LDL-C target achievement in people living with HIV: impact of combination lipid-lowering therapy. A retrospective cohort analysis

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Background: Real-world low-density lipoprotein cholesterol (LDL-C) target attainment remains low in people with HIV (PWH). Updated ESC/EAS 2025 guidelines underscore the need to reassess treatment patterns in clinical practice.

Methods: Retrospective observational longitudinal study including PWH ≥40 years, evaluated twice between 2020 and 2025 at the Modena HIV Metabolic Clinic, with complete laboratory and clinical follow-up data. Objective was to evaluate the real-world use and effectiveness of different lipid-lowering therapy (LLT) regimens in achieving guideline-based LDL-C targets.

Results: Among 588 PWH (71.8% male), median age was 60 years (IQR 56–64) and 97.4% had suppressed HIV viral load. According to cardiovascular (CV) risk classification, 29.3% were at moderate risk, 52% at high risk, 12.4% at very high risk and 6.3% at extreme risk. LDL-C target attainment increased from 19.6% at baseline to 28.8% at follow-up. Achievement rates declined with increasing CV risk. In multivariable analysis, combination LLT was the strongest predictor of LDL-C target attainment (odds ratio 5.7, 95% confidence interval 3.7–9.0, $P < 0.0001$), whereas statin dose escalation was not. Diabetes was also associated with greater odds of reaching LDL-C goals.

Conclusions: LDL-C control remains suboptimal in PWH, particularly among those at higher cardiovascular risk. Combination lipid-lowering therapy markedly increases the likelihood of achieving LDL-C targets, supporting broader adoption of combination strategies in routine HIV care.

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Introduction

Cardiovascular disease has emerged as a major cause of morbidity among people with HIV (PWH) [1]. This excess risk reflects traditional cardiovascular risk factors and HIV-related mechanisms, including persistent immune activation, chronic inflammation and long-term exposure to antiretroviral therapy [2,3]. Cardiovascular prevention remains an important challenge in aging PWH, particularly in those with multiple metabolic comorbidities [4].

Following the REPRIEVE trial [5], recent European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines recommend statin therapy for PWH aged 40 years or older in primary prevention [6]. Notably, the cardiovascular benefit observed in REPRIEVE appeared greater than expected from low-density lipoprotein cholesterol (LDL-C) reduction alone, suggesting additional mechanisms beyond lipid lowering. Real-world data suggest that a large proportion of PWH fail to reach LDL-C targets [7] with statins alone, emphasizing the need for integrated treatment strategies. However, real-world data on treatment patterns and LDL-C goal attainment in PWH remain limited.

In this retrospective cohort of PWH followed at the Modena HIV Metabolic Clinic, we aim to evaluate the real-world use and effectiveness of lipid-lowering therapy (LLT) in optimizing lipid control among PWH and to identify factors associated with successful LDL-C target achievement in this population.

Methods

Study design and population

Single-center retrospective observational cohort study conducted at the Modena HIV Metabolic Clinic, University of Modena and Reggio Emilia. The study included PWH aged $\geq$40 years who underwent two clinical evaluations between 2020 and 2025 and had complete lipid panel results available at both visits (follow-up: minimum 60 days and maximum 540 days). The final cohort consisted of all eligible PWH in the clinical database who fulfilled these criteria during the study period; no additional sampling procedure was applied. Data were extracted from electronic medical records and included demographic and anthropometric characteristics, cardiovascular comorbidities, HIV-related parameters, antiretroviral treatment exposure, lipid profile and LLT. Patients were referred to our Clinic in case of suboptimal metabolic control despite specialist care or based on patient choice. Cardiovascular risk was assessed at the first clinical evaluation using SCORE2 for individuals aged 40–69 years and SCORE2-OP for those aged 70 years or older [8,9]. Participants were then classified as being at moderate, high, very high or extreme cardiovascular risk according to ESC/EAS definitions [6]. In addition to calculated risk, clinical conditions relevant to guideline-based cardiovascular stratification were considered, including established atherosclerotic cardiovascular disease, diabetes mellitus, chronic kidney disease, hypertension and smoking status. LDL-C treatment goals were defined according to risk category: $<$100 mg/dl for moderate risk, $<$70 mg/dl for high risk, $<$55 mg/dl for very high or extreme risk. Since the updated classification introducing the "extreme risk" category was recently released, patients now considered at extreme risk had previously been classified as very high risk with an LDL-C target $<$55 mg/dl instead of $<$40 mg/dl. Because the ESC/EAS 2025 focused update was released after most clinical decisions in the study period had been made, risk categories and LDL-C treatment goals were applied retrospectively to reassess lipid control according to contemporary recommendations rather than to evaluate adherence to guidelines available at the time of care.

