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Research Paper

Achievement of LDL cholesterol targets in HIV-positive patients: a single center cohort study

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ABSTRACT

Background and aims: People living with HIV (PLWH) face an increased CardioVascular (CV) risk due to the interaction between risk factors, chronic inflammation and AntiRetroviral Therapies (ART) metabolic effects. However, standard risk models often underestimate this burden. Our study aims to evaluate: (i) the CV risk category and the relative LDL-C targets; (ii) the achievement of these targets; and (iii) factors associated with target achievement and HIV-related variables.

Methods and results: A retrospective analysis was conducted on 246 PLWH, aged ≥40, on ART followed at the Niguarda Hospital. Clinical and laboratory data were extracted from the hospital's electronic registries and ten-year CV risk was assessed using SCORE2. Only 27.2% of the analyzed cohort achieved the recommended LDL-C targets with further lower prevalence in patients in the "high" or "very high" risk categories. Patients who achieved their LDL-C target had a more favorable cardiovascular risk profile (LDL-C: 75.8 ± 18.1 vs 121.1 ± 33.4 mg/dL, $p < 0.001$; systolic blood pressure: 116.9 ± 12.4 vs 123.4 ± 15.7 mmHg, $p = 0.001$), and CV risk categories, being less frequently classified as high and very-high risk (20.8 vs 52.4%, $p < 0.0001$). No significant relation was found between LDL-C target achievement and HIV-specific variables.

Conclusions: LDL-C target achievement remains suboptimal and may not reflect adequate cardiovascular risk control in PLWH, supporting the need for more aggressive and HIV-tailored prevention strategies.

1. Introduction

Thanks to the effectiveness of antiretroviral therapy (ART) the life expectancy of People Living with HIV (PLWH) has markedly improved over recent years, progressively resembling that of the general population [1]. However, this demographic shift brings PLWH to face an increased prevalence of chronic diseases, particularly cardiovascular (CV) diseases [2,3]. The elevated CV risk in these patients results from a complex interplay of traditional risk factors, ART-induced metabolic alterations and persistent low-grade systemic inflammation. As a result, standard CV risk prediction models, such as SCORE2 [4], are currently reported to underestimate the true risk profile of these patients, leading to inadequate prevention strategies [5].

As the limitations of current tools in accurately capturing CV risk have become increasingly evident, there has been a growing emphasis on preventive strategies that can deliver reliable benefit across the diverse profiles of people living with HIV. Within this context, LDL-cholesterol (LDL-C) reduction has emerged as a central component of modern cardiovascular prevention [6], given its well-established causal role in atherosclerotic disease and the consistent association between greater LDL-C lowering and proportional risk reduction. This focus has been recently reinforced by the results of the REPRIEVE trial, which provided robust evidence that pitavastatin significantly reduces cardiovascular events in PLWH independently of baseline LDL-C concentrations or estimated risk category. These findings suggest that the benefit of statin therapy in this population is not adequately captured by traditional risk thresholds, and that relying solely on conventional prediction models may overlook individuals who stand to benefit from treatment [7].

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Although contemporary guidelines continue to adopt population-based risk stratification approaches to inform LDL-C targets and management strategies [6,8], the substantial heterogeneity in cardiovascular risk among PLWH indicates that a uniform approach may be insufficient. Instead, tailoring preventive interventions to the specific clinical and immunometabolic characteristics of each individual may offer a more accurate alignment between risk profile and therapeutic intensity, particularly for those classified as high or very-high risk.

Based on this background, the aim of our study was to evaluate, in a cohort of PLWH treated with ART: (i) the CV risk category and the corresponding LDL-C targets; (ii) the achievement of these targets; and (iii) the association between LDL-C target achievement and clinical, immunological, and therapeutic HIV-related parameters.

2. Methods

2.1. Population

A retrospective screening was conducted on the cohort of HIV-positive patients, followed at the HIV outpatient clinic of the Infective Diseases department of the Niguarda Hospital (Milan, Italy) as of 31st December 2025. The overall cohort consisted of 1553 patients on which inclusion and exclusion criteria were applied. In particular, inclusion criteria were: (i) HIV-positivity, (ii) age ≥40 years, (iii) receiving stable ART. Exclusion criteria were: (i) uncertain or negative HIV diagnosis, (ii) aged <40 years, (iii) not receiving ART or on unstable (less than 3 months) ART regimen, (iv) incomplete clinical or laboratory data.

As shown in Fig. 1, a total of 66 patients were excluded: those without serological confirmation of HIV infection (n = 11), individuals younger than 40 years (n = 34), patients with an unstable ART regimen (n = 8), and those with incomplete clinical or laboratory data (n = 13).

