

Distance from low-density lipoprotein cholesterol targets across cardiovascular risk strata in people living with HIV: a multicentre cohort study

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Highlights

- REPRIEVE supports broader statin use in people living with HIV (PLWH).
- At study entry, 73.6% of SCOLTA participants met criteria for statin therapy.
- Fewer than one in four eligible PLWH received statin therapy.
- LDL-C excess persisted despite statin treatment and increased with cardiovascular risk.
- LDL-C excess reveals a major gap between guidelines and clinical practice.

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DISTANCE FROM LOW-DENSITY LIPOPROTEIN CHOLESTEROL TARGETS ACROSS CARDIOVASCULAR RISK STRATA IN PEOPLE LIVING WITH HIV: A MULTICENTRE COHORT STUDY

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Abstract:

Introduction: Previous studies have described the gap between statin indication and prescription among people living with HIV (PLWH) using binary measures, which fail to capture the magnitude of residual lipid burden.

Objectives: To quantify lipid burden in PLWH by measuring the distance from recommended LDL-cholesterol (LDL-C) targets ("LDL-C excess") across cardiovascular risk categories.

Design: Multicentre, nationwide, prospective cohort study.

Methods: We analysed data from 2,190 PLWH enrolled in the SCOLTA cohorts between 2015 and 2025, contributing 13,512 clinical observations (visits). Cardiovascular risk was assessed using SCORE2. LDL-C targets were defined according to the minimum thresholds recommended by historical European AIDS Clinical Society guidelines. LDL-C excess was calculated as the difference between observed LDL-C and the corresponding target and summarised as mean values with 95% confidence intervals (CI).

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Results: The proportion of visits meeting statin therapy criteria increased from 64.6% in 2015 to approximately 80% after 2021, whereas statin prescription rose only from 12.5% to 25.4%. LDL-C targets were achieved in 9.7% of visits. Mean LDL-C excess was 18 mg/dL in low-risk, 40 mg/dL in the intermediate, and 51 mg/dL in high-risk individuals. The excess was lower but remained substantial even among statin-treated PLWH.

Conclusions: LDL-C excess highlights a clinically meaningful gap between guidelines and practice, particularly among intermediate- and high-risk PLWH, underscoring the urgent need for systematic lipid-lowering in the post-REPRIEVE era.

Key words: statin; HIV; cardiovascular diseases; prevention; Lipid management; LDL-cholesterol targets

Introduction

In people living with HIV (PLWH) on antiretroviral therapy (ART), achieving undetectable HIV-RNA is now the minimum objective of effective ART but not enough to control the chronic inflammation, and prevent serious non-AIDS events that emerged as relevant causes of morbidity and mortality, especially cardiovascular disease (CVD).[1] In addition, traditional CV risk factors largely prevalent in PLWH impact negatively on the occurrence and prognosis of CVD.[2,3] Among these risk factors, hypercholesterolemia has been recognized as a critical modifiable condition. Current international guidelines mandate preventive interventions for lifestyle modification, as well as pharmacological interventions on lipid levels, to improve CVD prognosis in HIV patients. The recommendations for lipid-lowering treatment initiation are based on the curvilinear relation between low-density lipoprotein cholesterol (LDL-C) and CVD risk and the evidence from randomized clinical trials (RCTs) demonstrating the efficacy of statins for primary prevention of CVD.[4] In PLWH, it has also been known for many years that a significant gap exists between statin eligible and treated people, with a substantial proportion of persons with lipid-lowering treatment indication not receiving drugs.[5] In fact, previous reports clearly emphasize the underutilization of statins in PLWH in clinical practice. In contrast, the European AIDS Clinical Society (EACS) guidelines include the recent recommendations provided by the European Society of Cardiology (ESC) and strongly advice an ambitious treatment goal, 1.4 mmol/L (55 mg/dL) of LDL-C for very high risk and 1.8 mmol/L (70 mg/dL) for high-risk people.[6,7]

The cumulative exposure to LDL-C plays a critical and progressive role in the process of atherosclerosis and strongly impacts on CVD. The REPRIEVE clinical trial has provided robust evidence showing a significantly lower risk of major CVD events in participants with HIV who received pitavastatin, than in those who received placebo, over a median of 5.1 years.[8] Consequently, HIV infection is recognized as a CVD “risk-enhancing” factor[9] and the indication to statin use is now extended for primary prevention to all PLWH aged 40-75 years.[10] Given the attention in recent years towards CVD in PLWH, comprehensive clinical interventions to impact on traditional CV risk factors control is conceivable.

We aimed at assessing and quantifying, in a clinical practice context, the excess of LDL-C versus LDL-C goal in PLWH enrolled in the Surveillance Cohort Long-Term Toxicity Antiretrovirals/antivirals (SCOLTA) project. This study involved several Italian sites that prospectively followed PLWH starting new antiretroviral regimens, allowing us to investigate factors associated with LDL-C excess.

