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ORIGINAL RESEARCH

Increased Adiposity and Dyslipidemia in Young Men Living with HIV Compared to Matched PrEP Users: A Cross-Sectional Study

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ABSTRACT

Introduction: This study compares anthropometric, metabolic, cardiovascular, and liver parameters in people living with HIV (PLWH) on antiretroviral therapy (ART), and men on pre-exposure prophylaxis (PrEP) in the same age group.

Methods: This was a single-center, cross-sectional study of males aged 18–50 years, receiving ART for HIV or PrEP for at least 6 months, consecutively enrolled at Policlinico Hospital, Milan. Lifestyle factors were assessed using the International Physical Activity Questionnaire and a food diary. Anthropometric measurements included body mass index (BMI), waist circumference, and bioimpedance analysis. Blood samples were analyzed for glycemic parameters, lipid profile, hepatic enzymes, and adipokines, including leptin. Hepatic steatosis and fibrosis were evaluated using FibroScan®. Group differences were assessed using chi-squared, *t* tests, and Mann–Whitney tests, while logistic regression determined associations with HIV status.

Results: Eighty-two participants were enrolled: 53 PLWH and 29 PrEP users. PLWH had significantly higher BMI, waist circumference, total fat mass, and triglycerides, as well as total and LDL cholesterol. PrEP users engaged in more vigorous-intensity activity, with no differences in dietary habits.

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Among PLWH, higher physical activity was associated with lower HOMA index. Leptin levels were significantly higher in PLWH compared to PrEP users. Multivariate analysis identified LDL cholesterol as independently associated with HIV status. ***Conclusion*****:** PLWH exhibited greater adiposity and dyslipidemia than PrEP users, with leptin emerging as a potential marker of metabolic dysfunction. Higher physical activity was linked to improved insulin sensitivity, underscoring the role of exercise in mitigating HIV-related metabolic dysregulation.

Keywords: HIV; Leptin; Metabolism; Physical activity; PrEP

Key Summary Points

Why carry out this study?

Despite the success of antiretroviral therapy (ART), people living with HIV (PLWH) face an increasing burden of metabolic, cardiovascular, and hepatic comorbidities, related to chronic inflammation and long-term treatment. Pre-exposure prophylaxis (PrEP) users—another population exposed to antiretroviral drugs and often underrepresented in research—may also experience treatment-related metabolic effects.

We aimed to compare anthropometric, metabolic, cardiovascular, and liver parameters between PLWH on ART and PrEP users.

What was learned from the study?

Young men living with HIV showed greater adiposity and a more adverse lipid profile than PrEP users, alongside higher leptin levels, suggesting early metabolic dysregulation.

In PLWH, higher levels of physical activity were associated with improved insulin sensitivity, highlighting exercise as a key modifiable factor to mitigate HIV-related metabolic risk.

INTRODUCTION

HIV infection remains a significant global public health challenge. Antiretroviral therapy (ART) has transformed its natural history, extending lifespan and quality of life for people living with HIV (PLWH). Nevertheless, PLWH still experience higher morbidity and mortality compared to the general population, with a growing burden of cardiovascular, metabolic, and hepatic comorbidities. These chronic complications likely reflect persistent HIV-related inflammation, immune activation, and lifelong exposure to ART.

Given the success of ART and consequent well-being, PLWH currently develop obesity and fat accumulation with ageing, driving a surge in metabolic comorbidities. This shift demands a broader focus on metabolic health beyond viral suppression. Sedentary lifestyles exacerbate visceral fat accumulation, fueling inflammation, while physical activity plays a key role in improving metabolism, reducing cardiovascular risk, and enhancing overall well-being [1].

Another group of people exposed to ART, despite being uninfected, is represented by pre-exposure prophylaxis (PrEP)-users. PrEP with tenofovir/emtricitabine (TDF/FTC) is a highly effective HIV prevention strategy. While PrEP is generally well tolerated, studies have reported mild renal and bone toxicity, particularly in older individuals, though these effects are often reversible upon discontinuation [2].

This study aims to comprehensively assess anthropometric, metabolic, cardiovascular, and liver parameters in young men, comparing PLWH in ART to PrEP users. Additionally, the inflammatory profile of both groups has been evaluated.

METHODS

This single-center, cross-sectional study consecutively enrolled men aged 18–50 years receiving ART for HIV or PrEP for at least 6 months at the Infectious Diseases Clinic of Policlinico Hospital, Milan, from November 2022 to September 2024.

