

Full Length Research Paper

Factors associated with viral suppression and rebound in adult HIV patients on antiretroviral therapy

Diemer Saint Calvaire Henri^{1*}, Longo Jean de Dieu², Woromogo Sylvain Honore³,
Doyama-Woza Rodrigue Herman², Fandema Emmanuel² and Gérard Grésenguet²

¹Department of Continuing Education, Faculty of Health Sciences, University of Bangui, Bangui.

²Department of Public Health, Faculty of Health Sciences, University of Bangui, Bangui.

³Communicable Diseases Unit, Interstate Center for Higher Education, Central African Public Health, Brazzaville.

Received 15 October, 2023; Accepted 30 November, 2023

Suppression of viral load and its maintenance are necessary for reducing morbidity and mortality linked to HIV infection. The present study aims to investigate the factors associated with viral load rebound in adults receiving antiretroviral treatment. The study was conducted in two outpatient treatment centers (CTAs) in Bangui. This cross-sectional analytical study was conducted from August 1 to 31, 2023. The study population comprised people living with HIV, followed by the two CTAs. This includes people living with HIV aged 18 and over, with at least two viral load results, the first of which is suppressed and who have agreed to participate in the study. The data were collected using an individual questionnaire designed and previously tested for clarity and length and through patient records. A total of 458 people living with HIV on antiretroviral treatment were enrolled in the study. The average age of our population was 42 years (± 9). Among the 458 participants with a suppressed viral load, 78(17%) experienced a virological rebound. The main factors associated with the rebound in viral load were transport difficulties, poor compliance with treatment, and a poor perception of the concept of suppressed viral load. This study revealed that the poor perception of viral load and transport difficulties were associated with the rebound. Efforts must be made by the National AIDS Control Program to scale up the multi-month dispensation of antiretrovirals. Each clinic should put in place an adherence-improving self-management strategy system. Finally, the quality of the messages to be provided to patients must be improved to avoid confusion.

Key words: Rebound viral load, adult, Bangui.

INTRODUCTION

UNAIDS data shows that 39 million people worldwide are living with HIV infection (UNAIDS, 2022). With the goal of its elimination by 2030, UNAIDS has set global targets

known as "95-95-95" in 2021. The third "95" involves suppressing viral load, a crucial condition for reducing morbidity and mortality linked to HIV infection. People

*Corresponding author. E-mail: diemerhenri@yahoo.fr.

living with HIV (PLWH) can now expect a life expectancy similar to that of individuals without HIV, provided they achieve and maintain viral suppression, making HIV a chronic and manageable disease (Lima et al., 2007). Non-adherence to antiretroviral therapy (ART) increases the likelihood of poor virologic outcomes, including viral nonsuppression, virologic rebound, disease progression, and HIV transmission, including the transmission of drug-resistant virus (Carrieri et al., 2003).

In the Central African Republic (CAR), the prevalence of HIV infection is estimated at 3.4% among adults aged 15 to 49, in a population estimated at 6,091,097 inhabitants in 2022 (National Committee for the Fight Against AIDS, 2023-2027). According to the "95-95-95" cascade, 58.7% of people living with HIV know their status, 49% know their status and are on antiretroviral treatment, and 37.4% have a viral load (National Committee for the Fight against AIDS, 2023-2027). Since 2021, the National AIDS Control Program has adopted a new first-line therapeutic regimen based on the combination of Dolutegravir and differentiated service delivery (DSD) models for treatment, notably the multi-month dispensation was adopted to facilitate the achievement of global targets.

To enhance the quality of life for people living with HIV (PLHIV), maintaining viral load suppression for as long as possible is crucial. This necessitates good compliance with treatment and support for patients on antiretroviral treatment. According to some studies, patients who had achieved viral suppression experienced a rebound in their viral load (Opoku et al., 2022; Mainaa et al., 2020). In CAR, no study has been conducted on the rebound of the viral load. In this context, the study aims to examine the factors associated with the rebound of the viral load in adults receiving antiretroviral treatment.

PATIENTS AND METHODS

Setting and type of study

The study was conducted in two outpatient treatment centers (CTA) in Bangui, the two major structures for caring for PLHIV in the CAR, with a large active queue. This cross-sectional analytical study was conducted from August 1 to 31, 2023.