Methods

We analysed data from the SCOLTA prospective database. The SCOLTA project, a multicentre observational cohort study, started in 2002 and prospectively follows PLWH who start treatment with new antiretroviral drugs, to identify toxicities and adverse events (AE) in a real-life setting.[11] The SCOLTA project uses an on-line pharmacovigilance program (www.cisai.it) and currently involves 30 Italian Infectious Disease Centres.

Briefly, both ART-naïve and ART-experienced PLWH can be included in SCOLTA if they are ≥ 18 years and agreed to enter the study. Clinical data collected include sex, age, ethnicity, weight, height, CDC stage, and previous ART history. Laboratory data include HIV-RNA, CD4+ T-cell count, and biochemical data, and are prospectively collected in anonymous form in a central database every six months. AEs are collected prospectively as soon as they are clinically observed. Currently, four cohorts are open to enrolment and

follow-up: dolutegravir (open 2015); bicitgravir (open 2019); doravirine (open 2020); cabotegravir (open 2022).

Ten-year CVD risk calculations were derived from the SCORE2 equation for moderate risk regions and used over the whole study period (2015-2025).

Among PLWH enrolled in the SCOLTA cohorts since 2002, we included all patients enrolled in the currently open cohorts (2015-2025). In this analysis, we included all enrolment and follow-up visits where at least one LDL-C was present. Moreover, if we could not assign a CV risk category, people were excluded from the analysis. Observation was truncated on 31st December 2025.

We evaluated according the EACS guidelines [6,7] LDL-C thresholds in 3 strata: low CVD risk if ten-year risk calculations by SCORE2 was <5.0%, in absence of other risk factors (diabetes, hypertension, current smoking, total cholesterol (TC) >310 mg/dL or LDL-C > 190 mg/dL, estimated glomerular filtration rate, eGFR, < 60 mL/min); intermediate risk if estimated 10-year CVD risk was between 5.0% and lower than 10.0% (or with any other risk factor); and high risk if SCORE2 was 10% or more or if the person was diagnosed with major CVD or chronic renal impairment. SCORE2 is not validated in people aged less than 40 years. However, since the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) 2019 guidelines[12] suggested that PLWH should be considered as a category at risk due to the infection (class of recommendation IIa, level of evidence C), we chose to also include this younger age category in the analysis, even if we did not include them as a high-risk category. Using the SCORE2 equation instead of the chart, we could calculate the score even in people younger than 40 (young age contributed to lower the score). People with evaluable CVD risk at the first evaluation in SCOLTA and at least one follow-up visit were included in the analysis (all variables needed to calculate SCORE 2 and/or previous CVD/renal impairment).

We considered candidates to receive statins people with LDL-C higher than the minimum goal, as follows.

We considered in this analysis a minimum possible goal, according to previous EACS guidelines 10.0 before the extension of statin indications,[13] that lipid control was reached in primary prevention if LDL-C was lower than 115 mg/dL in PLWH with low CVD risk, lower than 80 mg/dL with moderate CVD risk and lower than 55 mg/dL with high CVD risk or in secondary prevention. If we could not calculate LDL-C, we used the TC, using 190, 155 and 115 mg/dL respectively as the cut-off values. The historical LDL-C thresholds were used to assess a minimum acceptable care, not the optimal care, so the results likely underestimate the actual implementation gap in statin treatment. The distance from the goal (or excess) was calculated as the difference between the actual LDL-C value and the LDL-C threshold for the CVD risk category. The excess could be negative if the LDL-C value was lower than the threshold. TC values were only used as substitutes of LDL-C to evaluate the lipid control, whereas mean LDL-C excess were calculated only if the actual value was reported.

If PLWH were already on statins at study entry, they are considered candidates to receive them, regardless of their CVD risk and LDL-C level. In fact, even LDL-C were under the threshold, we assumed that statins were prescribed because the initial level of LDL-C was higher than indicated.

In addition, we evaluated the atherogenic index of plasma (AIP), which is the logarithmically transformed ratio of molar concentrations of triglycerides and high-density lipoprotein cholesterol (HDL-C),[14] and comprehensively reflects the atherogenic and anti-atherogenic factors. AIP has been shown to be a strong

marker for predicting the risk of coronary artery disease (CAD).[15] We aimed at describing the AIP trend over time and by group of statin treatment.

Information on concomitant pharmacological treatments and comorbidities is collected at baseline and updated every six months.

The ethical approval was originally obtained on 18 September 2002 by the Ethics Committee of the “L. Sacco” Hospital, where the principal investigator (dr. Rizzardini) was working at the time. Amendments were requested in 2013, 2019, 2020 and 2023: with the last amendment, the role of Principal Investigator was taken by dr. Bonfanti (IRCCS San Gerardo Monza), and the reference Ethics Committee changed.

Written consent for study participation was obtained from all participants, and the study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, and by Italian national laws.

Statistical analysis

Data were described using mean and standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR) for not normally distributed continuous variables and frequency (%) for categorical and ordinal variables.