Due to feasibility constraints, an in-depth analysis was performed on a randomly selected subgroup of the overall cohort. A computer-generated simple random sampling technique was applied to ensure that each subject had an equal probability of selection, thereby minimizing selection bias. 16% of the whole cohort was selected for the actual analysis with a final sample including 246 patients. Of these patients, clinical, laboratory, and therapeutical data were collected from hospital electronic registries.

The following parameters were recorded: (i) demographics (age, sex); (ii) CV risk factors including systolic and diastolic Blood Pressure (BP), hypertension, smoking status, diabetes mellitus, Body Mass Index (BMI); (iii) laboratory variables including total cholesterol, High Density Lipoprotein Cholesterol (HDL-C), LDL-C, triglycerides, fasting glucose, creatinine); (v) therapeutic data regarding ART and CV drugs; (vi) HIV-specific variables ($CD4^+$ count, HIV-RNA viral load, duration of HIV infection, total lymphocyte count, CD4/CD8 ratio).

Obesity was defined as a BMI >30 kg/m^2, arterial hypertension was defined as an office BP ≥ 140/90 mmHg or the use of anti-hypertensive drugs, while diabetes mellitus was defined as fasting glucose levels >126 mg/dL on two separate occasions or current treatment with antidiabetic medication.

The study protocol complies with the Helsinki Declaration and was approved by the institutional ethics committee. All participants provided informed written consent after being informed of the nature and purpose of the study.

2.2. Cardiovascular risk evaluation

Ten-year cardiovascular risk was assessed using the SCORE2 algorithm [4], categorizing patients into low (<1%), moderate (1–5%), high (5-10%) or very-high risk (≥10%). Patients with known clinical (previous acute coronary syndrome, coronary artery revascularization, stroke, transitory ischaemic attack, peripheral artery disease, peripheral vessels revascularization; n = 11) or imaging (atherosclerotic plaque determining a stenosis grade >50% on angiography or echography; n = 0) atherosclerotic disease were assigned to the very-high CV risk categories before SCORE2 calculation.

The relative LDL-C targets were defined according to the 2025 European Society of Cardiology (ESC) guidelines [6]. In particular, LDL-C targets were defined as <116 mg/dL for low-risk individuals, <100 mg/dL for those at moderate risk, <70 mg/dL for patients classified as

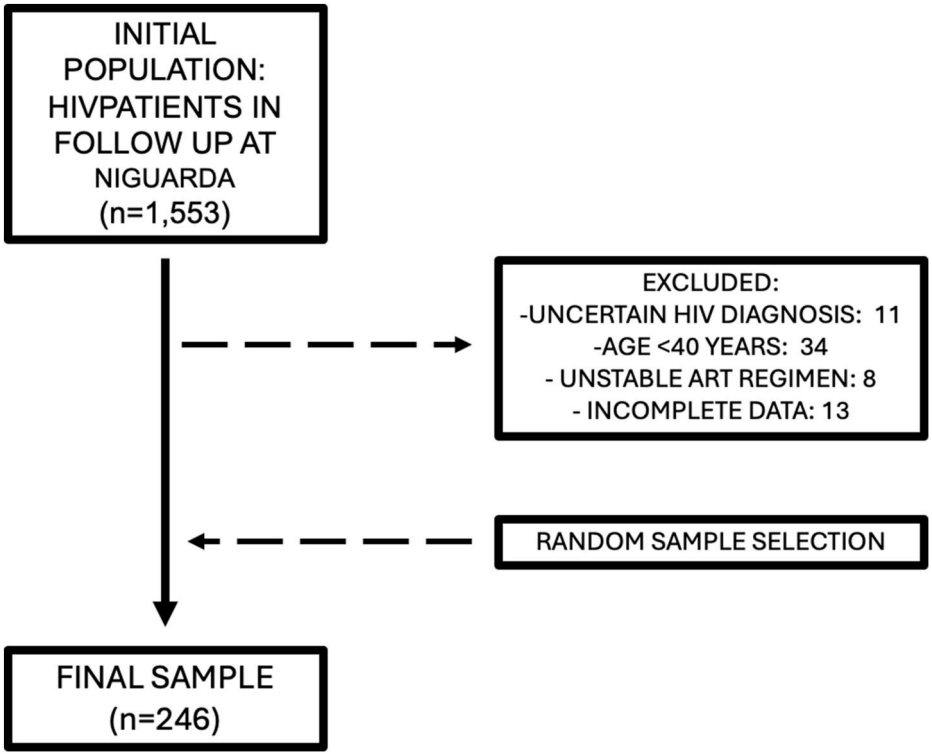

Fig. 1. Flowchart of the study population selection.

high risk and <55 mg/dL for very-high-risk subjects.

