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ORIGINAL ARTICLE

Predictors of Low-Level Viremia in People Living with HIV with Unsuppressed Viremia, A Retrospective Follow-up Study in Izmir

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Abstract

Introduction: Globally, approximately 40 million people are living with HIV (PWH), with a new HIV infection occurring every 2 minutes. In Türkiye, the number of PWH is increasing, posing challenges to achieving national-level virological suppression goals. Current antiretroviral therapies (ART), tailored to individual people with HIV, have significantly improved viral suppression and maintenance. However, some individuals experience low-level viremia (LLV) despite adherence to consistent drug therapy. This study aims to identify the determinants and implications of LLV and ART management strategies.

Methods: The study was conducted through a retrospective analysis of electronic medical records of 830 PWH followed at the Izmir Tepecik Training and Research Hospital of Health Sciences University over a 10-year period. Demographic characteristics, definitions of unsuppressed viremia, and ART regimens of the PWH included in this study were evaluated.

Results: Low-level viremia was diagnosed in 17.1% of the 99 PWH with unsuppressed viremia enrolled in the study. The presence of comorbidities was found to have a significant impact on the development of low-level viremia. Additionally, it was observed that individuals with LLV had lower rates of virological suppression compared to other groups.

Discussion and Conclusion: This study evaluated the determinants of low-level viremia in people living with HIV and highlighted the presence of comorbidities and the importance of individualized treatment approaches. Further research is needed to effectively manage low-level viremia in PWH.

Keywords: HIV; low-level viremia; Risk factors; Unsuppressed viremia.

Untreated HIV infection poses multifaceted challenges at both individual and public health levels due to its high transmissibility. Current global estimates indicate a staggering 40 million individuals living with HIV, with a new infection occurring every two minutes[1]. Within Türkiye, recent data from the Ministry of Health reveal approximately 39,437 individuals living with HIV, with around 5,600 new diagnoses within the past year[2]. In December 2020, UNAIDS published goals aiming for 95% of all people living with HIV to know their HIV status, 95% of those diagnosed with HIV to receive continuous antiretroviral treatment (ART), and 95% of those receiving treatment to achieve and sustain viral suppression[3]. The results of studies conducted in Türkiye, showing

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percentages of 48–50% for the first 95, 86–88% for the second 95, and 70–87% for the last 95, are challenging at the national level[4,5]. Despite the high rates of virological success among individuals diagnosed and treated for HIV, there is still a need for efforts to achieve viral suppression targets.

Today, personalized antiretroviral therapies have significantly improved viral suppression and maintenance rates. However, in some individuals, despite consistent medication adherence and the absence of drug interactions and genotypic resistance, low-level viremia (LLV) becomes apparent during follow-up.

In this study, our aim was to investigate cases of people with HIV (PWH) exhibiting LLV characteristics followed in our center, to identify potential risk factors for LLV, examine its effects on the development of future virological failure, and discuss related ART management strategies.

Materials and Methods

Study Setting and Design: We conducted a cross-sectional retrospective cohort study using electronic medical records of 830 HIV-infected individuals followed between October 1, 2013, and October 1, 2023 (a period of 10 years) at the Department of Infectious Diseases and Clinical Microbiology, Health Sciences University (HSU) Izmir Tepecik Training and Research Hospital. Inclusion criteria for the study cohort included confirmed HIV diagnosis, age 18 years and older, and individuals who met the definition of unsuppressed viremia at any time during their follow-up. The case group was selected by including individuals who were defined as having unsuppressed viremia within the study cohort. Individuals who exhibited different definitions of unsuppressed viremia during follow-up or showed consistent processes corresponding to the same definition at different times were included based on their variables at the time they matched the definition of unsuppressed viremia.

