with a prevalence of 7.40% of residual viremia. Thus, it was found that factors influencing residual replication were linked to a higher risk of virological failure and poor immune reconstitution. A better understanding of the influencing factors and adverse effects in various states of residual viremia is expected to provide important guidance for HIV treatment.

Introduction

The HIV/AIDS epidemic remains a significant public health burden worldwide, particularly in low- and middle-income countries (UNAIDS, 2020). The advent of combination antiretroviral therapy (cART) has resulted in a significant reduction in morbidity and mortality among people infected with human immunodeficiency virus type 1 (HIV-1) (Antiretroviral Therapy cohort collaboration, 2008; Palella *et al.,* 1998) Antiretroviral treatment (ART) must be started as early as possible, as soon as detected, as soon as treated, but the most appropriate moment must be assessed individually, taking into account the most beneficial combination for the patient and weighing the advantages and disadvantages. At the end of 2022, the treatment success rate among people living with HIV on ART was 71%. (UNAIDS, 2022). ART can limit viral replication to a viral load below 50 copies/ml and effectively prolong the lives of HIV/AIDS patients. However, in approximately 10% to 30% of patients, standard ART does not fully control viral replication, and these patients have low levels of viral replication in their plasma, called residual viremia. According to the WHO, residual viremia is defined as a viral load (VL) between 50 and 1,000 copies/ml (Bennett *et al.,* 2008).

Consequently, virological failure in different regions and countries, depending on medical and socio-economic contexts is defined as a viral load between 50 copies/ml, 200 copies/ml and 1000 copies/ml (Bennett *et al.,* 2008; Lesko *et al.,* 2020; WHO, 2013; CFDCA, 2017; Ryon *et al.,* 2018; Dybul *et al.,* 2002; WHO, 2015). Although low-level viremia frequently occurs during treatment, there is no consensus on how to manage HIV-infected patients with these viremias, and potential risk factors for residual viremia have not been identified. been widely studied (Elvstam *et al.,* 2021). Some studies have suggested that low-level viremia contributes to virological failure (Vandenhende *et al.,* 2015; Elvstam *et al.,* 2017), whereas other studies have found no additional risk of virological failure and resistance. to medications in patients with residual viremia, particularly those with a low viral load (less than 200 copies/ml) (Vandenhende *et al.,* 2015; Joya *et al.,* 2019).

Previous studies have mainly focused on factors related to virological failure, with few reports on the influencing factors and adverse effects of various states of residual viremia, and often with discordant results. Therefore one of the most complex and important areas of current research involves the clarification of factors influencing residual viremia and adverse outcomes of various conditions. Several factors can influence low-level HIV-1 viremia, and some key issues to consider include, initial viral load at the time of infection, strength and effectiveness of the host immune response, diversity HIV-1 genetics, duration of HIV infection and resistance to antiretroviral drugs (Ludo *et al.,* 2006; Deeks *et al.,* 2007; Hemelaar *et al.,* 2006). In addition to the characteristics cited above, treatment-related factors could influence the risk of residual viremia, with a higher risk for regimens based on protease inhibitors (PI) compared to those based on non-nucleoside inhibitors reverse transcriptase (NNRTI) or integrase strand transfer inhibitors (INSTI) (Wriden *et al.,* 2015; Doyle *et al.,* 2012; Vancoillie *et al.,* 2014).

Other studies have documented that non-compliance with ART is a major risk factor for residual viremic episodes (Mills *et al.,* 2006; Bijker *et al.,* 2017). However, this has not been studied extensively in the context of the widespread use of integrase strand transfer inhibitors such as dolutegravir, particularly in resource-limited settings, such as in Chad, where dolutegravir-based regimens are WHO-recommended options for first-line ART.

In Chad, data on residual viremia are rare and on the factors influencing persistent residual viremia in HIV patients on ART are rare. Most studies have focused on the phenomena of resistance mutations in HIV-infected patients on ART (Kiweew *et al.,* 2019; D'arminio *et al.,* 2000). The objective of this study was to determine the factors influencing low-level residual replication in HIV-1-infected patients under TLD followed at the AL-Nadjma Polyvalent Center in N'Djamena, Chad.

Materials and Methods

Study area and period

This was a retrospective study with an analytical aim which took place at the AL-NADJMA Polyvalent Center (APMS) in the commune of the 6th Arrondissement of the city of N'Djamena in Chad. The geographic coordinates produced by Globale Position System (GPS): are 12°107095 north latitude and 15°079048 east longitude. The study population consisted of patients infected with HIV-1 placed on TLD and monitored regularly for several years with a plasma viral load less than 1000 copies/mL measured every six months.