2.3. Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as count (percentage). Differences between groups were assessed using Student's t-test for continuous variables and χ^2 or Fisher's exact test for categorical variables. Pearson or Spearman correlation test was used to assess univariate associations between LDL-C target achievement and clinical or HIV-related variables. A multivariable logistic model with LDL-C target achievement as the dependent variable and age, sex, systolic BP and CV risk class was done showing Odds Ratio (OR) and relative 95% Confidence Interval (CI). All statistical analyses were performed using SPSS, with significance set at a two-tailed p-value <0.05.

3. Results

3.1. Population characteristics

The cohort included 246 patients (Table 1), with a mean age of 54.2 ± 9.7 years, equally distributed regarding sex (male 50.4%). Regarding CV disease and risk factors, 11 patients had a previous CV event, mean BMI was 24.6 ± 4.3 kg/m^2, with 9.3% of the patients classified as obese. Smoking was highly prevalent (50.8%) as well as hypertension (31.4%), while diabetes was present in only the 4.1% of the cohort. Mean systolic and diastolic BP values were 121.6 ± 15.1 mmHg and 74.6 ± 8.7 mmHg, respectively.

Biochemical parameters showed fasting glucose levels of 91.4 ± 21.9 mg/dL, total cholesterol of 185.3 ± 43.4 mg/dL, LDL-C of 108.7 ± 36.1 mg/dL, HDL-C of 53.3 ± 15.2 mg/dL, and triglycerides of 114.5 ± 53.3 mg/dL. Mean creatinine was 1.01 ± 0.33 mg/dL.

Concerning lipid-lowering therapies, 35.4% of patients were receiving statins, 12.2% ezetimibe, and 11.4% a combination of statin plus ezetimibe. Most patients were on rosuvastatin (n = 70) while 14 of them take atorvastatin. Mean dose was mainly low (8.0 ± 5.7 mg) for rosuvastatin and slightly higher for atorvastatin (26.4 ± 25.2 mg). Also regarding lipid-lowering therapies fenofibrate (2.1%) and omega-3 (1.2%) were less frequently used while no patient was treated with Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors. Finally, angiotensin converting enzyme inhibitors or angiotensin receptor blockers (17.5%) were the most frequent anti-hypertensive medications followed by beta-blockers (11.8%), diuretics (8.9%), calcium-channel blockers (6.5%) and alpha-blockers (2.4%).

The mean duration of HIV infection was 19.9 ± 10.7 years, and the average exposure to antiretroviral therapy was 17.1 ± 9.5 years. Most patients were treated with nucleoside reverse-transcriptase inhibitors (82.9%) and integrase strand-transfer inhibitors (80.9%). The use of Non-Nucleoside Reverse Transcriptase Inhibitors and protease inhibitors was 29.3% and 20.7%, respectively, while cobicistat was employed in 9.8% of regimens, and C–C chemokine receptor type 5 inhibitors only in 0.4%. Viral suppression (undetectable HIV-RNA) was present in 84.9% of the population; among those with detectable viremia, the mean HIV-RNA level was 5490.6 ± 2629.9 copies/mL. Immunological parameters showed a CD4$^+$ T-cell count of 0.8 ± 0.4 × 10^9/L (percentage 36.8 ± 7.8%) with a CD4/CD8 ratio of 1.1 ± 0.5.

3.2. Cardiovascular risk and LDL cholesterol target achievement

LDL-C target achievement was low, with only 27.2% of patients (n = 67) reaching guideline-recommended levels. The mean estimated cardiovascular risk was 5.5 ± 5.1, with 6.1% of patients classified as low risk, 50% as intermediate risk, 29.3% as high risk, and 14.6% as very high risk (Fig. 2, panel A).

Notably, the proportion of patients achieving LDL-C targets progressively decreased across increasing SCORE2 risk categories, from

Table 1
Population characteristics.

