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Effect of 2018 American College of Cardiology/American Heart Association Guideline Change on Statin Prescription for People Living with HIV

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ABSTRACT

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines were updated in 2018 to explicitly recommend statin use for primary cardiovascular disease prevention among people living with HIV (PLWH), but little is known about the effect of this guideline change. We aimed to assess the effect of the 2018 ACC/AHA guideline change on statin prescription among PLWH. We used data from an institutional HIV registry to identify PLWH aged 40–75 years, engaged in HIV care between June 2016 and May 2021, had a LDL cholesterol between 70 and 189 mg/dl, 10-year atherosclerotic cardiovascular disease (ASCVD) risk score ≥7.5%, no prior statin prescription, and no history of diabetes or ASCVD. Our outcome of interest was a new statin prescription within 12 months of eligibility. We estimated standardized risk difference (RD) with 95% confidence limits (CL) by comparing prescription probabilities before and after guideline change. Our study population comprised 251 PLWH (171 before, 80 after the guideline change), of whom 57% were aged <55 years, 82% were male, and 45% were non-Hispanic black. The standardized 12-month statin prescription risk was 43% (95% CL: 31%, 60%) after the guideline change and 19% (95% CL: 13%, 26%) before the guideline change (RD = 25%, 95% CL: 9.1%, 40%). Our results suggest that the 2018 ACC/AHA guideline change increased statin prescription among PLWH, but a sizable proportion of eligible PLWH were not prescribed statin. Future studies are needed to identify strategies to enhance implementation of statin prescription guidelines among PLWH.

1. Introduction

People living with HIV (PLWH) have a higher risk of cardiovascular disease (CVD) than the general population. (Islam et al., 2012; Currier et al., 2008) Even with long-term viral suppression, PLWH have up to a two-fold increased risk of incident atherosclerotic cardiovascular disease (ASCVD) compared with people without HIV. (Shah et al., 2018; Alonso et al., 2019) This excess risk is more apparent because of longer life expectancy afforded by modern antiretroviral therapy (ART) and may be attributable to HIV-specific factors (e.g., ART side effects and systemic inflammation related to HIV infection) and high prevalence of conventional CVD risk factors (e.g., hypertension and smoking) among PLWH. (Durstenfeld and Hsue, 2021; Hsue and Waters, 2019; Freiberg and So-Armah, 2016).

Lipid management using statins (hydroxymethylglutaryl-coenzyme A reductase inhibitors) is an effective strategy for preventing CVD and its related complications. (Taylor et al., 2013) Clinical practice guidelines from the American College of Cardiology(ACC)/American Heart

Abbreviations: PLWH, People Living with HIV; ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, Atherosclerotic Cardiovascular Disease; ART, Antiretroviral Therapy; LDL, Low-density Lipoprotein.

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Association (AHA) in 2013 recommended statins as first-line cholesterol-lowering medications in the general population with high ASCVD risk but did not explicitly specify guidance for PLWH. (Stone et al., 2013) Studies since 2013 reported under-prescribing of statins among eligible PLWH (with prevalence ranging from 23% to 66%), which were hypothesized as being attributable to potential lack of awareness of ASCVD risk among PLWH, lack of explicit statin prescribing guidelines for PLWH, drug-drug interactions, and toxicities. (Clement et al., 2016; Levy et al., 2018; Mosepele et al., 2018; Park et al., May 2016; Kelly et al., 2017; Ladapo et al., 2017; Riestenberg et al., Mar 2019) Consequently, practice change initiatives are needed to increase statin prescription among PLWH.

The new ACC/AHA guidelines released in 2018 (Grundy et al., 2019) (and explained in detail for PLWH (Feinstein et al., 2019)) included specific recommendations for statin prescriptions among PLWH for primary CVD prevention. The new guidelines explicitly identify HIV as a risk enhancer and recommend the initiation of moderate-intensity statin therapy for PLWH at "intermediate risk" (7.5%≤10-year ASCVD risk score <20%) and moderate- to high-intensity statins at "high risk" (10-year ASCVD risk score ≥20%). (Grundy et al., 2019; Feinstein et al., 2019) Changes in clinical practice guidelines may influence provider-prescribing behavior, (Markovitz et al., 2017) but unknown is the effect of the 2018 ACC/AHA guideline change on statin prescription among PLWH. Therefore, we aimed to estimate the effect of the 2018 ACC/AHA guideline change on statin prescription among PLWH in an urban safety-net health system.