Study Definitions and Variables

The current success of ART is measured by the complete suppression of HIV replication in treated individuals. Failure to stop virus replication within 6 months in individuals receiving antiretroviral therapy is defined as unsuppressed viremia[6,7]. Definitions of virologic failure in our study were planned according to national and international guidelines. Virological suppression was defined as a confirmed HIV-RNA level below the lower limits of detection of available assays (<50 copies/mL), virologic failure was defined as the inability to achieve or maintain suppression of viral replication to HIV-RNA level <200 copies/mL, incomplete virological response was defined as two consecutive plasma HIV-RNA levels ≥200 copies/mL after 24 weeks on an ARV regimen in an individual who has not yet had documented virologic suppression on that regimen, virological rebound was defined as after virologic suppression, confirmed HIV-RNA level ≥200 copies/mL, virological blip was defined as after virologic suppression, an isolated detectable HIV-RNA level that is followed by a return to virologic suppression (<50 copies/mL), and low-level viremia was defined as HIV RNA level being detectable (≥50 copies/mL) in two or more measurements but remaining at <200 copies/mL [7,8]. Current viremic status of the individual was defined by HIV RNA levels at the last visit, with HIV RNA <50 copies/mL considered suppressed. A history of international travel within the year prior to meeting the definition of unsuppressed viremia indicates at least one international trip taken within the last year before the defined period. Staging of the infection is based on the CD4+ T lymphocyte count and percentage detected at the individual's initial presentation, along with the clinical conditions present at the time of presentation[9].

Statistical Analysis

Individual data collected within the scope of the study were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) for MacOS 29.0 (IBM Corp., Armonk, NY) software package. Frequency and percentage were given as descriptive statistics for categorical variables, while median (interquartile range) was used for continuous variables. The Mann-Whitney U test was used for intergroup comparisons, and the Chi-square test or Fisher's Exact test was used for comparing categorical variables. Logistic regression analysis was used to examine predictors of low-level viremia. Results were considered statistically significant when the p-value was less than 0.05.

The study was approved by the Ethics Committee of Health Sciences University (HSU) Izmir Tepecik Training and Research Hospital on May 4, 2023, with decision number 2023/03 – 19. All procedures were in accordance with the ethical standards of our institution's human experiment committee and the Helsinki Declaration.

Results

Among 830 PWH followed up in our center, 99 (11.9%) experienced an unsuppressed viremic process and were included in our study. Low-level viremia was diagnosed in 17 (17.1%) of these cases, and the median age of the

study group was 42 (32-48) years. Among the individuals, 31.3% were married and 89% were male. The mean duration of follow-up for PWH in the study cohort was 75.8 months (12-300), with no significant difference in the duration of follow-up between the two groups compared. Upon examination of other sub-definitions of unsuppressed viremia, it was observed that 29 individuals had virological rebound (29.3%), 21 each had incomplete virological response and virological blip (21.2%), and 11 had virological failure (11.1%). Descriptive statistics for all variables evaluated in the study are presented in Table 1.

The analysis showed that the presence of comorbidities in individuals was significantly correlated with the development of low-level viremia compared to other sub-definitions of unsuppressed viremia. Additionally, it was shown that individuals with LLV had a statistically lower rate of virological suppression/success compared to other definitions of unsuppressed viremia during follow-up.

The types of comorbidities present in PWH with unsuppressed viremia and their significant impact on the development of low-level viremia were examined, revealing that the presence of any comorbidity did not

Table 1. Distribution of Demographic and Clinical Findings of Unsuppressed Viremic PWH