We aimed at evaluating the association between the LDL target achievement (according to CV risk) or the difference between the recorded LDL-C and the target value, in each visit, and PLWH and treatment characteristics. The distance between the recorded LDL-C and the target value is reported as mean and 95% confidence interval (95% CI).

As variables potentially associated with the dependent variable and/or the exposure, we included sex, age, ethnicity, drug cohort, hepatitis C virus coinfection (HCV), smoking habits, concomitant tenofovir disoproxil fumarate (TDF) use, diabetes, and hypertension in the multivariate model. Although open cohorts only included INSTIs (dolutegravir, bictegravir, cabotegravir) or NNRTIs (doravirine, injectable rilpivirine), PI could be used in association with dolutegravir. Moreover, in case of cohort treatment discontinuation, the last used regimen was recorded, and a post-interruption visit was included, where a PI-including regimen could be assigned. Thus, we also included PI use in the multivariate analysis. To evaluate the effect of within-person correlation, we also performed a sensitivity analysis, including the subjects' identifier.

New diagnoses of diabetes were evaluated using the Cox proportional hazard regression model, including sex, age, and initial level of blood glucose in the multivariate model analysing the effect of statin use: results were given as adjusted hazard ratios (aHR) and the corresponding 95% CI.

All Ps were two-sided, at the significance level <0.05 . Statistical analyses were performed using SAS for Windows 9.4 (SAS Institute, Cary, NC).

Results

Study Population

Overall, 13,512 observations were analysed, from 2,190 PLWH with a median observation time of 32 months (IQR 18-52). Characteristics of the study population by cohort are summarized in Table 1.

The proportion of candidates to statin treatment in each visit increased over time, from 64.6% in 2015 to a maximum of 81.5% in 2021 and remained about 80% since. Among candidates, the proportion of visits

where people were recorded on statins increased from 12.5% to 25.4% (Figure 1), representing respectively 19.3% and 32.3% of people in need of statin treatment.

Targets

LDL-C target was obtained in 9.7% of visits (Table 2). Overall, LDL-C was unavailable in 274 visits out of 10495 (2.6%) and replaced by the TC targets. The mean distance from the target was 18 mg/dL (95% CI 5-31) in the low, 40 mg/dL (95% CI 39-41) in the intermediate and 51 mg/dL (95% CI 49-52) in the high-risk category. By statin use, these values were significantly different (Table 2); the mean distance from the target was 27 mg/dL (95% CI 24-29) in the intermediate and 35 mg/dL (95% CI 33-38) in the high-risk category. LDL-C target was not obtained in 70.0% and 79.7% of PLWH at intermediate and high-risk CV profile. Figure 2 shows the distribution of the last measured LDL-C level in strata of CV risk, highlighting in red the proportion of measures outside the desired target.

Adjusting by age, sex, HCV coinfection, ethnicity, cohort drug, naïve status at study entry, TDF-including regimen, PI-including regimen, use of statin, diabetes, hypertension, and smoking status, the mean distance from the minimum considered target was -1 mg/dL (95% CI -5 to 2), 28 mg/dL (95% CI 24 to 31) and 47 mg/dL (95% CI 43 to 50) respectively in strata of CV risk. When we accounted for repeated measures and included the subjects' identifier in the model, the mean LDL-C excess was -1 mg/dL (95% CI -5 to 3), 28 mg/dL (95% CI 25 to 31) and 47 (95% CI 44 to 51), with minimal differences between models.

Nevertheless, the atherogenic index of plasma significantly improved, both in statin-treated and untreated people (Table 3).

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Over the whole study period, 517 PLWH were prescribed statins, and 43 (8.3%) discontinued the treatment during the observation period (18 started statins again): regrettably, the reason was not specifically collected in our database.

Using the CV risk definition and LDL-C thresholds of EACS guidelines 12.0, we analysed the LDL-C excess and target according to statin use (Table S). In this case, we only used the observation where LDL-C was present to evaluate how many people were candidates to statin. Then, we analysed a sample of 13203 visits (excluding 309 visits with only TC values), with 10265 candidates to statin. As expected, with the new criteria we found a slightly higher proportion of candidates (77.8% vs 77.4%) and a larger LDL-C mean excess (48 mg/dL in PLWH not on statin vs 31 mg/dL on statin). The mean distance from the target was 17 mg/dL (95% CI 16-18) in the low, 24 mg/dL (95% CI 23-26) in the moderate, 49 mg/dL (95% CI 48-50) in the high-risk, and 56 mg/dL (95% CI 55-57) in the very high-risk category. When the multivariate model including the people's identifier was run on this sample, we found that the mean LDL-C excess was -8 mg/dL in the low (95% CI -11 to -4), -2 mg/dL (95% CI -6 to 2) in the moderate, 33 mg/dL (95% CI 29 to 36) in the high-risk, and 50 mg/dL (95% CI 46 to 53) in the very high-risk category.