Variable	VALUE
Number	246
Age (years)	54.2 ± 9.7
Men, n (%)	124 (50.4%)
Cardiovascular risk factors	
Smoking, n (%)	125 (50.8%)
BMI (kg/m^2)	24.6 ± 4.3
Obesity, n (%)	23 (9.3%)
Diabetes, n (%)	10 (4.1%)
Arterial Hypertension, n (%)	77 (31.4%)
SBP (mmHg)	121.6 ± 15.1
DBP (mmHg)	74.6 ± 8.7
Previous CV events, n (%)	11 (4.4%)
Biochemical variables	
Glucose (mg/dl)	91.4 ± 21.9
Total Cholesterol (mg/dl)	185.3 ± 43.4
Triglycerides (mg/dl)	114.5 ± 53.3
HDL Cholesterol (mg/dl)	53.3 ± 15.2
LDL Cholesterol (mg/dl)	108.7 ± 36.1
Creatinine (mg/dl)	1.01 ± 0.33
Cardiovascular risk	
SCORE2	5.5 ± 5.1
Low risk, n (%)	15 (6.1%)
Intermediate risk, n (%)	123 (50%)
High risk, n (%)	72 (29.3%)
Very high risk, n (%)	36 (14.6%)
LDL Cholesterol Target Achievement, n (%)	67 (27.2%)
Lipid lowering therapies	
Statins alone, n (%)	87 (35.4%)
Ezetimibe alone, n (%)	30 (12.2%)
Statin + Ezetimibe, n (%)	28 (11.4%)
Rosuvastatin, n (%)	70 (28.5%)
Mean Rosuvastatin dose (mg)	8.0 ± 5.7
Atorvastatina, n (%)	14 (5.7%)
Mean Atorvastatina dose (mg)	26.4 ± 25.2
Other statins, n (%)	3 (1.2%)
Omega-3, n (%)	3 (1.2%)
Fenofibrate, n (%)	5 (2.1%)
PCSK9-inhibitors, n (%)	0 (0%)
Other cardiovascular therapy	
ACE-Inhibitors/ARBs, n (%)	43 (17.5%)
Beta-Blockers, n (%)	29 (11.8%)
Alpha- Blockers, n (%)	6 (2.4%)
Calcium Channel Blockers, n (%)	16 (6.5%)
Diuretics, n (%)	22 (8.9%)
HIV-Related variables and therapy	
HIV infection duration (years)	19.9 ± 10.7
HIV therapy duration (years)	17.1 ± 9.5
Undetectable HIV-RNA, n (%)	209 (84.9%)
Detectable HIV-RNA (copies/ml)	5490.6 ± 2629.9
Total lymphocytes (10^9/L)	2.4 ± 0.8
CD3$^+$CD4$^+$ lymphocytes (10^9/L)	0.8 ± 0.4
CD3$^+$CD4$^+$ lymphocytes (%)	36.8 ± 7.8
CD4/CD8 ratio	1.1 ± 0.5
White Blood Cells (10^9/L)	6.6 ± 2.1
Neutrophils (10^9/L)	3.8 ± 2.7
NRTIs, n (%)	204 (82.9%)
Abacavir, n (%)	46 (18.7%)
NNRTIs, n (%)	72 (29.3%)
PIs, n (%)	51 (20.7%)
INSTIs, n (%)	199 (80.9%)
CCR5 Inhibitors, n (%)	1 (0.4%)
Cobicitsat, n (%)	24 (9.8%)

Abbreviations: BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; CV = CardioVascular; HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; ACE = Angiotensin Converting Enzyme; PCSK9 = Proprotein Convertase Subtilisin/Kexin type 9 inhibitors; ARBs = Angiotensin II Receptor Blockers; NRTIs = Nucleoside/Nucleotide Reverse Transcriptase Inhibitors; NNRTIs = Non-Nucleoside Reverse Transcriptase Inhibitors; PIs = Protease Inhibitors; INSTIs = Integrase Strand Transfer Inhibitors; CCR5 Inhibitors = C–C chemokine receptor type 5 inhibitors.