2. Methods

2.1. Study design

We emulated a single-arm trial with historical comparison to address the aim. (Ip et al., 2013; Suissa, 2021) This quasi-experimental framework was the most relevant given that the clinical guideline change (i.e., the intervention) was universally applied to the eligible population from the time of dissemination. (Clarke et al., 2019) This study was approved by the North Texas Regional Institutional Review Board (IRB number: 2017–135).

2.2. Study population

We used data from HIV Care and Outcomes Registry (HIVCOR), which is a longitudinal registry of adult patients (≥18 years) who engaged in HIV care at JPS Health Network (JPS) any time after January 1, 2013. (Anikpo et al., 2021) JPS is an urban safety-net health system and a primary source of care for socioeconomically marginalized populations in Tarrant County, Texas, USA. The network comprises a 583-bed academic teaching hospital, over 40 satellite community health clinics, and a comprehensive HIV clinic (Healing Wings Clinic) that is partially supported by funding from the Ryan White HIV/AIDS Program. Individuals eligible for our study were aged 40–75 years, engaged in HIV care between June 2016 and May 2021, had LDL-cholesterol between 70 and 189 mg/dl (1.7 to 4.8 mmol/L), had "intermediate risk" (7.5%≤10-year ASCVD risk score<20%) or "high risk" (10-year ASCVD risk score ≥20%) of ASCVD, no history of diabetes or clinical ASCVD, and no prior statin prescription. Our eligibility criteria were based on the updates in the 2018 ACC/AHA guidelines (4.5.5. Adults with Chronic Inflammatory Disorders and HIV), (Grundy et al., 2019) which specifically indicated HIV as a risk enhancer and added statin recommendations for ASCVD primary prevention. We excluded patients with liver dysfunction (alanine transaminase [ALT] >168 U/L) who could be contraindicated for statins. (Gillett and Norrell, 2011) In addition, we excluded patients with "borderline risk" (5.0%≤10-year ASCVD risk score <7.5%) because the guidelines indicate weak recommendation for statins. We computed the 10-year ASCVD risk score using the pooled cohort equation(Stone et al., 2013) with a six-month look-back period for any predictors that were not measured at the eligible encounter, where encounter includes any in-person or telehealth visit in 15 Primary Care Medical Homes (PCMHs) and HIV clinic within JPS. History of clinical ASCVD included acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke/transient ischemic attack, and atherosclerotic-origin peripheral arterial disease. (Stone et al., 2013).

2.3. Intervention

Our intervention of interest was the 2018 ACC/AHA guideline change, which specifically provided recommendations for statin prescription among PLWH. (Grundy et al., 2019) The guidelines were originally released in digital format on November 10, 2018 and print format on June 18, 2019. The intervention group comprised PLWH who received care after the guideline change (December 1, 2018 – May 31, 2021 to allow a brief lag period for implementation after digital release). The historical comparison group comprised PLWH who received care before the guideline change (June 1, 2016 – November 30, 2018).

2.4. Outcome and covariates

Our primary outcome of interest was statin prescription, defined as a new prescription for statin (regardless of dosage) within 12 months of meeting eligibility criteria from a physician, advance practice professional, or HIV specialist who provided primary care to PLWH at one of 15 PCMHs or dedicated HIV clinic within JPS. We also explored statin prescriptions at 3 and 6 months after meeting the eligibility criteria for insight about potential time-specific effects.