Exploratory analyses

Since a major clinical concern about statin-related adverse effects, we analysed how many cases of diabetes were diagnosed during the observation. Overall, out of 2065 PLWH without diabetes at study entry, 43 (2.1%) were diagnosed with diabetes during the observation (median time at diagnosis 18 months, IQR 10-35): in 450 PLWH exposed to statin before the diagnosis, we found 17 (3.8%) new cases, whereas in 1,615 unexposed to statin, the new cases were 26 (1.6%). Including sex, age and blood glucose level at study entry in the model, we found that the main determinants of the risk of diabetes were age (adjusted HR by 1

year 1.04, 95% CI 1.01-1.07) and increased blood glucose at study entry (reference category <90 mg/dL: 90-99 mg/dL aHR 5.87, 95% CI 1.58-21.83; 100-109 mg/dL aHR 12.43, 95% CI 3.26-47.38; 110-125 mg/dL aHR 61.00, 95% CI 17.83-108.78). Adjusted HR for statin use was 1.24 (95% CI 0.65-2.36, $p=0.51$). However, since part of the sample entered the study when already on statin, and this was associated with blood glucose level ($p<0.0001$), we analysed 1783 PLWH who started statins after study entry: 27 (1.5%) were diagnosed with diabetes over the observation period, one out of 168 starting statin (0.6%) and 26 (1.6%) out of 1,615 never exposed. Age and blood glucose level remained the main determinants, but nothing significant could be inferred regarding statin treatment in this subgroup.

Discussion

In this multicentre, real-world cohort of Italian people living with HIV, a substantial and persistent gap exists between guideline recommended lipid management and routine clinical practice. Across more than 13,500 visits from 2,190 individuals enrolled in the SCOLTA project between 2015 and 2025, most patients met criteria for statin therapy, yet only a minority received treatment. LDL-C target attainment remained low across all cardiovascular risk strata, while the mean LDL-C excess above recommended targets was high, especially among those with moderate or high CV risk. The target of LDL-C remains not achieved also in statin treated PLWH. Despite the increasing awareness of cardio metabolic comorbidities and the recognition of HIV as an independent CVD risk enhancer by the 2018 ACC/AHA cholesterol management guidelines,[16] together with the availability of effective lipid-lowering therapies in PLWH, these findings highlight major and persistent weaknesses in CV prevention strategies, even in centres where the clinicians are theoretically confident with metabolic and CV problems in PLWH.

The most remarkable observation is the high proportion of PLWH who met the criteria for statin therapy, even exceeding 80% of all visits in the most recent years, in contrast with the relatively low prescription rates, which remained below one third of eligible individuals in 2025. Even after the publication of pivotal and robust data supporting statin use in PLWH, such as the REPRIEVE trial,[8] uptake within our cohort improved only modestly (from 28.0% in 2023 to 28.6% in 2024 and 32.3% in 2025). As a direct consequence of under-treatment, fewer than 10% of visits met LDL-C targets based on EACS guidelines. The calculated LDL-C excess provides a clear, quantitative measure of the magnitude of under-treatment, averaging 40 mg/dL above target in moderate risk and more than 50 mg/dL in high-risk individuals.

Despite the low proportion of treated patients, trends in lipid parameters, including reductions in the AIP, improved over time across all ART cohorts. These findings likely reflect the progressive inclusion of metabolically neutral ART regimens and the declining use of “lipid toxic” regimens. However, the improvement in AIP did not translate into adequate LDL-C target attainment.

Our results strongly confirm earlier studies reporting substantial gaps between statin indication and prescription among PLWH in Europe and North America.[5,17] Similar to the NAACCORD findings, clinician awareness and possible concerns about drug-drug interactions contribute to the under-treatment of dyslipidaemia.[18] In addition, PLWH with chronic HCV infection or active smoking habits were less likely to achieve LDL-C targets, reinforcing the known influence of comorbidities and lifestyle factors on lipid control.[19] The magnitude of LDL-C excess observed here is new specific data: it reflects a risk not captured by binary target attainment measures and supports the use of continuous metrics to monitor CV prevention effectiveness. A recent paper from REPRIEVE group found that the LDL-C concentrations in

PLWH were strongly related to major adverse cardiovascular events, highlighting the importance of LDL-C lowering in this population.[20]

Our findings confirm that, in the absence of adequate statin therapy, structural improvements in ART are insufficient to achieve guideline-recommended LDL-C reductions. In statin-treated patients, no relation emerged with incident diabetes.

Despite major advancements in HIV care and clear evidence supporting early lipid-lowering therapy, CV prevention still remains under-prioritized in PLWH. Several reasons may be advocated to explain this persistent gap: clinician hesitancy to prescribe statins due to drug–drug interaction concerns, perceived pill burden, and limited awareness of up-to-date guidelines.[21] Furthermore, SCORE2-based CV risk estimation may underestimate risk in PLWH, potentially contributing to underestimate the need of lipid-lowering treatment.[22] In addition, the ESC now recommends that statins be offered to all PLWH aged 40-75 years for primary prevention, regardless of their estimated risk score. This pragmatic approach acknowledges that HIV is a significant "risk enhancer" and that universal treatment for those over 40 is the most effective way to prevent major CV events at the population level. However, the theoretical indication needs to be effectively translated into a clinical context.