Sampling

The sampling was done voluntarily and consented. It began with an interview with patients living with HIV who were regularly monitored at the Al-Nadjma Polyvalent Center. A total of 135 patients on TLD with a viral load between 40 and 999 copies/mL were interviewed. Among them, 108 signed the informed consent form and agreed to participate in the study and 27 others refused to participate in the study.

Sample and data collection technique

Data collection and samples were carried out between April 2022 to December 2023. The information was collected using a structured questionnaire. The data collected were the sociodemographic characteristics of the patients (age, sex and marital status) and biological and clinical data (compliance, initial viral load, previous ARV treatment, year of initiation of ART, frequency of residual replication, therapeutic failure and success virological). The blood sample of 2 to 4 mL in 2 tubes containing an anticoagulant EDTA (Ethylene Diamine Tetra Acetic) per patient was carried out by puncture of the radial vein using a Venoject,® Vacutainers® needle of 7h30 minutes at 9:30 a.m. by a member of the team. The samples were sent to the Molecular Biology laboratory of the APMS center. The samples were centrifuged at 15,000 rpm for 10 minutes. The plasma is collected to be stored at -70°C for later use.

Real Time Polymerase Chain Reaction (RT-PCR) protocol

The viral genome was demonstrated using Real Time Polymerase Chain Reaction (RT-PCR) according to the protocol recommended by the company BIOCENTRIC. Extraction of viral RNA from plasma is automated. Being automated, two kits were used. The GenoXtract® kit in association with the GXT NA nucleic acid extraction kit version 1.0 (Hain Lifescience, Ref. 12.08.02), marketed by BIOCENTRIC. The extraction technique used was that recommended by BIOCENTRIC (Biocentric, 2019a). For amplification the main components of the Generic HIV Viral Charge Amplification Kit (Biocentric) for 220 tests (Ref. TR001-250IC) were used.

For a test, the reaction mixture was composed of the following elements: (3 µL of H2O without nuclease, 5 µL of the enzyme mix, 0.5 µL of the sense primer A, 0.5 µL of the anti-sense primer B, 0.5 µL of probe C) with the "reporter" the FAMTM fluorophore at 5' and the non-fluorescent MGB "quencher" at 3' and 0.5 µL of IC primers/Cy5-probes (Biocentric, 2019b).

After preparing the reaction mix solution, 10 µL of RNA eluate was added to each well already containing reaction mix. All the samples were placed in the thermocycler (FluoroCycler® 15 seconds, followed by 30 seconds of primer annealing at +62°C and 30 seconds of elongation at +72°C then the final elongation of 7 minutes between 50°C to 60°C. The FluoroSoftware® XT-IVD made it possible to generate rapid results with a summary report (Biocentric, 2019b).

Statistical analyzes of the data

The data from the interviews as well as the results of the plasmas tested were entered into an Excel spreadsheet in Microsoft Office 2010 software then converted to CSV and then exported to R Studio software version 4.0.4.2021 for analyses.

Concerning the analytical statistics, the Chi-square test and the Pearson test were used to compare the proportions (frequency of residual replication, therapeutic failure and virological success) and the variations in prevalence linked to the detection of replication viral residual as well as for their significance. The significance threshold was set at 0.05 and the p-value calculated using the Pearson test.

Results and Discussion

In this study, we enrolled 135 patients, 108 of whom agreed to participate with a plasma viral load below 1000 copies/ml, the average age was 40.58 ± 9.58 years, the oldest age group represented was that of [40 – 50 years old] or 41%.

70% (76/108) of the participants were female with a M/F sex ratio of 0.42.

Patients with an age range of 40 to 50 years were the most affected by the occurrence of low-level residual replication with 27.27% (12/44), 47.72% (21/44) were in virological success and 18.18% (8/44) in virological failure.

Followed by that of 29 -.39 years or 16.21% (6/37), these results were significant (p-value =0.025) (table 1).

Patients with an initial viral load between 40-200 copies/ml had a prevalence of 18.66% and those with an initial plasma viral load between 501 to 999 copies had a prevalence of 22.22% (p-value = 0.006) (table 1).

The majority of patients 88.88% (96/108) included were on prior ART consisting of Efavirenz + Emtricitabine + Tenofovir (Viraday®). A prevalence of 23.95% of low-level residual viremia was observed in these patients. These results are significant at the 5% level with a p-value = 0.005 (table 1).