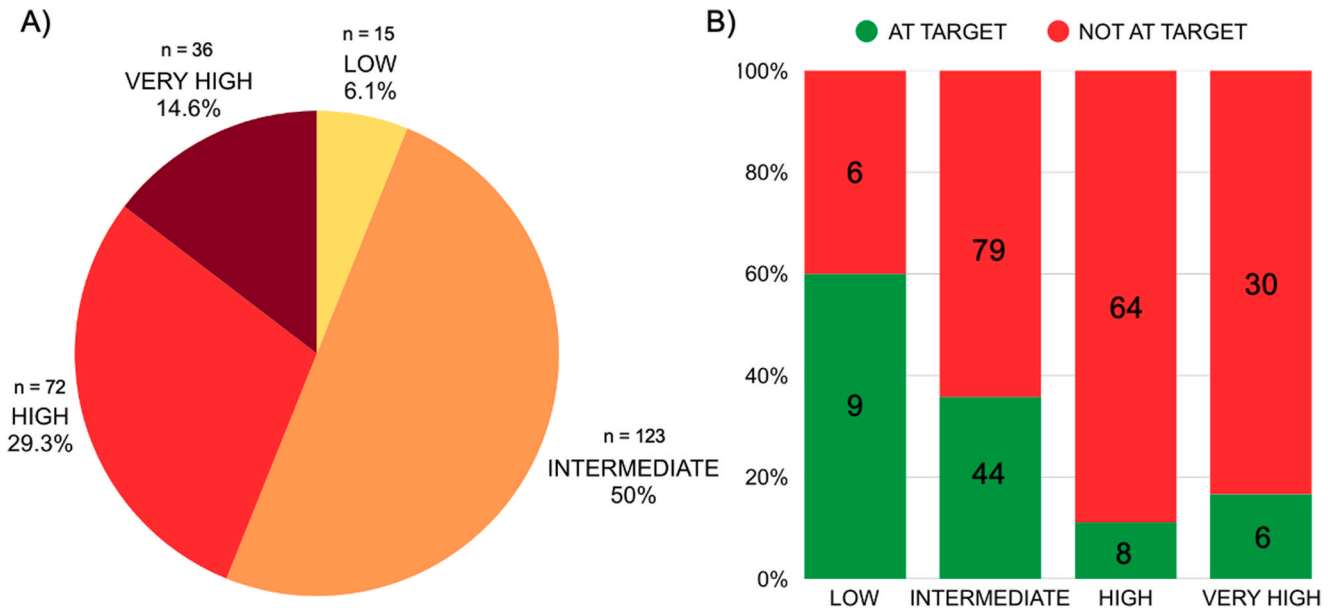

Fig. 2. Population distribution accordingly to SCORE2 risk categories (panel A) and relative target achievement (panel B).

33.3% in low-risk individuals and 31.7% in moderate-risk patients, to 12.5% and 13.8% in high- and very high-risk groups, respectively (Fig. 2, panel B).

When patients were divided accordingly to LDL-C target achievement (Table 2), the first group showed a significantly lower LDL-C (75.8 ± 18.1 vs 121.1 ± 33.4 mg/dL, $p < 0.001$) and total cholesterol (150.6 ± 29.9 vs 198.3 ± 40.5 mg/dL, $p < 0.0001$), as well as triglycerides (98.1 ± 49.6 vs 120.6 ± 53.5 mg/dL, $p = 0.002$) and systolic blood pressure (116.9 ± 12.4 vs 123.4 ± 15.7 mmHg, $p = 0.001$). Furthermore they showed a more favorable SCORE2 distribution being more often classified in the low–moderate classes (65.7 vs 44.2%) than in the high–very high ones (20.8 vs 52.4%, $p < 0.0001$). No differences were found in CV drugs particularly for rosuvastatin (similar prevalence of use and mean dose) while a slightly higher, but not significant, prevalence (7.5 vs 5.0%, $p = 0.519$) and mean dose (36.0 ± 26.1 vs 21.1 ± 24.6 mg, $p = 0.327$) were seen in patients who achieved their LDL-C target. Furthermore, no significant differences were also found for ART regimen or HIV-specific variables.

At univariate correlations, LDL-C target achievement was significantly associated with systolic BP ($r = -0.186$; $p = 0.003$), LDL-C ($r = -0.628$; $p < 0.001$), CV risk class ($r = -0.161$; $p = 0.011$). No statistically significant associations were observed between LDL-C target achievement and HIV-specific parameters, including CD4 count, viral load, ART duration, or regimen type.

At multivariable analysis age (per year, OR 0.908; 95% CI 0.832, 0.986; $p = 0.008$), sex (male, OR 3.923; 95% CI 1.412, 11.745; $p = 0.009$) and CV risk class (OR 0.858; 95% CI 0.722, 0.976; $p = 0.019$) were significantly associated with LDL-C target achievement.

4. Discussion

The main findings of this real-world retrospective study are that: (i) most PLWH were classified as having moderate or high CV risk; (ii) LDL-C target achievement was markedly low, with fewer than one-third of patients meeting guideline-recommended thresholds; and (iii) HIV-related variables, including virological, immunological, and treatment-related factors, were not significantly associated with LDL-C target attainment.

Regarding CV risk distribution, our findings are consistent with contemporary evidence showing that PLWH are disproportionately represented in higher risk categories. Tükenmez Tigen et al. reported that more than 70% of their cohort fell into high or very-high SCORE2 classes [9]. Similarly, Arbune et al. observed mean 10-year CV risk estimates approaching 10% in individuals over 40 years of age, along with a CV age exceeding chronological age by an average of 7.5 ± 5.10 years, supporting the concept of accelerated vascular aging in this population [10]. Collectively, these data reinforce the notion that CV risk in PLWH remains elevated despite effective viral suppression and advances in ART.