The low LDL-C target attainment in high-risk patients is particularly concerning. These individuals accumulate substantial atherogenic burden over time, and our LDL-C excess metric captures this unmet need more accurately than categorical goal attainment. The strong evidence of benefit demonstrated by the REPRIEVE study[8] should prompt more proactive statin initiation, even in PLWH without traditional high-CV risk.

Strengths and Limitations

The strength of this study lies in its large sample size, prospective design, long observation period, and inclusion of PLWH treated with modern ART regimens. The multicentre nature of SCOLTA enhances generalizability across diverse Italian clinical settings. Additionally, the introduction of the LDL-C excess metric represents a novel and clinically intuitive approach for evaluating good lipid control, in addition to the binary outcome.

However, the study has limitations. Its observational design prevents causal inference. Information on adherence to statins and ART, statin type and dose, and lifestyle modifications was not available. Laboratory markers of inflammation or immune activation—important considerations in CV risk among PLWH—were not collected. Lack of a non-HIV comparator group limits evaluation of whether the observed trends are specific to PLWH or reflect broader population changes. As a further limitation, we collected information about ethnicity but not country of origin: thus, if ethnicity was Caucasian, SCORE2 was calculated as if the person was Italian born, leading to underestimate or overestimate of the risk. Finally, some patients lacked complete SCORE2 data and were excluded.

Conclusions

In conclusion, this large, real-world study demonstrates that the majority of Italian PLWH meet criteria for statin therapy, yet pharmacological management remains insufficient or unrecognized. LDL-C target attainment is remarkably low, and significant LDL-C excess persists, particularly among those at the highest cardiovascular risk. Although lipid indices such as AIP show gradual improvement, these changes do not compensate for the lack of adequate statin therapy. The results of the distance from LDL-C target is a metric of implementation gap and highlight the need for stronger implementation of CV prevention strategies,

integration of lipid management into routine HIV care, and enhanced clinician awareness of current guidelines. More proactive statin use, supported by mounting evidence from recent clinical trials, is essential to reduce the growing burden of cardiovascular disease in ageing PLWH populations.

DECLARATIONS:**Data availability statement**

The data that support the findings of this study are not publicly available because they contain information that could compromise participant privacy. Data may be made available from the corresponding author upon reasonable request and with appropriate approvals.

Ethics approval statement

The original study protocol was approved on 18 September 2002, and four subsequent amendments were approved on 13 June 2013, 20 December 2019, 12 May 2020, and 12 June 2023 by the coordinating center, initially Hospital "L. Sacco"-University of Milan, Milan, Italy, and subsequently by all participating centers. Following the latest amendment, the coordinating centre became IRCCS San Gerardo, Monza, Italy. All participants provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki and applicable Italian national regulations.

Patient consent statement

All participants provided written informed consent for study participation.

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Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the authors used copilot only in order to improve readability and language of the work. After using this tool, the author(s) reviewed and edited the content as needed and takes full responsibility for the content of the published article.

Conflict of interest disclosure

GVDS received consultancy and/or speakers' fees from Gilead Science and ViiV Healthcare. **ADB** received speakers' honoraria from Gilead Sciences and ViiV Healthcare, has been an advisor for ViiV Healthcare, Gilead Sciences, and MSD, travel reimbursement by Gilead Sciences, and has received grant for research from Gilead Sciences and ViiV healthcare; **BMC** has received research grants, consultancy, and speaker's fees from Gilead, Viiv, MSD, GSK and J&J; **EP** trained personnel for Viiv and Gilead; **GM** has received consultancy and/or speakers' fees from Gilead Sciences, Janssen, Merck Sharp & Dohme, ViiV and Advanz Pharma; **LT** attended advisory boards or served as consultant or received grants for conferences participations from Gilead Sciences, ViiV Healthcare and MSD; **NS** received consultancy and/or speakers' fees from Gilead Science and ViiV Healthcare; **PB** has been on advisory board per Viiv, Gilead e MSD. The remaining authors (AG, BM, ER, ES, GC, GFP, GO, MAC, SF, SM, TB) declare that they have no conflicts of interest to disclose.

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Legend for figures.