Covariates included sociodemographic, HIV-related, and CVD-related factors. Sociodemographic factors included age, sex, race/ethnicity, and health insurance coverage. HIV-related factors included CD4+ cell count, antiretroviral therapy (ART) regimen, and viral suppression status (viral load <200 copies/ml). CVD-related factors included smoking status, body mass index (BMI), low-density lipoprotein cholesterol (LDL-cholesterol), systolic blood pressure, treated hypertension (documented antihypertensive prescription within 6-months prior to eligibility), and the 10-year ASCVD risk score. If any covariate measurements were missing at the time of eligibility, we used the most recent measurement from all available historical data at the time of eligibility (i.e., all available look-back period). (Brunelli et al., 2013).

2.5. Data analysis

We used a counterfactual framework(Maldonado and Greenland, 2002) to estimate the effect of the 2018 ACC/AHA guideline change on statin prescription overall. We intended to assess the effect of guideline change by risk groups (i.e., intermediate- or high-risk, which would inform statin dose), but inadequate sample sizes were available for subgroup analysis. We used flexible parametric time-to-event models30, (Royston and Lambert, 2011; Royston and Parmar, 2002) with guideline change as a time-dependent covariate to estimate standardized (using a form of the parametric *g*-formula (Hernán and Robins, 2020; Snowden et al., 2011)) 3-, 6-, and 12-month risk differences (RDs) with corresponding 95% confidence limits (CL). Person-time contribution for each individual began from the first encounter when all eligibility criteria were met until statin prescription (outcome of interest), last medical encounter at any PCMH or dedicated HIV clinic (censoring event), or end of the study period (censoring event; November 30, 2018 for historical comparison group, and May 31, 2021 for intervention group), whichever occurred first. We assessed data maturity to ensure stable effect estimation up to 12 months by comparing the actual and minimum acceptable number of people at risk using a one-sided 95% confidence limit boundary. (Gebski et al., 2018) The actual number of people at risk in our study was greater than the minimum number of people required for data maturity in both groups at 12 months

(Supplementary Table S1), which supported stable effect estimation. Effect estimates were standardized on covariates with assumed relations to statin prescriptions, for which distributions may be sensitive to temporal drift. Covariates for standardization included age as a restricted cubic spline with four knots (at 5%, 35%, 65%, and 95%) (Harrell, 2015), sex, race/ethnicity (Hispanic, non-Hispanic black, non-Hispanic white, or others), insurance type (uninsured, hospital-based medical assistance program [offered to eligible individuals who are uninsured], Ryan White assistance, public insurance [Medicaid or Medicare], or private insurance), CD4+ cell count (<200, 200–349, 350–500, or >500 cells/mm^3), ART regimen (no ART, protease inhibitor, or non-protease inhibitor regimen), and ASCVD risk category (intermediate risk: ≥7.5% – <20% or high risk: ≥20%). All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) and Stata 16.1 (StataCorp, College Station, TX).

3. Results

We identified 267 eligible PLWH, of whom 16 were excluded because of missing values for relevant covariates (Fig. 1). Our study population thus comprised 251 PLWH, of whom 171 were in the historical comparison group and 80 were in the intervention group. Table 1 summarizes the group-specific baseline characteristics of the study population. Overall, our study population had a median age of 53 years (interquartile range: 48–58 years) and was predominantly male (82%), non-Hispanic black (45%), and primarily covered by Medicare or Medicaid (47%). 41% were current smokers and 67% were overweight or obese (BMI ≥25 kg/m^2). Most patients were virally suppressed (67%) and 46% had a CD4+ cell count >500 cells/mm^3. Finally, 87% of PLWH had an intermediate-risk ASCVD risk score.