Study population

The study population consisted of individuals living with HIV, who were patients at the two CTAs. All patients with HIV aged 18 and over, possessing at least two viral load results, were included. The first of these results should indicate viral suppression, and participants must have agreed to participate in the study.

Sampling and variables studied

Any individual meeting the inclusion criteria and attending a consultation during the study period was included in the study. The main variables studied included:

1. Dependent variable: Viral load (defined as suppressed when lower than 1000 copies/ml and not suppressed when greater than 1000 copies/ml, according to WHO Guidelines (2017a, b).
2. Independent variables: Age, gender, marital status, profession, level of education, clinical stage, dates and results of viral load at 12 months, 24 months, 36 months, and 48 months, level of compliance, multi-month dispensation, presence of comorbidity, and the patient's perception of the notion of suppressed viral load.

Collection of data

Patients are recruited during their visit for treatment renewal after their informed consent. A nurse checks the patients' viral load results in their file. Patients meeting the inclusion criteria are referred to a medical student to collect the information. The data were collected using an individual questionnaire designed and previously tested for clarity and length and through patient records.

Data analysis

The data has been entered and analyzed using Epi info version 7 software. Bivariate analyses were conducted using Pearson's Chi-square test. The Chi-square test was used to compare proportions. A p value < 0.05 is considered statistically significant. Measures of association were estimated by the odds ratio (OR) and their 95% confidence interval (CI). The variables with a significant link with the variable to be explained were introduced into a multivariate model.

Ethical considerations

The study was carried out in strict compliance with the free and informed consent of patients and anonymity (the names of the participants are not mentioned on the questionnaires). Ethical approval was requested from the Ethics Committee of the Faculty of Health Sciences, University of Bangui.

RESULTS

Socio-demographic characteristics

A total of 458 people living with HIV and undergoing antiretroviral treatment were enrolled in the study. The average age of our population was 42 years (± 9), ranging from 18 to 74 years. Subjects aged 38 to 58 constituted the largest group, accounting for 56.3% of the participants. The population was predominantly composed of female subjects (68.1%). From an educational perspective, 67.7% of participants had attained a secondary level of education, and 60.7% were employed in the informal sector. Lastly, 63.8% of patients were living as a couple (either married or in a common-law relationship), and 21% reported facing challenges in covering transportation costs to reach the treatment center (Table 1).

Clinical, therapeutic and biological characteristics at the initiation of antiretroviral treatment

This study classified 62.9% of patients as WHO stage 1

Table 1. Distribution of participants according to their socio-demographic characteristics.

Item	Numbers (n=458)	Percent
Age in year		
18-38	154	33.6
38-58	258	56.3
58-78	46	10.1
Sex		
Women	312	68.1
Man	146	31.9
Educational level		
University	94	20.5
Secondary	310	67.7
Primary	44	9.6
Unschoolled	10	2.2
Professional situation		
Informal sector	278	60.7
Public/Private employee	120	26.2
Agropastoral sector	10	2.2
Pupil/Student	28	6.1
Unemployed	22	4.8
Marital status		
Couple (married or common-law)	292	63.8
Alone (single, widower)	166	36.2
Difficulty of transportation		
Yes	96	21.0
No	362	79.0

or 2 at treatment initiation. Approximately, 38.4% presented opportunistic infections, represented by tuberculosis (34 cases, or 38.6%), digestive candidiasis (18 cases, or 20.5%), polymyalgia (16 cases, or 18.2%), chronic diarrhea (14 cases, or 15.9%), and skin diseases (6 cases, or 6.8%). At initiation, most patients were on Tenofovir/Emtricitabine/Efavirenz (TDF/FTC/EFV) and Tenofovir/Lamivudine/Dolutegravir (TDF/3TC/DTG) combinations (Table 2).

Follow-up of patients after one year of treatment

In this series, 45.9% of patients received antiretroviral therapy for 5 years and 21.4% for 2 years. The presence of comorbidities was noted in 15 (6.6%) patients. These include high blood pressure and diabetes. All 346 patients (75.5%) on other treatment regimens were placed on dolutegravir-based combination therapy. Approximately, 71.2% of patients were considered compliant during the study (Table 3).