In our cohort, fewer than one-third of patients achieved LDL-C targets, confirming a persistent treatment gap in lipid management among PLWH. Similar findings have been reported in previous studies. Carrozzo et al. found that only 37% of high- or very-high-risk PLWH were receiving lipid-lowering therapy, and nearly half failed to achieve any LDL-C goal [11]. However, it is important to acknowledge that suboptimal LDL-C target attainment is not exclusive to PLWH. In the SANTORINI study, based on a European high-risk population only 20.1% of the patients achieved guideline-recommended LDL-C levels [12], while the BRING-UP registry, which included nearly 4800 patients in secondary prevention, showed that 32.6% of patients reached LDL-C <55 mg/dL at baseline [13]. Nevertheless, given the disproportionately elevated CV risk in PLWH, therapeutic inertia may have even greater clinical implications in this population.

Approximately 40% of patients in our cohort were treated with lipid-lowering therapy, predominantly statins. Rosuvastatin was the most commonly prescribed agent, generally at low doses, while atorvastatin was used less frequently but at slightly higher doses. These findings suggest a suboptimal intensity of lipid-lowering therapy, with a substantial proportion of patients receiving low-dose statins despite a high CV risk profile. Although statin intensity was not formally categorized according to guideline definitions, the observed dosing suggests a predominance of low-intensity regimens. This pattern may also be partly explained by concerns regarding potential drug–drug interactions between antiretroviral therapy and statins, which may lead clinicians to favor lower statin doses. In fact, several agents used in HIV therapy, above all protease inhibitors and pharmacokinetic boosters such as ritonavir, may interfere with statin metabolism through cytochrome P450 pathways, increasing the risk of adverse effects [14]. As a consequence, clinicians often adopt more conservative dosing strategies, which may partly explain the relatively low statin doses observed in our population and, in this way, contribute to the suboptimal achievement of LDL-C targets.

Table 2
Population characteristics according to therapeutic target achievement.

Variable	Not at LDL cholesterol target	LDL-cholesterol target achived	p-value
Patients, n (%)	179 (72.8%)	67 (27.2%)	-
Age (years)	54.5 ± 9.7	53.7 ± 9.9	0.635
Men, n (%)	97 (52.5%)	30 (44.8%)	0.174
Women, n (%)	85 (47.5%)	37 (55.2%)	0.174
Cardiovascular risk factors			
Smoking, n (%)	92 (51.4%)	33 (49.2%)	0.438
BMI (kg/m2)	24.8 ± 4.4	24.3 ± 4.3	0.531
Obesity, n (%)	13 (7.2%)	10 (14.9%)	0.630
Diabetes, n (%)	6 (3.3%)	4 (5.9%)	0.467
Arterial Hypertension, n (%)	56 (31.3%)	21 (31.3%)	1.000
SBP (mmHg)	123.4 ± 15.7	116.9 ± 12.4	0.001
DBP (mmHg)	75.1 ± 8.1	73.3 ± 10.2	0.167
Previous CV events, n (%)	8 (4.4%)	3 (4.5%)	0.996
Biochemical variables			
Glucose (mg/dl)	91.3 ± 21.8	90.7 ± 22.4	0.868
Total Cholesterol (mg/dl)	198.3 ± 40.5	150.6 ± 29.9	<0.0001
Triglycerides (mg/dl)	120.6 ± 53.5	98.1 ± 49.6	0.002
HDL Cholesterol (mg/dl)	53.1 ± 14.5	53.8 ± 17.2	0.748
LDL Cholesterol (mg/dl)	121.1 ± 33.4	75.8 ± 18.1	<0.001
Creatinine (mg/dl)	1.01 ± 0.31	0.99 ± 0.37	0.237
Cardiovascular risk			
SCORE 2	5.8 ± 4.9	4.7 ± 5.3	0.140
Risk Class	6 (3.4%)	9 (13.5%)	<0.0001
- Low, n (%)	79 (44.2%)	44 (65.7%)	
- Moderate, n (%)	64 (35.7%)	8 (11.9%)	
- High, n (%)	30 (16.7%)	6 (8.9%)	
- Very high, n (%)			
Cardiovascular therapy			
Statins alone, n (%)	63 (35.2%)	24 (35.8%)	1.000
Ezetimibe alone, n (%)	19 (10.6%)	11 (16.4%)	0.273
Statin + Ezetimibe, n (%)	17 (9.5%)	11 (16.4%)	0.174
Rosuvastatin, n (%)	51 (28.5%)	19 (28.4%)	1.000
Mean Rosuvastatin dose (mg)	7.9 ± 1.7	8.2 ± 2.3	0.337
Atorvastatina, n (%)	9 (5.0%)	5 (7.5%)	0.519
Mean Atorvastatina dose (mg)	21.1 ± 24.6	36.0 ± 26.1	0.327
Other statins, n (%)	3 (1.7%)	0 (0%)	-
Omega-3, n (%)	2 (1.1%)	1 (1.5%)	1.000
Fenofibrate, n (%)	5 (3.8%)	0 (0%)	-
PCSK9-inhibitors, n (%)	0 (0%)	0 (0%)	-
Other cardiovascular therapy			
Ace-Inhibitors/ARBs, n (%)	28 (15.6%)	15 (22.4%)	0.076
Beta-Blockers, n (%)	19 (10.6%)	10 (14.9%)	0.377
Alpha- Blockers, n (%)	5 (2.8%)	1 (1.5%)	1.000
Calcium Channel Blockers, n (%)	9 (5.1%)	7 (10.4%)	0.148
Diuretics, n (%)	14 (7.8%)	8 (11.9%)	0.322
HIV-related variables and therapy			
HIV infection duration (years)	20.1 ± 10.7	19.3 ± 10.6	0.593
HIV therapy duration (years)	17.2 ± 9.4	16.9 ± 9.8	0.849
Undetectable HIV-RNA, n (%)	153 (85.5%)	56 (83.6%)	0.425
Detectable HIV-RNA (copies/ml)	6459.5 ± 3164.3	3288.4 ± 1050	0.357
Total lymphocytes (10^9/L)	2.5 ± 0.9	2.4 ± 0.8	0.667
$CD3^+CD4^+$ lymphocytes (10^9/L)	0.8 ± 0.3	0.8 ± 0.4	0.473
$CD3^+CD4^+$ lymphocytes (%)	34.3 ± 10.9	43.5 ± 8.9	0.098
CD4/CD8 ratio	1.1 ± 0.6	0.9 ± 0.5	0.668
White Blood Cells (10^9/L)	6.6 ± 2.1	6.7 ± 1.9	0.744
Neutrophils (10^9/L)	3.8 ± 3.1	3.8 ± 1.5	0.986
NRTI	151 (84.3%)	53 (79.1%)	0.214
Abacavir, n (%)	35 (19.5%)	11 (16.4%)	0.714
NNRTIs, n (%)	50 (27.9%)	22 (32.8%)	0.274
PIs, n (%)	35 (19.5%)	16 (23.9%)	0.281
INSTIs, n (%)	147 (82.1%)	52 (77.6%)	0.265
CCR5 Inhibitors, n (%)	1 (0.5%)	0 (0%)	-
Cobicitsat, n (%)	19 (10.6%)	5 (7.4%)	0.630