The prevalence was 7.40% in non-compliant patients with a P-value = 0.014%. These results are significant at the 5% level.

Patients who were on ART in the years 2011 to 2015 had a 25% prevalence of low-level residual replication (Table 1).

In this study, the primary influencing factor for low-level residual viremia in patients on ART was age as a demographic factor of PLHIV on ART. The age group of patients between 40 and 50 years old had a prevalence of 27.27% followed by those aged 29 to 39 years old with 16.21%.

The present study results obtained were lower than those of 30.99% obtained in patients aged 55 years and 26.85% in the age group of 25 to 34 years by Yuan *et al.,* (2022) in the Jiangsu region in China on patients with low-level viremia.

Two reasons could explain these results. Firstly through the lack of psychosocial care and a late diagnosis of the disease, secondly with increasing age, the immune system deteriorates, which could affect the body's ability to control viral replication and would lead to to transient residual viremia in some older people infected with HIV-1.

The present study showed that the risk of low-level residual viremia was much high in patients with an initial viral load between less than 40 to 200 copies/ml, i.e. a rate of 18.66%. This result could be explained by the fact that the continued presence of HIV- in the body with low viral loads could affect the immune system and increase the risk of long-term complications (residual viremia). A virological failure rate of 72.22% was observed in patients with an initial plasma viral load between 501 to 999 copies/ml. According to a study conducted by Crowell *et al.,* (2020), individuals with a viral load of high initial viral load have a higher risk of developing residual viremia than those with a low viral load before treatment. On the other hand, Esber *et al.,* (2019), assert that the risk of virological failure increased by 5.49 times when the viral load reached 500 to 999 copies/ml in patients infected with HIV-1. These two statements could support our results.

The most prescribed prior treatment regimen in our study was Viraday® 88.88% (96/108) composed of 2 non-nucleoside reverse transcriptase inhibitors (NNRTIs) and 1 nucleoside reverse transcriptase inhibitors (NRTIs) (Efavirenz/Emtricitabine/Tenofovir). The study revealed a rate of 23.95% of the occurrence of low-level residual viremia in patients which was linked to this therapeutic regimen (table 1). Until now, no study had yet described the risk factor for residual viremia of this therapeutic regimen based on 2 NNRTIs and 1 NRTI, however Zhang *et al.,* (2020) reported in their studies that the risk of viremia low level is due to the combination zidovudine/lamivudine/nevirapine which was 2.26 times higher and that this low level viremia was even higher with protease inhibitors (PI) than with regimens based on NNRTI. However, recent studies by Rello *et al.,* (2022) and Hsu *et al.,* (2022) have shown that diets based on integrase inhibitors (INSTI) present a higher risk than those based on NNRTIs.

The majority of patients included in our study were well compliant with a percentage of 92.59%. On the other hand, 7.40% of patients were not compliant, among them 25% had episodes of low-level residual viremia. On the other hand, this result could be explained by the fact that despite the free antiretroviral treatment, this has not removed the financial obstacles to compliance; some patients included in this study affirm that due to lack of means of transport they do not were no longer able to go to large PLHIV centers to renew their prescriptions and others confirm to us that due to an insufficient understanding of the disease they turn to traditional treatments in view of abandoning ART.

Some authors also assert that most HIV/AIDS patients do not reveal their HIV status to their loved ones for fear of being stigmatized; hence their inability to obtain support from those close to them Denardo *et al.,* (2022). According to studies conducted by Kao *et al.,* (2021); Rello (2022) who highlighted that almost half of people with low-level residual viremia have poor compliance with antiretroviral treatment.

Table.1 Factors influencing residual replication and virological outcome of participants