Results of the last viral load and patients' perception of the concept of "suppressed viral load"

Among the 458 participants with suppressed viral load, 78 (17%) experienced a virological rebound. Regarding the perception of the concept of suppressed viral load, 392 participants (85.6%) declared that this means that the viral load is reduced below a threshold and that the virus remains in the body; however, 66 participants (14.4%) think that the virus has completely disappeared in the body.

Factors associated with viral load rebound

In Univariate analysis, the following parameters were associated with the rebound: educational level, marital status, difficulty of transportation, compliance with treatment and poor perception of the concept of suppressed viral load. In multivariate analysis the following factors were associated with the rebound:

Table 2. Distribution of participants according to their clinical, therapeutic and biological characteristics at the initiation of antiretroviral treatment.

Item	Numbers (n=458)	Percent
WHO clinical stage		
Stage 1	168	36.7
Stage 2	120	26.2
Stage 3	134	29.3
Stage 4	36	7.9
Presence of opportunistic infections		
Yes	176	38.4
No	282	61.6
Therapeutic protocol		
TDF/FTC/EFV	246	53.7
TDF/3TC/DTG	112	24.5
AZT/3TC/NVP	62	13.5
AZT/3TC/EFV	28	6.1
ABC/3TC/NVP	10	2.2

Table 3. Distribution of participants according to their follow-up after one year of treatment and last viral load result.

Item	Numbers (n=458)	Percent
Time elapsed after start of treatment		
2	98	21.4
3	80	17.5
4	70	15.3
5	210	45.9
Presence of comorbidity		
Yes	30	6.6
No	428	93.4
Compliance at time of survey		
Yes	326	71.2
No	172	28.8

difficulty of transportation (OR = 4.27 [2.32-7.88], $p = 0.030$), poor adherence (OR = 0.90 [0.02-0.69], $p = 0.000$) and poor perception of the concept of suppressed viral load (OR = 7.19 [4.05-15.25], $p = 0.001$) (Table 4).

DISCUSSION

The present study aimed to determine the proportion of people living with HIV who experienced a rebound in viral load after suppression and the associated factors. In this study, 17% of participants showed a rebound after viral load suppression. This proportion is higher than that

reported by Craw et al. (2020) in the USA and lower than that reported by Opoku et al. (2022) and Mainaa et al. (2020) in Ghana and Kenya, respectively.

According to the "95-95-95" cascade in CAR, only 37.4% of patients on antiretroviral treatment had a suppressed viral load in 2022 (National Committee for the Fight Against AIDS, 2023-2027). If a few people living with HIV with a suppressed viral load are unable to maintain it, it poses a danger both to themselves, as they are exposed to the risk of mortality, and to the population due to the risk of disease transmission.

This study did not highlight a significant link between viral load rebound and gender. Some studies have found

Table 4. Factors associated with viral load rebound.

Determinants	Bounce	No Bounce	GOLD (95% CI)	p	ORa (95% CI)	p
Age (year)						
[18-38]	32	122	1		-	-
[38-58]	42	216	1.35 [0.81-2.25]	0.250	-	-
[58-78]	4	42	2.75 [0.92-8.25]	0.061	-	-
Sex						
Male	28	118	1	0.401	-	-
Feminine	50	262	1.24 [0.75-2.07]	-	-	-
Educational level						
Never and primary	22	32	1	0.000	1	0.154
Secondary and higher	56	348	4.27 [2.32-7.88]	-	2.71 [0.69-5.47]	-
Marital status						
Living as a couple	40	252	1	0.012	1	0.088
Living all alone	38	128	0.53 [0.33-0.88]	-	0.75 [0.28-3.29]	-
Difficulty of transportation						
Yes	40	56	1	0.000	1	0.030
No	38	324	6.09 [3.60-10.31]	-	4.27 [2.32-7.88]	-
WHO clinical stage						
1 & 2	44	244	1	0.194	-	-
3 & 4	34	136	0.72 [0.44-1.18]	-	-	-
Treatment regimen at initiation						
DTG-based association	20	92	1	0.789	-	-
Association based on EFV or NVP	58	288	1.08 [0.62-1.89]	-	-	-
Presence of comorbidity						
Yes	6	24	1	0.654	-	-
No	72	356	1.24 [0.49-3.13]	-	-	-
Compliance with treatment						
Yes	8	318	1	0.000	1	0.000
No	70	61	0.02 [0.01-0.05]	-	0.09 [0.02-0.69]	-
Perception of the concept of suppressed viral load						
Reduction of viral load	38	28	1	0.000	1	0.001
Total disappearance of the virus	40	352	11.94 [6.64-21.49]	-	7.19 [4.05-15.25]	-