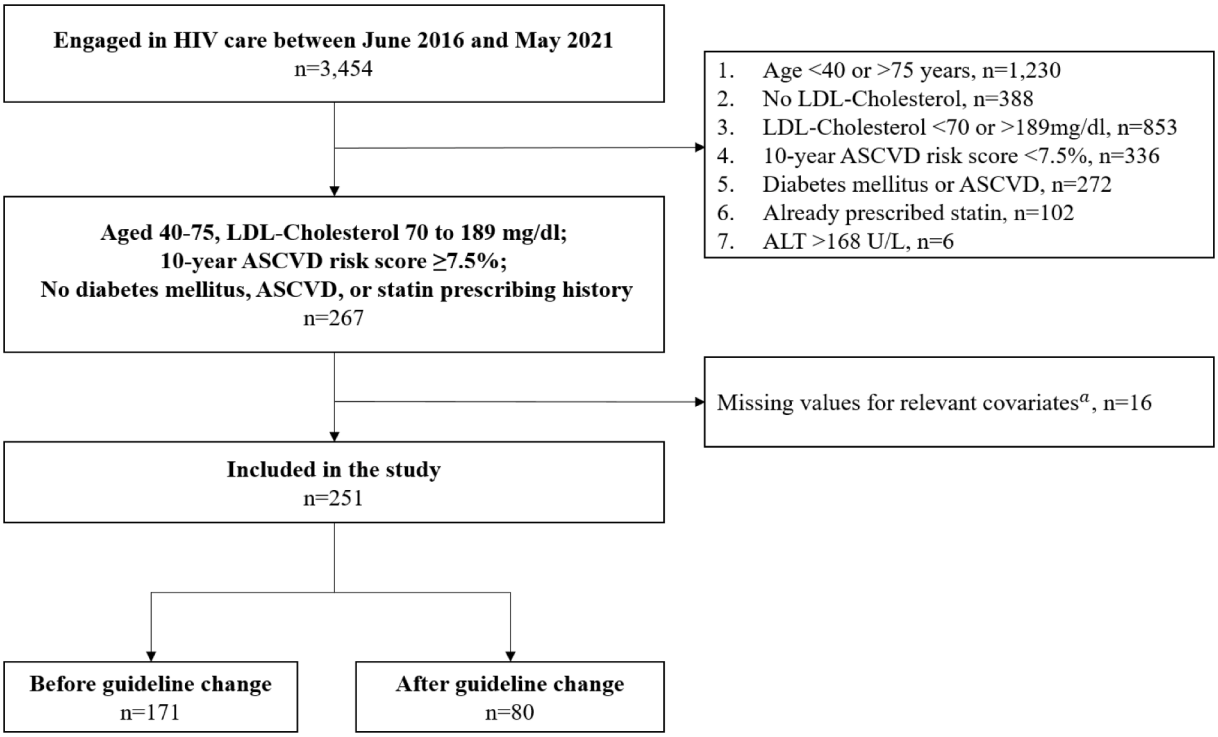
Fig. 2 illustrates the standardized risk curve of statin prescriptions for the entire study population before and after the 2018 guideline change. Table 2 summarizes the crude and standardized time-specific comparisons of prescription risks for the study population before and after the 2018 guideline change at 3, 6, and 12 months. The crude risk of statin prescription at 12 months was 41% (95% CL: 29%, 58%) after guideline change and 20% (95% CL: 14%, 28%)) before guideline change (RD = 21%, 95% CL: 5.7%, 37%). The standardized risk at 12 months was 43% (95% CL: 31%, 60%) after guideline change and 19% (95% CL: 13%, 26%) before guideline change (RD = 25%, 95% CL: 9.1%, 40%).

4. Discussion

Our study was designed to evaluate whether the 2018 ACC/AHA guideline change influenced statin prescription among PLWH in an urban safety-net health system. Our results suggest that the guideline change increased statin prescriptions by 25% (data are compatible with estimates between 9.1% and 40%). This effect became progressively stronger throughout the 1-year follow-up period. Nevertheless, several issues require further consideration when interpreting the findings.

Limitations

The estimates from analyses of single-arm interventions with historical comparisons are sensitive to violations of exchangeability (i.e., lack comparability between intervention and historical comparison groups that can manifest as confounding or selection biases (Greenland and Robins, 1986; Flanders and Eldridge, 2015). One potential violation is whether other planned or unplanned interventions were concurrent with the intervention of interest. For example, access to care was disrupted and adapted from in-person to telehealth visits starting March 2020 because of the coronavirus pandemic, which could have affected prescription patterns in the intervention group. Published evidence suggests that telehealth transition during the pandemic did not affect statin prescription patterns, (Mizuno et al., 2021) but we further explored whether access to care differed between the intervention and comparison groups in our study population. Our results suggest that the proportion of PLWH with a healthcare encounter (either primary care or HIV care) was modestly lower in the intervention group (Supplementary Table S2). Consequently, the risk of statin prescription was higher in the



[a] Patients with missing values on insurance, CD4 measurement, or antiretroviral therapy regimen at baseline.