Abbreviations: BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; PCSK9 = Proprotein Convertase Subtilisin/Kexin type 9 inhibitors; ACE = Angiotensin Converting Enzyme; ARBs = Angiotensin II Receptor Blockers; NRTIs = Nucleoside/Nucleotide Reverse Transcriptase Inhibitors; NNRTIs = Non-Nucleoside Reverse Transcriptase Inhibitors; PIs = Protease Inhibitors; INSTIs = Integrase Strand Transfer Inhibitors; CCR5 Inhibitors = and C–C chemokine receptor type 5 inhibitors.

We did not observe any significant association between LDL-C target achievement and HIV-specific variables, including CD4 count, CD4/CD8 ratio, viral suppression, duration of infection, or ART regimen. At multivariable analysis, LDL-C target attainment was independently associated only with age and CV risk class (all with a OR lower than 1 meaning that the higher the parameter the lower the probability of LDL-C target achievement) and male sex. To our knowledge, no previous study has specifically evaluated the role of HIV-related variables in predicting LDL-C target achievement. However, several studies have demonstrated that HIV-related factors influence overall CV risk. For example, data from the Swiss HIV Cohort showed that a nadir CD4 T-cell count <200 cells/mm^3 and prior exposure to abacavir were independently associated with incident CV events, and that their inclusion modestly improved risk prediction beyond SCORE2 [15]. Similarly, in a large US cohort, lower CD4 counts and poor ART adherence were associated with increased CV risk, whereas sustained viral suppression appeared protective, particularly in the early phases of infection [16]. Taken together, these findings suggest that cumulative HIV exposure, immune dysregulation and specific ART drugs contribute to CV risk. In our cohort, characterized by high rates of viral suppression, the lack of association between HIV-related variables and LDL-C target attainment may indicate that lipid control is primarily driven by traditional CV risk factors.

In this context, current risk prediction models may not adequately capture the true CV risk burden in PLWH. SCORE2, although recommended, does not incorporate HIV-specific variables and is known to underestimate CV risk in this population [17]. Alternative models, such as the D:A:D risk equation and the Pooled Cohort Equations, have been proposed in PLWH, although their performance remains variable and not fully validated across different settings. In particular, the D:A:D study proposed a dedicated risk score integrating traditional CV determinants with HIV-related variables, such as $CD4^+$ lymphocyte count, cumulative exposure to protease inhibitors and nucleoside reverse transcriptase inhibitors, and the use of abacavir [18]. However, in a recent prospective cohort study comparing the predictive performance of D:A:D, SCORE2 and the Pooled Cohort Equations (PCE), the first one showed higher specificity but markedly lower sensitivity than SCORE2, indicating that the addition of HIV-specific variables provides only limited improvement in risk prediction [19]. At the same time, although SCORE2 and PCE are more easily applicable in routine clinical practice, they are known to systematically underestimate CV risk in PLWH, potentially leading to suboptimal risk stratification and preventive the best management in these patients [14].