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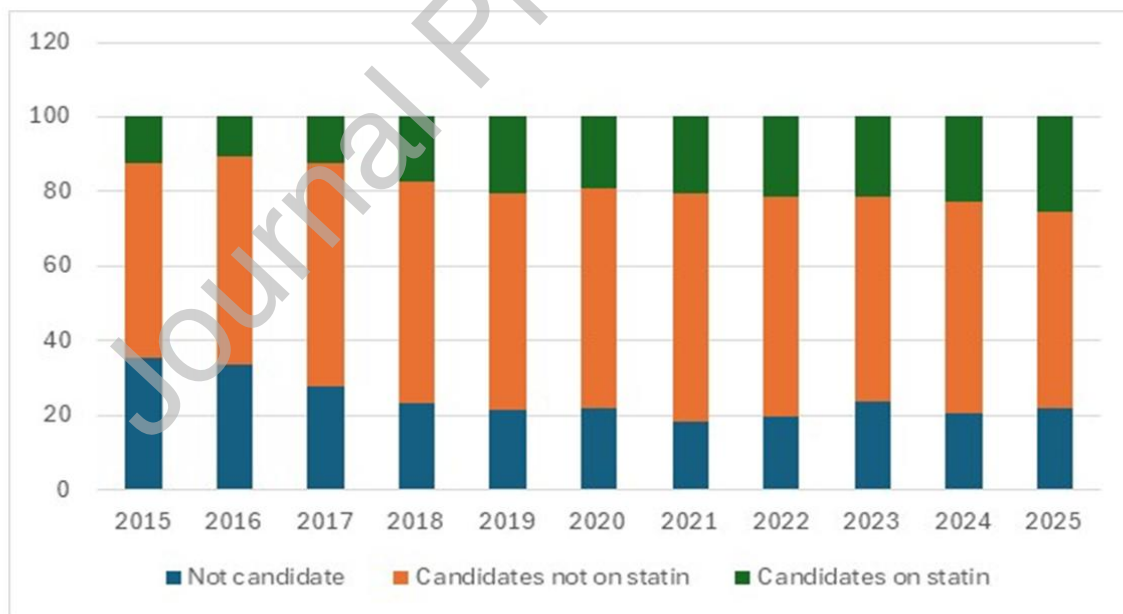


Figure 1. Candidates (%) to statin treatment and on statins by observational year.

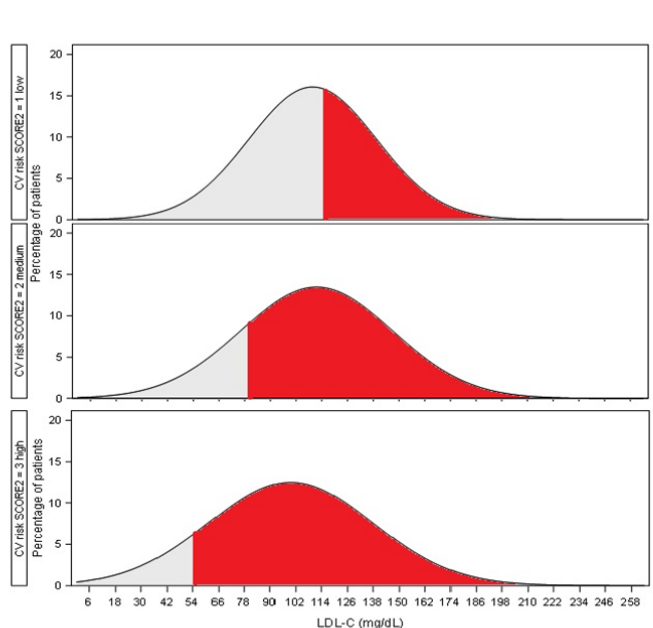


Figure 2. Distribution of last measured LDL-C by CVD risk strata (2015-2025). Grey area: on target; red area: not on target.

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Table 1. Characteristics of 2190 PLWH at enrolment in the SCOLTA project.