that women are more likely to experience rebound, while others have reported the opposite (Craw et al., 2020; Henrich et al., 2012; Palmer et al., 2018; Mujugira et al., 2016). Age is an important factor in decision-making in this work; adults aged 39 and over were more likely to have a rebound in viral load than those under 39. However, the study did not find a significant link between age and rebound. This result corroborates that of Palmer (2018) and differs from Craw et al. (2020) who demonstrated a more significant risk in subjects under 39 years and Mujugira et al. (2016) who showed that the risk increases with age.

Educational level and marital status were not significantly associated with the risk of rebound, consistent with the results of other studies carried out in Africa (Okopu et al., 2022; Mainaa et al., 2020). Transport difficulties were found to be associated with viral load rebound. Easy access to the treatment center is crucial for determining compliance with antiretroviral treatment. In this context, the WHO recommends differentiated approaches to the provision of care to people living with HIV, particularly the multi-month dispensation of antiretroviral drugs, which can limit the number of patient visits to treatment centers (Mujugira et al., 2016). In CAR, differentiated approaches are only implemented in certain pilot centers. This study found a significant link between transport difficulties and viral load rebound.

The results of the present study differ from those of Okopu et al. (2022) and Mainaa et al. (2020), who found a link, in particular, with the advanced clinical stages (II to IV) of the WHO. The study did not highlight a significant link between initial treatment and viral load rebound. This finding differs from that of Palmer et al. (2018) who found a link between the rebound of the viral load and the initiation of treatment with non-boosted protease inhibitors, and those of Taner et al. (2016), Okopu et al. (2020), and Mainaa et al. (2020) who found a link between the rebound and initiation of treatment with non-nucleoside reverse transcriptase inhibitors. In 2019, 12 of 18 countries included in a WHO-led survey of non-nucleoside reverse transcriptase inhibitors (Efavirenz and Nevirapine) reported levels of pre-treatment drug resistance exceeding the recommended threshold of 10%. Thus, the WHO has recommended Dolutegravir, an integrase inhibitor, as a first and second-line treatment (WHO, 2021). This result could be explained by the fact that since 2021, almost all patients have been switched to combination therapy based on Dolutegravir.

Comorbidities were not significantly associated with viral load rebound, which aligns with the results of Opoku et al. (2022). Compliance with treatment is a crucial element for the success of treatment. The present work found a significant link between non-compliance with treatment and the rebound in viral load, corroborating the results of several authors (Opoku et al., 2022; Mainaa et al., 2020; Bulage et al., 2017; O'Connor et al., 2017).

During this study, patients' perceptions of suppressed

viral load were investigated. Some patients with a suppressed load believe that the virus has completely disappeared from the body.

This misconception may lead patients to relax compliance with treatment. This study found a significant link between a misperception of the concept of suppressed viral load and the rebound of viral load. This emphasizes the need for those responsible for therapeutic education to review their messages.

Limitation of the study

This study has several limitations. Notably, it did not consider the duration of antiretroviral treatment and the level of initial viral suppression. Nevertheless, the findings hold valuable implications for clinicians and those overseeing the AIDS control program.