Consequently, even patients achieving guideline-recommended LDL-C targets may not attain optimal risk control. Importantly, LDL-C target

achievement should not be interpreted as synonymous with adequate cardiovascular risk control in this population. Reaching guideline-recommended LDL-C thresholds does not necessarily translate into equivalently low residual risk. PLWH may require more intensive lipid-lowering strategies or lower LDL-C targets to achieve comparable risk reduction to that observed in the general population.

In PLWH traditional lipid thresholds and risk categories derived from the general population may not fully reflect the complex interplay between chronic low-grade inflammation, immune dysregulation, metabolic alterations, and long-term exposure to ART.

From a clinical perspective, apparent target achievement should therefore be interpreted with caution, as patients may remain biologically undertreated despite meeting numerical thresholds. These findings underscore the need for improved risk stratification tools integrating both traditional and HIV-specific determinants. Furthermore, this reinforces the need for individualized CV prevention strategies that extend beyond standard thresholds and better reflect the true risk profile of PLWH.

A potential strategy to address this gap is to intensify lipid-lowering therapy, including broader use of statins and, when appropriate, newer agents. In our cohort none of the patients were treated with PCSK9 inhibitors, even if these agents represent a promising option for individuals who fail to achieve LDL-C targets despite conventional lipid-lowering therapy. PCSK9-inhibitors in PLWH are safe, well-tolerated and free of any interaction with ART [20,21]. Furthermore, emerging evidence suggests that PCSK9 inhibition may improve coronary endothelial function and reduce lipoprotein(a) levels in PLWH [22,23].

The results of the REPRIEVE trial support a more proactive approach, demonstrating that pitavastatin significantly reduces CV events in PLWH irrespective of baseline LDL-C levels or estimated risk category [7]. These findings support a paradigm shift from a strictly risk-based approach toward a more comprehensive preventive strategy in this population. The observed 35% reduction in major CV events highlights the benefit of statins not only through LDL-C lowering but also via anti-inflammatory and pleiotropic effects. However, widespread implementation should be carefully balanced against the risk of overtreatment and considerations of cost-effectiveness, particularly in resource-limited settings.

Beyond its therapeutic implications, REPRIEVE also highlights a broader conceptual issue: the persistent dissociation between virological control and CV health in PLWH. Despite effective ART and viral suppression, residual CV risk remains substantial. This discrepancy is reflected in our cohort, where optimal virological control coexisted with poor LDL-C target attainment and a high burden of modifiable CV risk factors. These observations emphasize that viral suppression alone is insufficient to ensure adequate CV protection and that comprehensive cardiometabolic management should be an integral component of long-term HIV care.

Several limitations of our study should be acknowledged. Firstly, in-depth analyses were performed only in a smaller sample subgroup for feasibility and limited resources reasons. Although, we implement a random selection of the cohort, we cannot completely exclude a selection bias that could have affected the results of our study. Due to this, our study could be underpowered to detect modest associations, particularly with HIV-related variables. Also regarding HIV-related variables the presence of a high viral suppression (84.9% of the subjects) could further limit the statistical power to detect significant findings. Secondly, the retrospective single-center design may limit generalizability. Thirdly, the cross-sectional nature of the analysis precludes assessment of longitudinal outcomes. Finally, potential confounders that may have affected our results including adherence to therapy and socioeconomic factors were not systematically collected. Furthermore, also other variables that could help refine CV risk stratification (such as C-reactive protein or lipoprotein(a)) were not systematically assessed in our cohort.

5. Conclusion

In this cohort of HIV-positive patients on stable ART, LDL-C target achievement was low, with fewer than one-third of patients reaching guideline-recommended levels, and this does not necessarily reflect adequate cardiovascular risk control. Despite good virological control, CV prevention remains suboptimal, as current risk models fail to fully capture the additional burden linked to chronic HIV infection and long-term therapy. This underestimation underscores the need for more intensive lipid-lowering strategies and the development of refined predictive tools that integrate HIV-specific factors, in order to achieve more effective and individualized CV risk management.

Data availability statement

Data will be available upon request to the corresponding author.

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Declaration of competing interest

The authors report no conflict of interest.

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