	N	Dolutegravir N=894	Bictegravir N=603	Doravirine N=261	Cabotegravir N=432	P
Male sex, n (%)	2190	665 (74.4)	458 (76.0)	184 (70.5)	333 (77.1)	0.23
Age, years (mean $\pm$ SD)	2190	49.0 $\pm$ 12.6	49.5 $\pm$ 12.9	52.7 $\pm$ 12.2	49.0 $\pm$ 11.7	0.0003
Caucasian ethnicity, n (%)	2190	814 (91.1)	536 (88.9)	226 (86.6)	415 (96.1)	<0.0001
BMI, kg/m ² (mean $\pm$ SD)	2033	24.5 $\pm$ 4.3	25.5 $\pm$ 4.4	26.0 $\pm$ 5.1	25.0 $\pm$ 3.7	<0.0001
BMI $\geq$ 30.0, n (%)	2033	74 (8.8)	78 (14.3)	38 (16.2)	36 (8.8)	0.0003
Intravenous drug use, n (%)	2190	132 (14.8)	94 (15.6)	39 (14.9)	48 (11.1)	0.20
HCV positive, n (%)	2125	160 (17.9)	105 (17.4)	47 (18.0)	66 (15.3)	0.54
CDC stage C, n (%)	2141	198 (22.1)	123 (20.4)	69 (26.4)	74 (17.1)	0.037
CD4 cells/mm ³ , median (IQR)	2183	590 (386-838)	586 (351-830)	663 (488-910)	765 (560-1033)	<0.0001
Naïve, n (%)	2190	219 (24.5)	144 (23.9)	20 (7.7)	0	<0.0001
Diabetes, n (%)	2190	46 (5.1)	41 (6.8)	19 (7.3)	19 (4.4)	0.22
Hypertension, n (%)	2190	198 (22.1)	156 (25.9)	89 (34.1)	95 (22.0)	0.0005
LDL-C, mg/dL (mean $\pm$ SD)	2146	112 $\pm$ 37	109 $\pm$ 37	118 $\pm$ 42	111 $\pm$ 32	0.011
AIP (median, IQR)	2186	0.40 (0.21-0.63)	0.36 (0.18-0.58)	0.39 (0.23-0.62)	0.29 (0.10-0.47)	<0.0001
Previous cardiovascular event, n (%)	2190	32 (3.6)	32 (5.3)	16 (6.1)	18 (4.2)	0.22
Smoking habits, n (%)	2190					
Never		296 (33.1)	234 (38.8)	99 (37.9)	194 (44.9)	
Current		344 (38.5)	247 (41.0)	89 (34.1)	136 (31.5)	
Former		133 (14.9)	69 (11.4)	53 (20.3)	83 (19.2)	
ND		121 (13.5)	53 (8.8)	20 (7.7)	19 (4.4)	<0.0001
TDF-including regimen, n (%)	2190	130 (14.5)	0	167 (64.0)	0	<0.0001
Candidate to statin use, n (%)	2190	638 (71.4)	439 (72.8)	216 (82.8)	319 (73.8)	0.003
On statin at T0, n (%) (in 1612 candidate PLWH)	1612	109 (17.1)	95 (21.6)	60 (27.8)	68 (21.3)	0.007
Started statin after T0 (candidate PLWH), n (%)	1280	97 (18.3)	37 (10.8)	5 (3.2)	20 (8.0)	<0.0001
CV risk, n (%)	1290					
Low		318 (36.6)	189 (31.3)	67 (25.7)	170 (39.4)	
Medium		433 (48.4)	298 (49.4)	126 (48.3)	210 (48.6)	
High		143 (16.0)	116 (19.2)	68 (26.0)	52 (12.0)	<0.0001
Observation time, months, median (IQR)	2190	45 (21-74)	34 (20-49)	26 (14-41)	23 (15-31)	<0.0001

AIP: Atherogenic Index of Plasma; BMI: body mass index; CVD: cardiovascular disease; HCV: hepatitis C virus; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; ND: not determined; PLWH: people living with HIV; SD: standard deviation; TDF: tenofovir disoproxil fumarate.

Table 2 LDL-C excess (mg/dL) in candidates to statin use (n=10495).

	N	On statin N (%)	LDL-C excess, mg/dL mean (95% confidence interval)		Target N (%)			
			On statin N=2748	Not on statin N=7747	On statin N=2748		Not on statin N=7747	
					On target	Not on target	On target	Not on target
Overall	10495	2748 (26.2)	26 (24 – 27)	42 (42 – 43)	832 (30.3)	1916 (69.7)	190 (2.4)	7557 (97.6)
Sex								
Women	2558	644 (25.2)	25 (22 – 29)	40 (29 – 41)	209 (32.4)	435 (67.6)	30 (1.6)	1884 (98.4)
Men	7937	2104 (26.5)	26 (24 – 28)	43 (42 – 44)	623 (29.6)	1481 (70.4)	160 (2.7)	5673 (97.3)
						P=0.17		P=0.004
Cohort								
Dolutegravir	5389	1421 (26.4)	29 (26 – 31)	44 (43 – 45)	399 (28.1)	1022 (71.9)	127 (3.2)	3841 (96.8)
Bictegravir	2451	617 (25.2)	21 (18 – 24)	42 (41 – 43)	216 (35.0)	401 (65.0)	37 (2.0)	1797 (98.0)
Doravirine	1072	310 (28.9)	29 (24 – 32)	41 (39 – 43)	86 (27.7)	224 (72.3)	14 (1.8)	748 (98.2)
Cabotegravir	1583	400 (25.3)	21 (17 – 25)	40 (38 – 42)	131 (32.8)	269 (67.2)	12 (1.0)	1171 (99.0)
						P=0.008		P<0.0001
CV risk								
Low	2021	358 (17.7)	-3 (-6 – 1)	22 (21 – 23)	212 (59.2)	146 (40.8)	33 (2.0)	1630 (98.0)
Medium	6124	1394 (22.8)	27 (24 – 29)	44 (43 – 45)	418 (30.0)	976 (70.0)	108 (2.3)	4622 (97.7)
High	2350	996 (42.4)	35 (33 – 38)	62 (60 – 64)	202 (20.3)	794 (79.7)	49 (3.6)	1305 (96.4)

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P<0.0001

P=0.008

Differences among sex and cohort drugs were performed using the chi-square test, and across CV risk class using the Mantel-Hanszel chi-square