Conclusion

The study uncovered associations between poor perception of viral load and transport difficulties with viral rebound. To address these issues, the National AIDS Control Program should intensify efforts to expand the multi-month dispensation of antiretrovirals, aiming to reduce transportation costs to treatment centers. Enhancing viral suppression and minimizing rebound could be achieved by implementing adherence-improving self-management strategy systems in each clinic. Such systems have demonstrated effectiveness in reducing viral loads, increasing quality-adjusted life-years, and saving resources (De Bruin et al., 2017). Additionally, there is a crucial need to enhance the quality of messages provided to patients to prevent confusion.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

REFERENCES

- Bulage L, Ssewanyana I, Nankabirwa V, Nsubuga F, Kihembo C, Pande G (2017). Factors associated with virological non-suppression among HIV positive patients on antiretroviral therapy in Uganda, August 2014–July 2015. *BMC Infectious Diseases*. 17(1):1-11.
- Carrieri MP, Raffi F, Lewden C (2003). Impact of early versus late adherence to highly active antiretroviral therapy on immunovirological response: A 3-year follow-up study. *Antiviral Therapy* 8:585-594.
- Craw JA, Beer L, Tie Y, Jaenicke T, Shouse RL, Prejean J (2020). Viral rebound among persons diagnosed with HIV who achieved viral suppression, United States. *Journal of Acquired Immune Deficiency Syndromes* 84(2):133-140. <https://doi.org/10.1097/QAI.0000000000002321>.
- De Bruin M, Oberjé EJM, Viechtbauer W, Nobel HE, Hilgsmann M, van Nieuwkoop C (2017). Effectiveness and cost-effectiveness of a nurse-delivered intervention to improve adherence to treatment for HIV: a pragmatic, multicentre, open-label, randomised clinical trial.

- Lancet Infectious Diseases 17(6):595-604.
- Henrich TJ, Wood BR, Kuritzkes DR (2012). Increased risk of virologic rebound in patients on antiviral therapy with a detectable HIV load <48 copies/ml. PLoS ONE 7(11):e50065.
- Lima VD, Hogg RS, Harrigan PR (2007). Continued improvement in survival among HIV-infected individuals with newer forms of highly active antiretroviral therapy. AIDS 21:685-892.
- Mainaa EK, Mureithia H, Adana AA, Muriukib J, Lwembab RM, Bukusia EA (2020). Incidences and factors associated with viral suppression or rebound among HIV patients on combination antiretroviral therapy from three counties in Kenya. International Journal of Infectious Diseases 97(1):151-158
- Mujugira A, Celum C, Tappero JW, Ronald A, Mugo N (2016). Younger Age Predicts Failure to Achieve Viral Suppression and Virologic Rebound Among HIV-1-Infected Persons in Serodiscordant Partnerships. AIDS Research and Human Retroviruses 32(2):148-154.
- National Committee for the Fight against AIDS (2023-2027). National strategic plan to combat HIV and AIDS in the Central African Republic.
- O'Connor J, Smith C, Lampe FC, Johnson MA, Chadwick DR, Nelson M (2017). Durability of viral suppression with first-line antiretroviral therapy in patients with HIV in the UK: an observational cohort study. Lancet HIV 4(7):e295-302.
- Opoku S, Asamoah Sakyi S, Kwame Ayisi-Boateng N, Kwame Enimil A, Senu E, Owusu Ansah R (2022). Factors associated with viral suppression and rebound among adult HIV patients on treatment: a retrospective study in Ghana. AIDS Research and Therapy 19:21.
- Palmer A, Gabler K, Rachlis B, Ding E, Chia J, Bacani N (2018). Viral suppression and viral rebound among young adults living with HIV in Canada. Medicine 97(22):e10562.
- Taner Z, Lachowsky N, Ding E, Samji H, Hull M, Cescon A (2016). Predictors of viral suppression and rebound among HIV-positive men who have sex with men in a large multi-site Canadian cohort. BMC Infectious Diseases 16:590. DOI 10.1186/s12879-016-1926-z.
- UNAIDS (2022). Global AIDS Update Report 2022. License: CC BY-NC-SA 3.0 IGO. Available at: www.unaids.org/en/resources/documents/2022/in-danger-global-aids-update
- World Health Organization (WHO) (2021). Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization. License: CC BY-NC-SA 3.0 IGO. Available at: <http://www.who.int/publications-details-redirect/WHO-HIV-2021>
- World Health Organization (WHO) (2017). Key considerations for differentiated delivery of antiretroviral treatments to special populations: children, adolescents, pregnant or lactating women and key populations. Geneva: World Health Organization; (WHO/HIV/2017.34). License: CC BY-NC-SA 3.0 IGO. Available at: <http://www.who.int/publications-details-redirect/WHO-HIV-2017.34>