Study outcome

The primary study outcome was LDL-C target achievement at follow-up according to cardiovascular risk category. Secondary outcomes included changes in LDL-C levels between baseline and follow-up, temporal changes in LLT use, and the frequency of treatment intensification strategies. Combination LLT referred to the concurrent use of two or more lipid-lowering agents. Statin intensity was categorized according to expected LDL-C reduction in routine clinical practice.

Statistical analysis

Continuous variables were summarized as medians and interquartile ranges (IQR), categorical variables were expressed as counts and percentages. Between-group comparisons were performed using Kruskal–Wallis or chi-square tests, as appropriate. Multivariable logistic regression models were used to identify predictors of LDL-C target attainment at follow-up. Covariates considered in the analysis included cardiovascular risk category, diabetes, new LLT prescription, statin dose escalation, use of combination therapy and current antiretroviral exposure. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). A two-sided P value $<$0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics, version 26 (IBM Corporation, Armonk, NY, USA) and RStudio Version 2025.05.0+496.

Results

The study included 588 PWH with a median age of 60 years (IQR 56–64); 71.8% were male and 97.4% had suppressed HIV viral load. According to SCORE2/SCORE2-OP classification, 172 individuals (29.3%) were at moderate cardiovascular risk, 306 (52.0%) at high risk, 73 (12.4%) at very high risk and 37 (6.3%) at extreme risk.

Individuals in higher cardiovascular risk groups were older and more likely to have diabetes, hypertension and current smoking (Table S1, Supplemental Digital Content, https://links.lww.com/QAD/D951). HIV-related parameters, including current virological suppression and immunological status, were broadly comparable across risk groups (Table S1, Supplemental Digital Content, https://links.lww.com/QAD/D951).

At baseline, LDL-C levels and rates of LDL-C target achievement differed according to cardiovascular risk category. Participants at moderate risk had the highest proportion of target attainment, whereas those at high, very high and extreme risk had progressively lower proportions of patients already at target (Table S2, Supplemental Digital Content, https://links.lww.com/QAD/D951). Across the whole cohort, LDL-C target attainment increased from 19.6% at baseline to 28.8% at follow-up ($P < 0.0001$). However, this overall improvement masked substantial heterogeneity across cardiovascular risk groups. At follow-up, 46.5% of individuals at moderate risk achieved LDL-C targets, compared with 22.9% at high risk, 15.1% at very high risk and 21.6% at extreme risk (Table S2).

As illustrated in Fig. 1, both LDL-C values and LDL-C goal attainment showed a gradient across cardiovascular risk categories. Median LDL-C values declined modestly between baseline and follow-up in the moderate and high-risk groups, whereas more limited changes were observed in very high and extreme risk groups. Despite some temporal improvement, the proportion of participants meeting guideline-recommended LDL-C goals remained low across higher-risk categories.

Lipid-lowering therapy use increased over time. At follow-up, a greater proportion of patients were receiving statins and other lipid-lowering agents than at baseline. Treatment intensification occurred through several pathways, initiation