Factors influencing RRB	Virological result of patients					95% CI	p-value
	N	RRB	SV	EV	Invalid		
N/Patients /%	108	24(22.22%)	59(54.6%)	21(19.4%)	4(3.70%)		**0.025**
Age groups of patients							
18-28 years old	10(9.0%)	2(20%)	6(60%)	2(20%)	00	[-11.4 ; 6.66]	
29-39 years old	37(34%)	6(16.21%)	23(62.16%)	8(21.62%)	00	[-36.20 ; 25.79]	
40-50 years old	44(41%)	12(27.27%)	21(47.72%)	8(18.18%)	3(6.81%)	[-46.82 ; 35.17]	
51-61 years old	15(14%)	4(26.66%)	9(60%)	1(6.66%)	1(6.66%)	[-17.24 ; 10.75]	
62-72 years old	02(2%)	00	00	2(100%)	00	[-2.70 ; 1.29]	
Initial CV/copies/ml							
<40–200 copies/ml	75(69.44%)	14(18.66%)	54(72%)	5(6.66%)	2(2.66%)	[-77.04 ; 61.83]	**0.006**
201-500 copes/ml	15(13.88%)	6(40%)	5(33.33%)	3(20%)	1(6.66%)	[-17.07 ; 10.68]	
501-999 copiest/ml	18(16.66%)	4(22.22%)	00	13(72.22%)	1(5.55%)	[-20.21 ; 13.10]	
Previous ARV treatment							
Viraday	96(88.88%)	23(23.95%)	54(56.25%)	15(15.26%)	4(4.12%)	[-97.51 ; 80.24]	**0.005**
Duovir N	09(8.33%)	01(11.11%)	03(33.33%)	05(55.55%)	00	[-10.68 ; 5.97]	
Truvada	02(1.85%)	00	02(100%)	00	00	[-2.42 ; 1.27]	
Ataz + Truvada	01(0.92%)	00	00	01(100%)	00	[-0.006 ; 0.14]	
Compliance							**0.014**
Yes	100(92.59%)	22(22%)	57(57%)	18(18%)	3(3%)	[-101.40 ; 83.77]	
No	08(7.40%)	02(25%)	02(25%)	03(37.5%)	1(12.5%)	[-9.65. ; 5.26]	
Year of initiation of treatment/Years							**0.021**
2000-2005	13(12.03%)	03(23.07%)	08(61.53%)	02(15.38%)	00	[-14.97 ; 9.08]	
2006-2010	27(25%)	07(25.92%)	15(55.55%)	04(14.81%)	01(3.70%)	[-29.44 ; 20.55]	
2011-2015	40(37.03%)	06(15%)	21(52.5%)	10(25%)	03(7.5%)	[-42.51 ; 31.54]	
2016-2020	28(25.92%)	08(28.57%)	14(50%)	05(17.85%)	00	[-30.38 ; 21.45]	

Legend: N: This is the number, RRB: Residual low-level replication, SV: Virological success, EV: Virological failure

The factors that influenced residual replication at low levels of viremia were also linked to the year of treatment. In this study, we found that patients who were on ART in the years 2016 to 2020 had a prevalence of 28.57% of low-level residual replication.

Our results are lower than those of 46% published by Ryscavage *et al.,* (2014); Dinoso *et al.,* (2009) and Maldarelli *et al.,* (2007) who found that residual replication was stable in PLHIV on ART stable for more than 11 years. They affirm that this prevalence is due to the drug pressure which pushed the virus towards the reservoirs of the RR which are the sanctuary (Central Nervous System) and independent anatomical reservoirs (intestines, lymphoid tissues, genital compartments and the lymphoid system). Antiretroviral therapy does not have perfect effectiveness in these reservoirs, and does not block viral spread 100%. The objective of this study was to determine the factors influencing the residual replication of patients infected with HIV-1 on Tenofovir, Lamuvidine and Dolutegravir (TLD) followed at the Polyvalent Al-Nadjima/APMS center in N'Djamena, Chad. This study showed that age, a high initial baseline viral load, previous ARV treatment and notion of compliance were also factors influencing the occurrence of residual replication. Although there is no consensus on the management of residual viremia in current guidelines. But based on the existing strategy, we suggest that the scope of residual viremia surveillance be expanded by conducting further studies on the prevalence of viremia

in Chad, its causes, clinical significance and management strategies. burden, with subsequent unified management guidelines, this should facilitate virological control as well as the development of new therapeutic regimen strategies.

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Authors Contributions

Asbagui Faysala Oscar: Designed the research protocol, Naibi Keitoyo Amedé and Brahim Boy Otchom: Revised the research protocol, Asbagui Faysala Oscar and Ahmat Mahamat Ahmat: Carried out the collection and processing of the samples, Ahmat Mahamat Ahmat and Mahamat Nour Aguid: Supervised the analysis of the samples, Asbagui Faysala Oscar and Naibi Keitoyo Amedé: Analyzed and interpreted the results, Nan-Arabe Lodoum, Moudine Ouadjonre François and Mahamat Koulbou Abdoulaye: Have reread and made their corrections to the document, Asbagui Faysala Oscar, Naibi Keitoyo Amedé and Brahim Boy Otchom: Approved the final version of the document.

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Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical Approval Ethical authorization for this study was obtained from the National Bioethics Committee of Chad (CNBT).

Declaration of informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of Interest The authors declare no competing interests.

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