The study population was restricted by design to cisgender men in order to ensure comparability between PrEP users and PLWH, and to minimize confounding related to sex-specific differences in body composition and metabolic profiles. Sex was recorded as male at birth and gender identity as cisgender male for all participants. Patients were referred to the Metabolic Disease Outpatient Clinic for metabolic evaluation. Exclusion criteria are detailed in the Supplementary Materials (Supplementary methods) [3–21].

A comprehensive lifestyle assessment was conducted, including dietary intake through a semi-quantitative food diary. Adherence to the Mediterranean diet was assessed using a 13-point score, assigning 1 point for meeting predefined intake cut-offs for key food groups; participants were classified as having low (0–4), moderate (5–8), or high (9–13) adherence [11]. Physical activity was evaluated using the long-form International Physical Activity Questionnaire (IPAQ), which quantified total activity in metabolic equivalents of tasks-minutes (METs-minutes) and classified participants as having low (≤ 600 METs), moderate (700–2999 METs) or high activity levels (≥ 3000 METs), with vigorous activity specifically assessed as part of the questionnaire [12].

Anthropometric measurements included BMI classification (lean: < 25 kg/m^2, overweight: 25–29.9 kg/m^2, obese: ≥ 30 kg/m^2), waist circumference (elevated if > 94 cm) [13], and bioimpedance analysis to assess total and regional lean and fat mass distribution. Hypertension, type 2 diabetes (T2DM), and dyslipidemia were diagnosed according to International Guidelines and described in supplementary methods.

Fasting blood samples were collected to assess glycemic parameters, lipid profile, kidney function, and liver enzymes. In PLWH, virological and immunological parameters were analyzed. Inflammatory and adipokine profiles were measured using Luminex technology, including assays for chemerin, IL-1β, IL-6, leptin, PBEF/visfatin, resistin, TNF-α, Acrp30/adiponectin and RBP4.

Hepatic steatosis was diagnosed by a controlled attenuation parameter > 248 dB/m at FibroScan® [14]. Metabolic dysfunction associated steatotic liver disease (MASLD) was diagnosed based on the presence of steatosis plus ≥ 1 cardiometabolic risk factor (overweight/obesity, diabetes/prediabetes, hypertension, or dyslipidemia), after excluding other causes of steatotic liver disease [15]. Hepatic fibrosis was assessed by liver stiffness measurement (LSM) > 8 Kpa at Fibroscan [16] and non-invasive fibrosis score (Fibrosis-4 (FIB-4) and FibroScan-AST (FAST) [17].

In participants > 40 years, the SCORE2 cardiovascular risk algorithm was applied to stratify them into low-to-intermediate, high, or very high-risk categories [18]. Eco-Color Doppler of the supra-aortic trunks was performed to evaluate intima-media thickness (IMT) [19], carotid plaques, and stiffness [20]. Transthoracic echocardiography evaluated cardiac anatomy and function and thickness of epicardial fat (normal if < 9.5 mm) [21]. The panel of administered tests and references can be found in the Supplementary methods.

The study was conducted in accordance with the Declaration of Helsinki (1964) and its later amendments; written informed consent to participate and consent for publication were obtained from all participants, and the protocol was approved by the Institutional Review Board of Policlinico di Milano Hospital (protocol code 2581, approval date: 19/09/2022).

Statistical Analysis

Statistical analyses included descriptive statistics, group comparisons using chi-squared, *t* tests, Mann–Whitney, and ANOVA when appropriate. Correlations between variables were analyzed using the Pearson correlation coefficient. Univariable and multivariable logistic regression analyses were performed to identify variables associated with HIV status in the cohort, adjusting for age. Clinically relevant variables were prioritized in collinearity. A two-tailed *p* value of ≤ 0.05 was considered statistically significant. All data were analyzed using Stata version 17 software (StataCorp, College Station, TX, USA).

RESULTS

Eighty-two males were enrolled (median age of 38 years): 53 PLWH and 29 PrEP users. Among PLWH, 85% had a CD4 + lymphocyte count > 500/uL, and 98% were virologically suppressed, with a median ART exposure of 36 months (7–216), predominantly INSTI-based regimens (89%). Among the 53 PLWH, 18 (34%) were receiving a dual-drug antiretroviral regimen and 35 (66%) a triple-drug regimen. PrEP users had a median time of TDF/FTC exposure of 19 months (6–84), with 41% following a daily regimen.