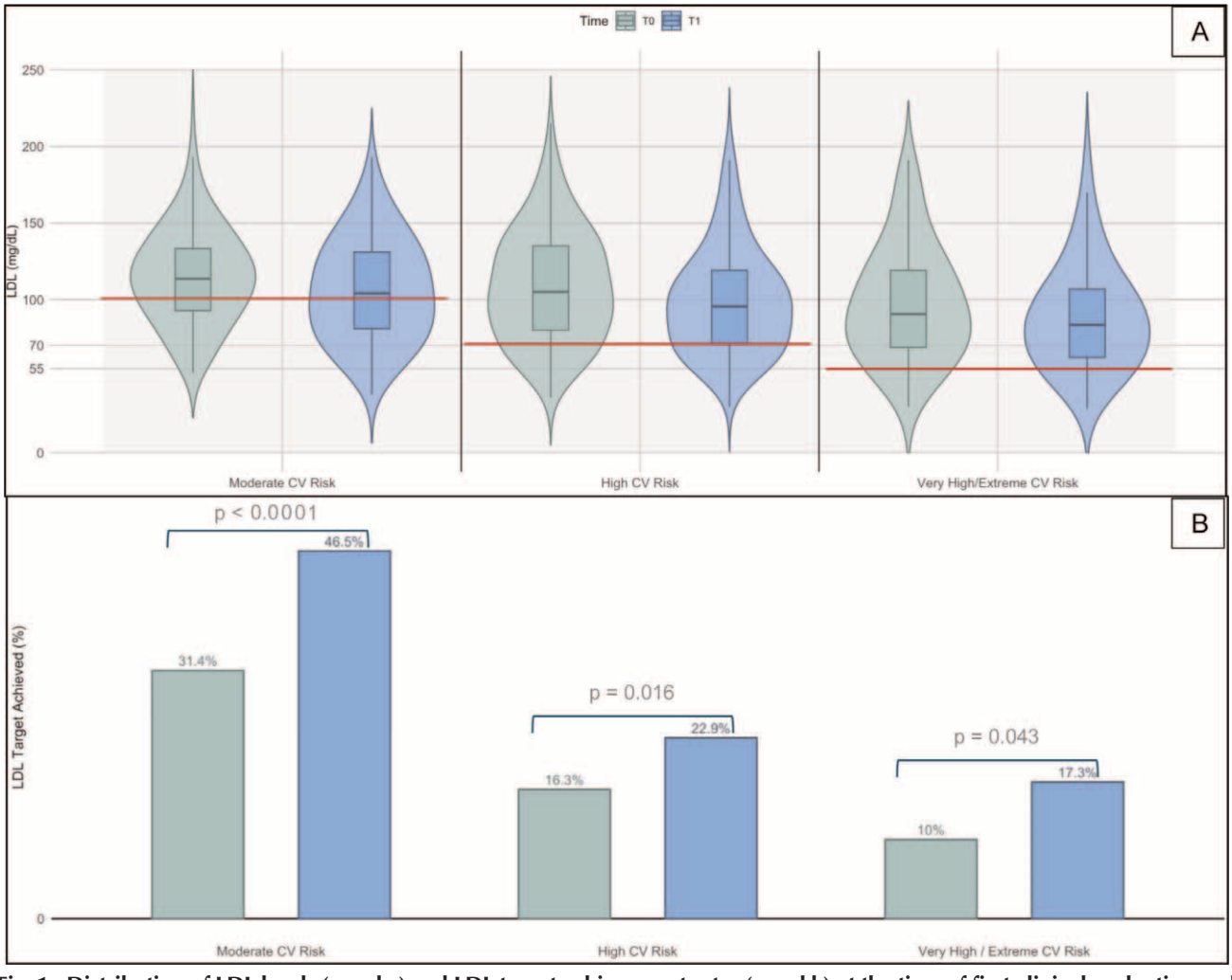

Fig. 1. Distribution of LDL levels (panel a) and LDL target achievement rates (panel b) at the time of first clinical evaluation and follow-up in moderate, high and very high to extreme cardiovascular risk PWH. LDL, low-density lipoprotein; PWH, people with HIV.

of a new lipid-lowering agent in previously untreated individuals, escalation of statin dose, and the adoption of combination regimens. Overall, 12.1% of participants switched from monotherapy to combination therapy between baseline and follow-up. Combination regimens were predominantly based on statin plus ezetimibe, accounting for 110 of 116 combination regimens at baseline and 181 of 197 at follow-up; combinations including bempedoic acid or PCSK9 inhibitors were uncommon. (Table S2, Supplemental Digital Content, https://links.lww.com/QAD/D951).

Among participants initiating LLT, high-intensity statin therapy was associated with the largest reduction in LDL-C, whereas moderate-intensity statins produced more modest reductions. Treatment intensification by statin dose escalation alone did not translate into a higher probability of guideline target achievement in the adjusted analyses.

An independent inverse association was observed between LDL-C target achievement and cardiovascular (CV) risk category, with increasing risk levels corresponding to progressively lower odds of target attainment in multivariate logistic analyses (high CV risk, OR = 0.210, 95% CI (0.130–0.337); very high CV risk, OR = 0.082, 95% CI (0.036–0.187; extreme CV risk, OR = 0.077, 95% CI (0.028–0.210), $P < 0.0001$).

The strongest positive predictor of LDL-C target achievement was combination LLT, which was associated with an approximately six-fold increase in the odds of reaching target LDL-C levels (OR 5.7, 95% CI 3.7–9.0, $P < 0.0001$). Diabetes was also independently associated with higher odds of target attainment, by contrast, statin dose escalation and new LLT prescription alone were not independently associated with LDL-C goal achievement.

Table 1 summarizes the multivariable predictors of LDL-C target achievement. In addition, the analysis confirms the inverse relationship between higher cardiovascular risk categories and successful LDL-C control. Current nucleoside reverse transcriptase inhibitors (NRTI) exposure retained a modest positive association in the adjusted model, although the main clinically relevant message of the analysis remains the strength of the association between combined lipid-lowering regimens and goal attainment.

Discussion

In this real-world cohort of PWH, LDL-C target attainment was suboptimal, and combination LLT played a central role in improving control, underscoring the importance of tailored, risk-adapted strategies that integrate both metabolic and HIV-specific factors, particularly for those at highest cardiovascular risk. Although LDL-C target attainment remained suboptimal, achievement improved during follow-up in parallel with increased use of LLT and a notable shift toward combination regimens.