Variables	Total (n=99) n (%) or Median (IQR*)	Other (n=82) n (%) or Median (IQR*)	Low-level viremia (n=17) n (%) or Median (IQR*)	p*
Age (years)	42 (32-48)	41.5 (32-49)	43 (32-47)	0.623
Gender				1.000
Male	89 (89.9)	73 (89)	16 (94.1)	
Woman	10 (10.1)	9 (11)	1 (5.9)	
Marital status				0.509
Married	31 (31.3)	27 (32.9)	4 (23.5)	
Single	68 (68.7)	55 (67.1)	13 (76.5)	
Education status				0.436
Illiterate	1 (1)	1 (1.2)	0 (0)	
Primary School	39 (39.4)	33 (40.2)	6 (35.3)	
Middle School	18 (18.2)	17 (20.7)	1 (5.9)	
High School	19 (19.2)	15 (18.3)	4 (23.5)	
University	22 (22.2)	16 (19.5)	6 (35.3)	
Alcohol consumption	53 (53.5)	43 (52.4)	10 (58.8)	0.831
Smoking	55 (55.6)	48 (58.5)	7 (41.2)	0.297
Substance dependence	14 (14.1)	12 (14.6)	2 (11.8)	1.000
Travel abroad	14 (14.1)	12 (14.6)	2 (11.8)	1.000
Baseline CD4+ T- lymphocyte (Cell/mm3)	300 (92-465)	300 (124-460)	222 (70-465)	0.448
Nadir CD4+ T lymphocyte (Cell/mm3)	261 (78-465)	267 (90-482)	163 (70-414)	0.567
Baseline HIV RNA (x103) (copies/mm3)	336 (91.2-1130)	318.5 (73.2-972)	525 (184-1920)	0.947
Presence of comorbidity	55 (55.6)	40 (48.8)	15 (88.2)	0.007
Presence of OI	24 (24.2)	20 (24.4)	4 (23.5)	1.000
Stages of HIV				0.873
Stage-1	19 (19.2)	16 (19.5)	3 (17.6)	
Stage-2	39 (39.4)	33 (40.2)	6 (35.3)	
Stage-3	41 (41.4)	33 (40.2)	8 (47.1)	
Side effect	1 (1)	1 (1.2)	0 (0)	1.000
Number of Co-medication pills	2 (1-4)	2 (1-4)	2 (2-5)	0.623
Presence of Co-medication	44 (44.4)	35 (42.7)	9 (52.9)	0.612
Current viremia status**				0.013
Suppressed	66 (67.3)	60 (73.2)	6 (37.5)	
Unsuppressed	32 (32.7)	22 (26.8)	10 (62.5)	

IQR: Interquartile Range; ART: Antiretroviral treatment; LLV: Low-level viremia; OI: Opportunistic infection; *p-value ≤0.05 is considered statistically significant. ** HIV RNA <50 copies/mL was defined as suppressed. One patient in the LLV group was lost to follow-up.

Table 2. Distribution of Comorbidities in Unsuppressed Viremic PWH

	Total n (%)	Other n (%)	Low-level viremia n (%)	p*
Comorbidities				
DM	8 (8.1)	5 (6.1)	3 (17.6)	0.136
HT	6 (6.1)	5 (6.1)	1 (5.9)	1.000
Dyslipidemia	12 (12.1)	10 (12.2)	2 (11.8)	1.000
CAD	4 (4)	3 (3.7)	1 (5.9)	0.535
Syphilis	34 (34.3)	29 (35.4)	5 (29.4)	0.849
TB	10 (10.1)	9 (11)	1 (5.9)	1.000
Hep B	2 (2)	2 (2.4)	0 (0)	1.000
Malignancy	4 (4)	2 (2.4)	2 (11.8)	0.135
Osteopenia/Osteoporosis	13 (13.1)	10 (12.2)	3 (17.6)	0.692
Psychiatric disorders	10 (10.1)	8 (9.8)	2 (11.8)	0.680
Epilepsy	5 (5.1)	3 (3.7)	2 (11.8)	0.203

DM: Diabetes Mellitus; HT: Hypertension; CAD: Coroner artery disease; TB: Tuberculosis; Hep B: Hepatitis B. *p value ≤0.05 was considered statistically significant.