Lifestyle factors such as alcohol consumption, smoking, and adherence to Mediterranean diet were comparable between groups. Physical activity levels showed no significant differences in total activity or IPAQ domain-specific metrics (work, transport, domestic, leisure, walking, or sitting time) between the groups, but higher vigorous physical activity was more frequent in PrEP users compared to PLWH (1920 vs. 1120 METs, $p = 0.041$). A detailed comparison of lifestyle, diet, and physical activity domains is reported in Supplementary Table 1.

PLWH had significantly higher BMI (24.6 vs. 22.9 kg/m^2, $p = 0.015$) and waist circumference (90 vs. 87 cm, $p = 0.011$) compared to PrEP users. Bioimpedance analysis revealed greater adiposity in PLWH compared to PrEP users, including higher total fat mass (22.2 vs. 15.15 kg, $p = 0.009$), trunk fat mass (8.2 vs. 5.1 kg, $p = 0.016$), and leg fat mass (6.9 vs. 4.5 kg, $p = 0.04$). The prevalence of overweight was also significantly higher in PLWH compared to PrEP users (43% vs. 24%, $p = 0.041$).

Regarding metabolic parameters, PLWH had significantly higher total cholesterol (173 vs. 154.5 mg/dL, $p = 0.014$), triglycerides (89 vs. 77.5 mg/dL, $p = 0.044$), and LDL cholesterol (111.8 vs. 89.2 mg/dL, $p = 0.004$) than PrEP users. Only two participants in the entire cohort were on statin therapy (one on atorvastatin and one on rosuvastatin), both in the HIV group, while no PrEP users were treated with statins. Given the very low prevalence of statin use and the limited sample size, these variables were not included in the multivariable models. Sensitivity analyses excluding the two statin-treated individuals did not change the results, and the main findings remained unchanged. No significant differences were observed in glycemic parameters, hypertension prevalence, or creatinine levels between the groups. A detailed comparison in composition metrics and metabolic comorbidities is shown in Supplementary Table 2.

Hepatic and cardiovascular assessments showed no significant differences between the groups. However, a non-significant trend toward higher MASLD prevalence was observed in PLWH compared to PrEP users (38% vs. 24%, $p = 0.067$). Advanced liver fibrosis was rare (1%), with only one PLWH presenting with LSM > 8 kPa. Clinical and metabolic parameters are summarized in Table 1 and Supplementary Tables 1–3.

Notably, the HOMA index was significantly increased in PLWH engaging in low–moderate physical activity compared to PrEP users (2.26 vs. 1.45, $p = 0.005$) at the same level of activity (Fig. 1A). Moreover, plasma leptin levels were significantly higher in PLWH (2029 vs. 889 pg/ml, $p = 0.036$) compared to PrEP without any differences in other cytokines/adipokines (Fig. 1B). Interestingly, leptin levels correlated positively with BMI, waist circumference, fat mass, and HOMA index in both groups (Fig. 1C). A detailed comparison in liver and cardiovascular parameters is presented in Supplementary Table 3.

In univariate analysis, factors significantly associated with HIV status included BMI (OR: 1.137, 95% CI: 1.001–1.292), waist circumference (OR: 1.060, 95% CI: 1.007–1.114), fat mass at bioimpedance analysis (OR: 1.063, 95% CI: 1.007–1.123), overweight status (OR: 2.780, 95% CI: 1.004–7.702), total cholesterol (OR: 1.021, 95% CI: 1.005–1.037), triglycerides (OR: 1.013, CI: 1.000–1.026), and LDL cholesterol (OR: 1.028, 95% CI: 1.009–1.049). In multivariate analysis, LDLc remained independently associated with HIV status (OR: 1.032, 95% CI: 1.004–1.061). Complete univariable and multivariable regression results are provided in Supplementary Table 4.