PWH with diabetes were more likely to reach LDL-C goals, possibly reflecting more focused cardiometabolic management, while those in higher cardiovascular risk categories had markedly lower odds of successful achievement despite broader use of therapy, underscoring persistent gaps in managing the patients most in need of aggressive intervention. HIV-specific factors, including antiretroviral regimen composition, may also influence lipid outcomes, although the small proportion of patients receiving protease inhibitors in our cohort limits any firm conclusion on this point.

Our findings are consistent with observations from the general population. Large European observational studies such as DA VINCI and SANTORINI have shown that fewer than one quarter of very high-risk individuals achieve contemporary LDL-C goals, largely because treatment often remains centered on statin monotherapy and combination regimens are underused [10–13]. The present study extends these observations to PWH, a population in which cardiovascular risk is increased by both traditional and HIV-related mechanisms [1].

A clinically relevant finding of this study is the strong association between combination LLT, predominantly statin plus ezetimibe, and LDL-C target achievement. Treatment with combination therapy was associated with a more than fivefold higher likelihood of achieving LDL-C

Table 1. Multivariable logistic regression analysis for the prediction of LDL target achievement.

Variable	Adjusted OR	95% CI	*P* value
Combination lipid-lowering therapy	5.73	3.65–9.00	**<0.0001**
Diabetes	3.05	1.75–5.29	**<0.0001**
High CV risk	0.21	0.13–0.34	**<0.0001**
Very high CV risk	0.08	0.04–0.19	**<0.0001**
Extreme CV risk	0.07	0.03–0.21	**<0.0001**
Current NRTI exposure	1.65	1.08–2.52	**0.022**

CI, confidence interval; CV, cardiovascular; OR, odds ratio.

targets. As LDL-C targets become increasingly stringent, particularly in high and very-high risk patients, statin monotherapy may be insufficient for many individuals. In this context, combining agents with complementary mechanisms of action represents a more effective strategy for achieving guideline targets.

In this cohort, combinations were predominantly based on statin plus ezetimibe, consistent with current clinical practice, whereas regimens including bempedoic acid or PCSK9 inhibitors were less frequent. The observed effect of combination therapy suggests that earlier use of such regimens should be considered in PWH who remain above target despite statin treatment.

Diabetes was also associated with higher LDL-C target attainment, possibly reflecting closer cardiometabolic monitoring and more aggressive treatment in this subgroup [14,15]. By contrast, individuals in higher cardiovascular risk categories remained less likely to achieve LDL-C goals, suggesting that current practice may still be insufficiently aligned with contemporary guideline recommendations.

Several factors may contribute to poor LDL-C control in routine HIV care. Drug–drug interaction concerns with antiretroviral therapy may limit statin dosing [16], while metabolic effects of certain antiretroviral regimens can complicate dyslipidemia management [17]. In addition, barriers such as limited familiarity with newer lipid-lowering agents and reimbursement constraints may restrict broader implementation of combination therapy. Recent ESC/EAS guideline updates recommend both a universal statin strategy for PWH aged 40 years or older and a more intensive, target-oriented approach for individuals at higher cardiovascular risk [6]. Our findings support this paradigm and suggest that earlier use of combination LLT may improve LDL-C control in routine HIV care. Furthermore, beyond supporting intensified lipid-lowering strategies, the findings of REPRIEVE underscore the urgent need to define HIV-specific LDL-C targets based on prospective cardiovascular outcome data in people with HIV, rather than relying exclusively on risk stratification models derived from the general population. Moreover, cardiovascular risk in PWH extends beyond atherosclerotic disease, including heart failure phenotypes potentially linked to myocardial fibrosis and steatosis, conditions in which the nonlipid effects of statins may also be relevant. This study has limitations. Its retrospective single-center design does not allow causal inference and may limit generalizability. Selection bias cannot be excluded, as the study population consisted exclusively of patients evaluated at the Metabolic Clinic. In addition, data on the use of SGLT2 inhibitors and GLP-1 receptor agonists were not systematically collected, preventing assessment of their potential contribution to cardiometabolic outcomes. Nevertheless, the study also has strengths, including a relatively large sample size and repeated clinical and laboratory evaluations.

Overall, LDL-C target attainment remains inadequate in PWH, particularly among those at highest cardiovascular risk. While combination LLT, mainly statin plus ezetimibe, was associated with improved target achievement, these findings also underscore the need for prospective HIV-specific cardiovascular outcome data to define optimal LDL-C targets and treatment strategies in this population.

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Conflicts of interest

There are no conflicts of interest.

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