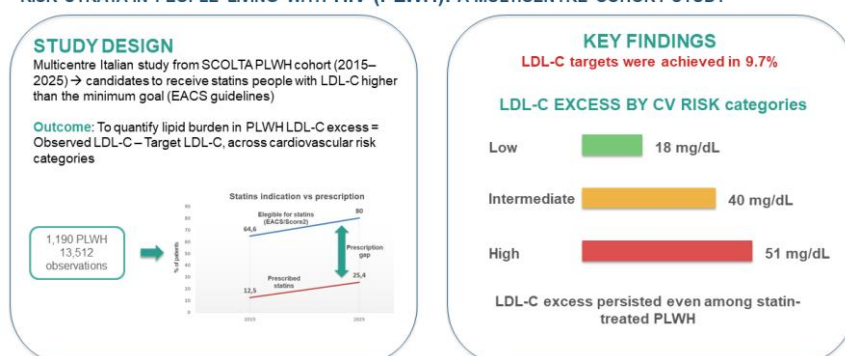
Table 3: Atherogenic index of plasma (n=13512).

	N=13401	All Mean (95% CI)	On statin Mean (95% CI)	Not on statin Mean (95% CI)
Year				
2015	255	0.47 (0.43 – 0.52)	0.64 (0.53 – 0.75)	0.45 (0.40 – 0.50)
2016	596	0.41 (0.38 – 0.44)	0.50 (0.42 – 0.58)	0.40 (0.37 – 0.43)
2017	631	0.41 (0.38 – 0.43)	0.51 (0.44 – 0.58)	0.39 (0.36 – 0.42)
2018	654	0.43 (0.40 – 0.45)	0.53 (0.48 – 0.57)	0.41 (0.38 – 0.43)
2019	982	0.41 (0.40 – 0.43)	0.50 (0.46 – 0.55)	0.39 (0.37 – 0.41)
2020	1156	0.38 (0.36 – 0.39)	0.49 (0.45 – 0.52)	0.35 (0.33 – 0.37)
2021	1503	0.36 (0.35 – 0.38)	0.47 (0.43 – 0.50)	0.34 (0.32 – 0.35)
2022	1843	0.36 (0.35 – 0.38)	0.47 (0.44 – 0.50)	0.34 (0.32 – 0.35)
2023	2166	0.33 (0.32 – 0.34)	0.39 (0.37 – 0.42)	0.31 (0.30 – 0.32)
2024	2186	0.34 (0.32 – 0.35)	0.38 (0.36 – 0.41)	0.32 (0.31 – 0.33)
2025	1429	0.32 (0.30 – 0.33)	0.36 (0.33 – 0.39)	0.30 (0.29 – 0.32)
CVD risk				
Low	4176	0.27 (0.27 – 0.28)	0.35 (0.32 – 0.38)	0.27 (0.26 – 0.28)
Medium	6800	0.38 (0.37 – 0.39)	0.43 (0.41 – 0.44)	0.37 (0.36 – 0.38)
High	2425	0.46 (0.45 – 0.47)	0.48 (0.46 – 0.50)	0.45 (0.43 – 0.46)

CI: confidence interval; CVD: cardiovascular disease.

Graphical Abstract

DISTANCE FROM LOW-DENSITY LIPOPROTEIN CHOLESTEROL TARGETS ACROSS CARDIOVASCULAR RISK STRATA IN PEOPLE LIVING WITH HIV (PLWH): A MULTICENTRE COHORT STUDY



CONCLUSIONS: LDL-C excess highlights residual lipid burden, especially in intermediate- and high-risk PLWH, supporting systematic lipid-lowering therapy in the post-REPRIEVE era.

Declaration of Interest Statement

- ☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
- ☐ The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for this journal and was not involved in the editorial review or the decision to publish this article.
- ☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

GVDS received consultancy and/or speakers' fees from Gilead Science and ViiV Healthcare; **ADB** received speakers' honoraria from Gilead Sciences and ViiV Healthcare, has been an advisor for ViiV Healthcare, Gilead Sciences, and MSD, travel reimbursement by Gilead Sciences, and has received grant for research from Gilead Sciences and ViiV healthcare; **BMC** has received research grants, consultancy, and speaker's fees from Gilead, ViiV, MSD, GSK and J&J; **EP** trained personnel for ViiV and Gilead; **GM** has received consultancy and/or speakers' fees from Gilead Sciences, Janssen, Merck Sharp & Dohme, ViiV and Advanz Pharma; **LT** attended advisory boards or served as consultant or received grants for conferences participations from Gilead Sciences, ViiV Healthcare and MSD; **NS** received consultancy and/or speakers' fees from Gilead Science and ViiV Healthcare; **PB** has been on advisory board per ViiV, Gilead e MSD.

The remaining authors (AG, BM, ER, ES, GC, GFP, GO, MAC, SF, SM, TB) declare that they have no conflicts of interest to disclose.

Prof. Giuseppe De Socio