Table 1 Characteristics of PLWH and PrEP users and main metabolic and anthropometric parameters

	PLWH ($n = 53$)	PrEP ($n = 29$)	p-value
Viral and antiretroviral therapy features			
Median age (range)—years	38.5 (23–52)	37 (24–49)	/
CD4 + lymphocyte count—no. (%)			
< 200/uL	0	/	/
200–499/uL	7 (13)		
≥ 500/uL	46 (87)		
Median CD4/CD8 ratio (range)	0.99 (0.24–3.24)	/	/
Plasmatic HIV RNA—no. (%)			
< 50 cp/mL	52 (98)	/	/
50–99 cp/mL	1 (2)		
≥ 100 cp/mL	0		
Median time since first treatment start (range)—months	36 (7–216)	19 (6–84)	/
Current ART regimen—no. (%)			
INSTI-based	47 (89)	/	/
PI-based	1 (2)		
NNRTI-based	5 (9)		
PrEP regimen type—no. (%)			
Daily only	/	12 (41)	/
On-demand only		11(38)	
Alternating daily- on demand		6 (21)	
Lifestyle features			
Vigorous physical activity, METs	1120 (0–2448)	1920 (1440–3840)	0.041
Mediterranean diet adherence			
Low	3 (6%)	5 (17%)	0.07
Moderate	43 (81%)	17 (59%)	
High	7 (13%)	7 (24%)	
Metabolic and anthropometric features			
BMI, Kg/m.^{2} median (range)	24.6 (22.5–27.8)	22.9 (20.9–24.7)	0.015
Waist circumference, cm	90 (86–102)	87 (80–91.5)	0.011
Overweight, n (%)	23 (43%)	7 (24%)	0.041
FAT (Fat mass), Kg	22.2 (15.3–32.1)	15.15 (12.95–21.25)	0.009

Table 1 continued

	PLWH ($n = 53$)	PrEP ($n = 29$)	p-value
Dyslipidemia, *n* (%)	17 (32%)	11 (38%)	0.12
Triglycerides, mg/dl	89 (66–135)	77.5 (56.5–96.5)	0.044
LDL, mg/dl	111.8 (89.8–136)	89.2 (71–111.8)	0.004
High LDL, *n* (%)	33 (62%)	10 (34%)	0.016
Hypertension, *n* (%)	2 (4%)	1 (3%)	0.23
Type 2 diabetes, *n* (%)	1 (2%)	0 (0%)	0.45
Hepatic features			
MASLD	20 (38%)	7 (24%)	0.06
LSM > 8 kPa	1 (2%)	0 (0%)	0.17
FIB4 > 2.45, *n* (%)	4 (8%)	0 (0%)	0.30
FAST > 0.67, *n* (%)	1 (2%)	0 (0%)	0.70
Cardiovascular features			
CV risk categories (on 26 HIV and 8 PrEP aged > 40 years old)			
Low-intermediate	10 (19%)	4 (14%)	0.26
High	15 (28%)	4 (14%)	
Very high	1 (2%)	0 (0%)	
PWV (m/s)	5.805 (5.315–6.465)	5.72 (5.0475–6.315)	0.33
Carotid Plaques, *n* (%)	4 (8%)	0 (0%)	0.13
EAT > 9.5 mm, *n* (%)	6 (11%)	4 (14%)	0.27

BMI body mass index, *EAT* epicardial adipose tissue, *FAST* FibroScan-AST, *FAT* fat mass, *FFM* FIB-4, Fibrosis-4, INSTI, integrase strand transfer inhibitor, *LDL* low-density lipoprotein cholesterol, *LSM* Liver Stiffness Measurement, *MASLD* Metabolic Dysfunction–Associated Steatotic Liver Disease, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *PI* protease inhibitor, *PWV* pulse wave velocity

DISCUSSION

This study compares metabolic, anthropometric, cardiovascular, and liver parameters in PLWH and PrEP users below 50 years of age; two groups with different ART exposure and different inflammatory backgrounds. PLWH exhibited greater adiposity and dyslipidemia, while engaged in less vigorous physical activity compared to PrEP users. These findings highlight the need for tailored metabolic interventions in HIV care, integrating physical activity and lipid management. In addition, PLWH also exhibited higher levels of leptin, a key hormone in adipose tissue metabolism.