Fig. 1. Selection of people living with HIV who were eligible for statin prescriptions.

Table 1
Baseline characteristics of statin-eligible people living with HIV engaged in care between June 1, 2016 and May 31, 2021.

Characteristics	Before guideline change (n = 171)	After guideline change (n = 80)
Age, median (IQR), years	53(48–59)	53(49–58)
40–54	94 (55%)	50 (62%)
55–75	77 (45%)	30 (38%)
Sex		
Female	34 (20%)	11 (14%)
Male	137 (80%)	69 (86%)
Race/Ethnicity		
Hispanic	25 (15%)	13 (16%)
Non-Hispanic black	79 (46%)	33 (41%)
Non-Hispanic white	62 (36%)	30 (38%)
Others	5 (2.9%)	4 (5.0%)
Insurance		
Uninsured	5 (2.9%)	8 (10%)
Hospital-based medical assistance program	5 (2.9%)	4 (5.0%)
Ryan White assistance	41 (24%)	24 (30%)
Medicaid or Medicare	91 (53%)	28 (35%)
Private insurance	29 (17%)	16 (20%)
Smoking Status		
Current smoker	65 (38%)	38 (47%)
Former or non-smoker	106 (62%)	42 (53%)
BMI Category		
Underweight	3 (1.8%)	4 (5.0%)
Normal	59 (34%)	18 (23%)
Overweight	63 (37%)	29 (36%)
Obese	46 (27%)	29 (36%)
LDL-Cholesterol, median(IQR), mg/dl	120 (93–157)	103 (87–144)
Systolic Blood Pressure, median (IQR), mmHg	136 (126–146)	135 (122–148)
Treated Hypertension		
Yes	73 (43%)	30 (38%)
No	98 (57%)	50 (62%)
CD4+ cell count, cells/mm3		
<200	27 (16%)	20 (25%)
200–349	30 (17%)	16 (20%)
350–500	27 (16%)	15 (19%)
>500	87 (51%)	29 (36%)
ART Regimen		
No ART	16 (9.4%)	7 (8.8%)
Protease Inhibitor	82 (48%)	40 (50%)
Non-Protease Inhibitor	73 (42%)	33 (41%)
Viral Suppression		
Yes	115 (68%)	51 (65%)
No	54 (32%)	28 (35%)
10-year ASCVD Risk Score		
≥7.5% – <20% (Intermediate)	151 (88%)	67 (84%)
≥20% (High)	20 (12%)	13 (16%)

IQR, interquartile range; BMI, body mass index; LDL, low-density lipoprotein; ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease. Note: Some percentages may not sum to 100% because of rounding.

intervention group despite fewer opportunities for statin prescription.

Another potential violation of exchangeability is temporal drift, which occurs when the baseline distribution of covariates related to the outcome of interest changes over time. (Ip et al., 2013) The baseline distribution of some measured covariates were different between groups in our study (e.g., insurance status) and were adjusted in our analyses, but unknown are differences in the distribution of unmeasured covariates. Nevertheless, our estimates may not be sensitive to critical unmeasured baseline confounding factors because the crude and standardized estimates were roughly identical despite adjustment for several key covariates.