Table 3. Distribution of Antiretroviral treatment in Unsuppressed Viremic PWH

Variables	Total n (%)	Other n (%)	Low-level viremia n (%)	p*
Initial ART classification 1				0.514
Integrase inhibitors	78 (78.8)	63 (76.8)	15 (88.2)	
Other	21 (21.2)	19 (23.2)	2 (11.8)	
Initial ART classification 2				1.000
Next-generation Integrase inhibitors	40 (40.4)	33 (40.2)	7 (41.2)	
Other	59 (59.6)	49 (59.8)	10 (58.8)	
Classification during unsuppressed viremia 1				1.000
Integrase inhibitors	87 (87.9)	72 (87.8)	15 (88.2)	
Other	12 (12.1)	10 (12.2)	2 (11.8)	
Classification during unsuppressed viremia 1				0.563
Next-generation Integrase inhibitors	50 (50.5)	43 (52.4)	7 (41.2)	
Other	49 (49.5)	39 (47.6)	10 (58.8)	

ART: Antiretroviral treatment, LLV: Low-level viremia; *p-value ≤0.05 is considered statistically significant. ** Bictegravir, Dolutegravir.

have a statistically significant effect on LLV development (Table 2). Due to insufficient numbers, statistical analysis for rare comorbidities in our cases was not feasible, and only descriptive analysis was performed (Supplementary Table).

The ART regimens used by individuals with unsuppressed viremia in our study were evaluated, and the significant differences in treatment options among PWH with LLV were investigated. It was demonstrated that whether the initial treatment given to individuals at the time of diagnosis belonged to the integrase inhibitor class or not, or specifically whether it belonged to the new generation integrase class or not, did not result in statistical significance in terms of LLV development. Furthermore, when analyzing the ARTs used by individuals during periods that met the definition of unsuppressed viremia, similar findings were observed; the use of integrase inhibitor class drugs or more specifically, new generation integrase inhibitors, did not show significant differences in the LLV group (Table 3).

While comorbidity and failure to achieve viral suppression during follow-up were identified as significant variables in the univariate analysis, no variable yielded statistically significant results in the multivariate analysis.

Discussion

This study aims to evaluate the determinants of low-level viremia in PWH with unsuppressed viremia. Our results indicate that out of the 99 individuals included in the study with unsuppressed viremia, 17 (17.1%) were diagnosed with low-level viremia. This finding is consistent with previously reported rates in the literature[10-13].

In our study, demographic variables such as age, gender, and educational status did not play a statistically significant role among the determinants of low-level viremia, suggesting that the social dimension of demographic characteristics in HIV management should be considered from a broader perspective[14]. However, the presence of comorbidities was found to have a statistically significant effect on the development of low-level viremia in univariate analysis. These results emphasize the critical importance of managing comorbidities in individuals undergoing HIV treatment for the control of low-level viremia[13-15].

On the other hand, the examination of ART options found that the treatment options received by individuals with low-level viremia did not differ significantly from those of other groups. This finding suggests that specific classes of antiretroviral drugs may not be preferred in the management of low-level viremia, considering the effective ART options with high resistance barriers and rapid viral suppression available today, but rather treatment should be managed with a personalized approach[7,14].

The fact that viral suppression in the follow-up of PWH with low-level viremia was significantly lower than in individuals with non-suppressible viremia shows the importance of conducting studies with a similar methodology to our study and determining possible predictors[16].

A strength of this study is that it was conducted in an experienced clinical setting in HIV healthcare, with clinicians following current literature on the management of unsuppressed viremia and particularly LLV cases.

Limitations of the Study

The study is cross-sectional and single-center, and therefore, the results may not be generalizable due to the limitation of the case set. Our study design was retrospective and relied on existing clinical records; therefore, our results may have been overestimated or underestimated due to the possibility of undocumented additional clinical factors in the medical records.

Conclusion

In conclusion, this study, by evaluating the determinants of low-level viremia in PWH with unsuppressed viremia, emphasizes the importance of the presence of comorbidities and personalized treatment approaches. In light of these findings, further research on a larger scale and in different populations is needed to understand and effectively manage the determinants of low-level viremia in PWH.

Ethics Committee Approval: The study was approved by the Ethics Committee of Health Sciences University (HSU) Izmir Tepecik Training and Research Hospital on May 4, 2023, with decision number 2023/03 – 19. All procedures were in accordance with the ethical standards of our institution's human experiment committee and the Helsinki Declaration.

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