Our findings of increased adiposity in PLWH align with the shifting paradigm in HIV care, where excess adiposity has become a key challenge. Weight gain following ART initiation, particularly with INSTIs, has been well documented, with studies reporting an average increase of 3–5 kg within 2 years [22]. The mechanism remains unclear, with some attributing weight gain to the "return to health" phenomenon [22], while others suggesting a

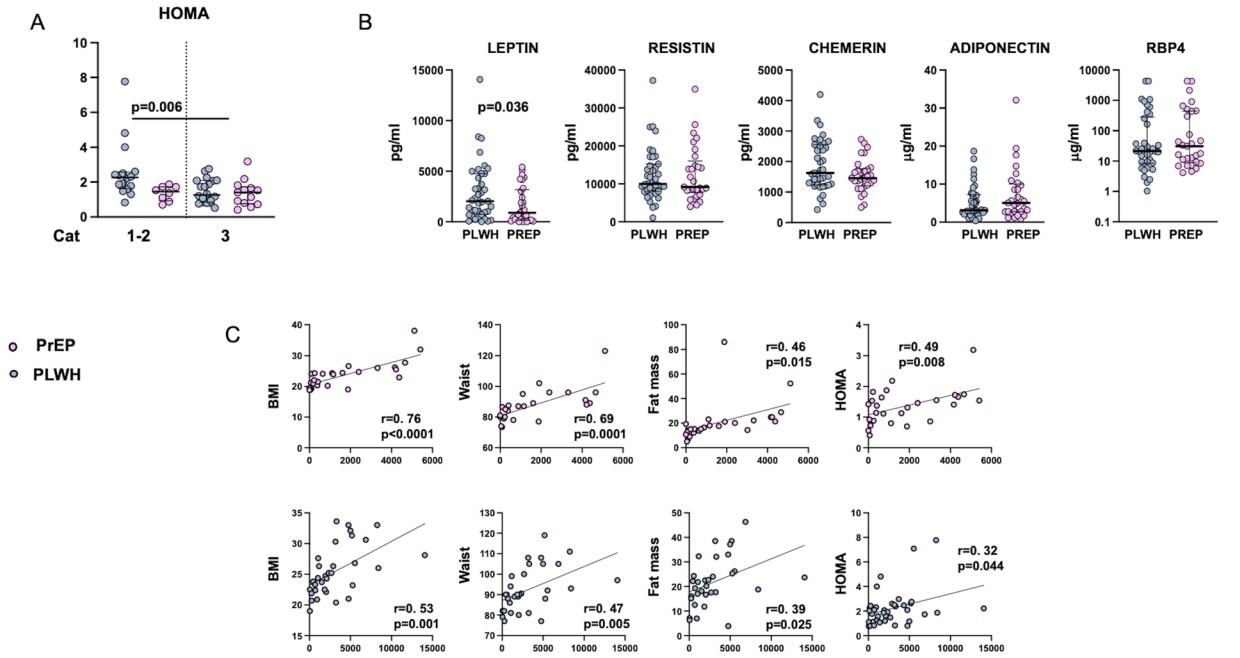

Fig. 1 **A** HOMA index in PrEP users and PLWH stratified by low to moderate (*1–2*) and high levels (*3*) of physical activity. **B** Serum levels of leptin (pg/ml), resistin (pg/ml), chemerin (pg/ml), adiponectin (µg/ml), and RBP4 (µg/ml) among the two groups. **C** Correlations between leptin levels and BMI, waist circumference, fat mass and HOMA index in PrEP users (*pink dots*) and PLWH (*gray dots*). *PrEP* pre-exposure prophylaxis, *PLWH* people living with HIV, *HOMA-IR* Homeostatic Model Assessment of Insulin Resistance, *BMI* body mass index, *RBP4* retinol-binding protein 4

role for INSTI-induced adipogenesis [23]. Interestingly, emerging data suggest that weight gain post-ART switch is primarily due to the removal of weight-suppressive agents like TDF, rather than an intrinsic obesogenic effect of INSTIs [24].

Lifestyle factors, including poor diet and sedentary behavior, further contribute to adiposity in both PLWH and general population. In our findings, while overall physical activity was comparable between groups, PrEP users engaged in more vigorous exercise, which may partly account for their lower adiposity. Notably, lower physical activity in PLWH was associated with a significantly higher HOMA index, reinforcing the role of exercise in modulating insulin sensitivity. This aligns with studies linking low physical activity in PLWH to insulin resistance and β-cell dysfunction [25]. Given the high cardiometabolic risk in PLWH, our findings highlight the need to incorporate structured exercise programs into HIV care.

A novel aspect of this study is the association between HIV status, adiposity, and leptin levels. Leptin was significantly elevated in PLWH, correlating with BMI, waist circumference, and total body fat, reinforcing its potential as a biomarker of metabolic dysfunction in this population. Previous studies showed that HIV-related inflammation and ART exposure may drive leptin dysregulation, particularly in the context of lipodystrophy [26]. Further research is needed to determine leptin's role in metabolic disturbances and its potential as a therapeutic target in HIV care.