The computation of the ASCVD risk score could introduce selection bias, primarily from the exclusion of eligible patients from the study. For example, if a time-dependent predictor was not measured at the same time as other predictors, we used the most recent predictor measurement within a six-month look-back period to compute the ASCVD score. If this predictor measurement was not available within the six-month look-back period or underestimated the value at the time other predictors were measured, then the ASCVD score could be underestimated, and eligible patients could have been inadvertently excluded. If exclusion was more common in the intervention group (e.g., because of concurrent pandemic-related care disruptions) and these patients were not prescribed statins, then our estimate for the effect of guideline change on statin prescription may be biased away from the null (i.e., overestimated). For further insight, we explored the absolute difference between the most recent and earliest eligible measurements of systolic blood pressure and LDL cholesterol among statin-eligible patients who had multiple measurements within the six-month look-back period (Supplementary Table S3). We observed small absolute differences between measurements, particularly in the intervention group. Nevertheless, these differences had limited effects on ASCVD score, which provides reassurance against severe bias.

Cumulative evidence

Our literature search did not identify prior studies that evaluated the effect of the 2018 ACC/AHA guideline change on statin prescriptions among PLWH. We expanded our search to the general population and identified one study (Tunoa et al., 2020) that evaluated the effect of the 2018 ACC/AHA guidelines on lipid monitoring but not statin prescription. We also identified one study (Nardolillo et al., 2021) that compared statin prescriptions between PLWH and a matched cohort of people without HIV after the 2018 guideline change in a safety-net health system. The authors reported 2.5% (95% CL: −12%, 17%) higher absolute prevalence of statin prescription among PLWH. (Nardolillo et al., 2021) This study addresses a different question from our study but provides insight into potential differences in statin prescription by HIV status after guideline change.

We expanded our search to studies in the general population after the 2013 ACC/AHA guideline change and identified one study that evaluated the effect of guideline change on statin prescription. Markowitz et al. (Markovitz et al., 2017) reported 0.8% (95% CL: 0.6%, 0.9%) increase in statin prescription after the 2013 ACC/AHA guideline change in the Veterans Affairs system. Our results suggest potentially larger effect of guideline change, but this difference may be attributable to variations in health systems, study populations, and study periods. For example, our study was conducted in a safety-net health system supported by funding from the Ryan White program. Additionally, the baseline prescription risk in the study by Markowitz et al. was 45%, which was substantially higher than the baseline prescription risk in our setting. Thus, our findings may be generalizable to other safety-net health systems or similar clinics supported by the Ryan White program, but not necessarily to settings with different payer distributions or case mixes.

Implications

Our findings suggest a potential increase in statin prescriptions among PLWH after the 2018 AHA/ACC guideline change, which is encouraging given the growing importance of CVD prevention among PLWH. Nevertheless, imprecision and the net effect of biases could have resulted in overestimated effects of guideline change. Consequently, our findings may be most useful for understanding that guideline change alone is insufficient for optimizing statin prescriptions among PLWH. Consistent with other settings, a sizable proportion of eligible PLWH in our population were not prescribed statin therapy.

Future studies are needed to identify strategies to enhance implementation of statin prescription guidelines. A key challenge is the identification of PLWH eligible for statin prescriptions. The 2018 AHA/ACC guidelines are based on the AHA/ACC pooled cohort equation to estimate CVD risk and identify eligible individuals, but no risk prediction model has emerged as superior to other models among PLWH. Even the D:A:D model, which was developed for PLWH, may substantially underestimate CVD risk and result in missed opportunities for statin prescription. (Anikpo et al., 2021) Direct comparisons of CVD risk prediction models and possible updating of models for local populations are

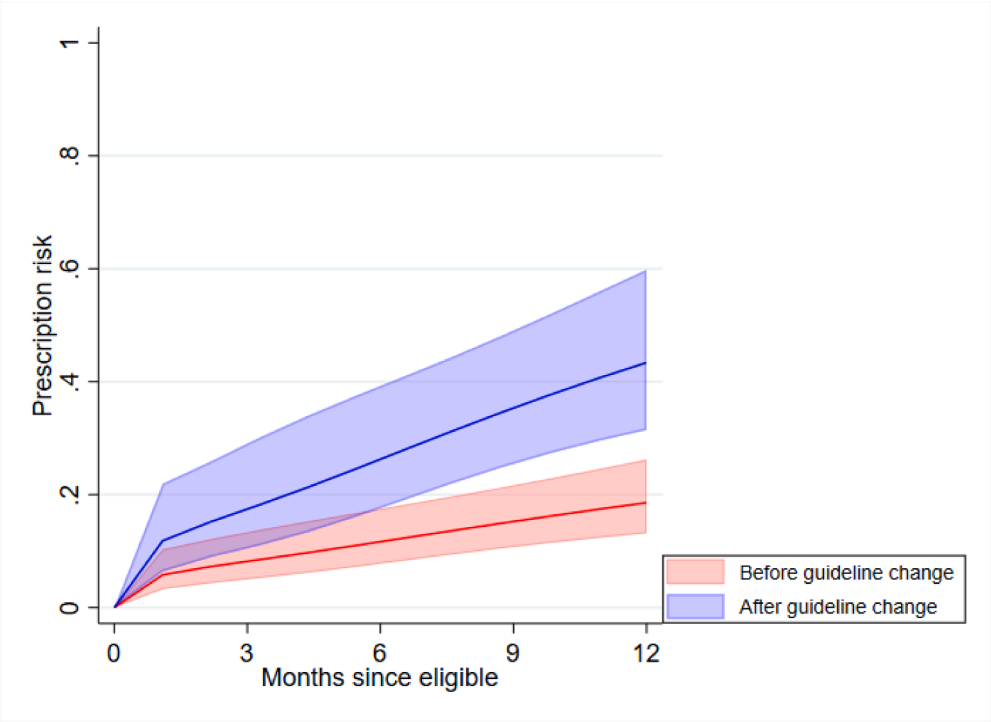


Fig. 2. Standardized[a] statin prescription risk before and after the 2018 ACC/AHA guideline change among people living with HIV.
[a]Standardized for age, sex, race/ethnicity, insurance type, CD4+ cell count, antiretroviral therapy regimen, and CVD risk category.

Table 2
Time-specific comparisons of statin prescription risk before and after 2018 ACC/AHA guideline change among people living with HIV.

Time since eligible	Prescription risk (95% CL[a])			Risk difference (95% CL)
	Analysis	Before guideline	After guideline	
3 months	Crude	8.9% (4.4%, 18%)	15% (7.1%, 33%)	6.5% (-6.9%, 20%)
	Standardized[b]	8.8% (4.5%, 17%)	15% (6.9%, 31%)	5.7% (-6.7%, 18%)
6 months	Crude	12% (7.8%, 19%)	29% (19%, 43%)	17% (3.7%, 30%)
	Standardized	11% (7.4%, 18%)	29% (20%, 44%)	18% (5.0%, 31%)
12 months	Crude	20% (14%, 28%)	41% (29%, 58%)	21% (5.7%, 37%)
	Standardized	19% (13%, 26%)	43% (31%, 60%)	25% (9.1%, 40%)

[a] CL: confidence limits.
[b] Standardized for age, sex, race/ethnicity, insurance type, CD4+ cell count, antiretroviral therapy regimen, and ASCVD risk category.

needed. In addition, evidence regarding barriers to statin prescription among PLWH on which to intervene is limited but emerging. For example, time constraints impede HIV providers from focusing on ASCVD risk assessment and prevention given that care delivery prioritizes HIV management. (Ober et al., 2021) Lack of cardiovascular disease-specific knowledge and uncertainty about drug-drug-interaction between statins and ART are additional reported barriers. (Ober et al., 2021) Barriers to statin prescription among people without HIV may also be relevant to PLWH. These barriers include poor patient-provider relationships and concerns about patient adherence, cost, and over-reliance on statins. (Ober et al., 2021; Butalia et al., Nov 2020; Kedward and Dakin, 2003) A stepped-wedge cluster randomized trial is in progress at Los Angeles community health clinics to intervene in organization-, provider-, and patient-level barriers to statin prescription. (Takada et al., 2020) Results from this trial and related future studies may be useful for identifying promising strategies to implement across settings to increase statin prescription.

Declaration of Competing Interest

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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2023.102175.

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