Our study demonstrates a strong link between HIV status and dyslipidemia, with PLWH showing significantly higher lipid levels than PrEP users. In multivariate analysis, LDL cholesterol remained independently associated with HIV status, suggesting that dyslipidemia in PLWH stems from intrinsic disease-related metabolic changes. This aligns with evidence implicating HIV-related inflammation and ART exposure in

dyslipidemia and cardiovascular risk [27], reinforcing the need for early lipid monitoring and potential statin therapy, as supported by the REPRIEVE trial [28].

Although hepatic steatosis, fibrosis, and cardiovascular disease markers were comparable among the two groups, MASLD showed a non-significant trend toward higher prevalence in PLWH compared to PrEP users. As MASLD surpasses HBV and HCV co-infections as the leading cause of liver disease in PLWH, and given its well-established impact on liver, cardiovascular outcomes, and overall mortality, early screening and targeted interventions are crucial.

The study's main limitation is its small sample size, potentially limiting statistical power. However, a sample size calculation was performed at the study design stage based on expected differences in metabolic risk between PLWH and HIV-negative individuals, using T2DM prevalence as a proxy of metabolic risk, as previously reported [29], and, despite the reduction due to the single-center design and strict inclusion criteria, the achieved sample size was sufficient to detect significant differences in the primary outcomes. Another limitation is the cross-sectional design, which precludes causal inference and does not allow assessment of temporal or predictive relationships between HIV status, lifestyle factors, and metabolic outcomes. The restriction to cisgender men limits generalizability and warrants studies in women and gender-diverse populations. However, a key strength is the detailed metabolic characterization of PLWH and PrEP users, a population often underrepresented in research.

CONCLUSION

PLWH exhibited greater adiposity and dyslipidemia than PrEP users, with leptin emerging as a key marker of metabolic dysfunction. Notably, higher physical activity levels were associated with improved insulin sensitivity, reinforcing the role of exercise in mitigating HIV-related metabolic risks. These findings highlight the need for targeted metabolic interventions and further research into the long-term metabolic impact of ART in both PLWH and HIV-negative individuals.

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Author Contributions. Conceptualization: Alessandra Bandera, Rosa Lombardi, Serena Ludovisi; Data curation: Felice Cinque, Arianna Liparoti and Stefania Varchetta; Serological analysis: Elena Trombetta, Marta Tornese; Project administration, Alessandra Bandera, Rosa Lombardi; Data acquisition: Cristina Bertelli, Giuseppina Pisano, Erika Fatta, Annalisa Cespiati, Giovanna Oberti, Silvia Gentile, Anna Ludovica Fracanzani, Giorgio Bozzi, Valeria Castelli, Serena Ludovisi, Antonio Muscatello; Analysis and interpretation of data: Felice Cinque, Arianna Liparoti, Stefania Varchetta, Rosa Lombardi; Writing – original draft: Felice Cinque, Arianna Liparoti, Stefania Varchetta; Writing – review & editing: Rosa Lombardi, Alessandra Bandera. All authors critically reviewed the manuscript and approved the publication.

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Data Availability. The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest. Alessandra Bandera received speaker's honoraria and fees for attending advisory boards from Astra-Zeneca, Biomerieux, Gilead, Janssen-Cilag, Nordic Pharma, Pfizer, Qiagen, SOBI, Takeda, ViiV, and received research grants from Gilead. Rosa Lombardi received research grants from Gilead. Felice Cinque, Arianna Liparoti, Stefania Varchetta, Giorgio Bozzi, Valeria Castelli, Serena Ludovisi, Antonio Muscatello, Elena Trombetta, Marta Tornese, Bianca Mariani, Cristina Bertelli, Giuseppina Pisano, Erika Fatta, Annalisa Cespiati, Giovanna Oberti, Silvia Gentile, Anna Ludovica Fracanzani, declare no conflicts of interest.

Ethical Approval. The study was conducted in accordance with the Declaration of Helsinki (1964) and its later amendments; written informed consent to participate and consent for publication were obtained from all participants, and the protocol was approved by the Institutional Review Board of Policlinico di Milano Hospital (protocol code 2581, approval date: 19/09/2022).

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