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Hepatic Markers and Immunological Trajectories in a Cohort of Patients with HIV and Hepatitis C Virus Coinfection Treated with Direct-Acting Antivirals

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Abstract

Persons with HIV (PWH) have disproportionate hepatitis C virus (HCV) infection prevalence and liver-related morbidity and mortality. These sequelae may be alleviated by curative direct-acting antiviral (DAA) treatment; however, longitudinal effects of DAAs on clinical biomarkers are not well-characterized. We included PWH enrolled in the HIV Outpatient Study (HOPS) who were prescribed DAAs and DAA-naïve PWH of comparable age, sex, race/ethnicity, and fibrosis-4 (FIB-4) profiles. We contrasted the DAA effect on longitudinal trajectories of immunological and hepatic markers using generalized linear mixed models (GLMM) from 2010 to 2020. Of 347 PWH/HCV coinfection, median age was 53.8 years, 30.5% were women, 67.1% were publicly insured, 44.4% were non-Hispanic Black, and 153 (44.1%) were prescribed DAAs (median follow-up = 3.55 years). In multivariable GLMM analysis, DAA treatment was associated with [mean (95% confidence interval)] faster decline in alanine aminotransferase of -7.86 $\mu\text{U/L/year}$ (-15.39 , -0.33) and faster increase in platelets of 6.99 $\mu\text{U/L/year}$ (2.89 , 11.09). Changes in aspartate aminotransferase were comparable between groups. FIB-4 decreased in the DAA-treated but not the DAA-naïve group: -0.26 (-0.41 , -0.11) versus 0.02 (-0.16 , 0.20)/year, respectively. There was a faster increase in cluster of differentiation (CD)4 count of 0.05 (0.03 – 0.08) and CD8 count of 0.04 (0.02 – 0.07) log cells/mL/year in the DAA-treated compared with the DAA-

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Authors' Contributions

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

Author Disclosure Statement

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naïve group ($p < .001$), but not in the CD4/CD8 ratio ($p = .36$). Among U.S. PWH/HCV coinfection treated with DAAs, we found modest changes in immunological markers and substantial improvements in hepatic markers modeled over 4 years of DAA treatment. Curative DAA treatment is critical to mitigate advanced liver fibrosis.

Keywords

DAA; direct-acting antiviral; HIV; HCV; hepatitis C treatment

Introduction

The Centers for Disease Control and Prevention (CDC) last estimated that in 2009, approximately 21% of persons with HIV (PWH) were coinfecting with hepatitis C virus (HCV), and coinfection prevalence varied depending on HIV risk category.¹ This high prevalence of HIV/HCV coinfection is clinically significant because HIV alters the natural history of HCV infection and is associated with considerable morbidity and mortality, liver-related and overall.^{2–4} Direct-acting antivirals (DAAs) are curative nearly universally and are highly tolerated compared with prior HCV infection treatment options. Sustained virologic response (SVR) rates among PWH approximate SVR rates in persons without HIV (>96%).^{5–12} Simoncini et al. found the SVR rate of 94% with DAA treatment since 2014 among HIV Outpatient Study (HOPS) participants who had HIV/HCV coinfection and had no ribavirin (RBV) or interferon (IFN) treatment from 2010 to 2018.¹³

Because many PWH/HCV coinfection have or can achieve SVR, there is an interest in profiling the immunological and hepatic markers in those treated with DAAs (without IFN and/or RBV) compared with untreated persons. There exists literature describing mixed immunological marker outcomes of DAA treatment in persons with HCV infection with or without HIV coinfection. Previous studies of PWH/HCV coinfection who achieved SVR, but were treated with pegylated IFN and RBV, did not show improvements in absolute or percent cluster of differentiation (CD)4 and CD8 cell counts nor CD4/CD8 ratios during a median of 8 years of follow-up.¹⁴ In two other recent studies of PWH/HCV infection treated with IFN-free DAA regimens, similar findings were observed, including no increase in absolute or percent CD4 cell count nor CD4/CD8 ratios after 1 month and 13 months, respectively, of completing DAA treatment.^{15,16} However, in another study with a 12-month follow-up, CD4 cell count and percentages increased, but only for persons without cirrhosis; and there was a neutral effect of DAA treatment on CD4/CD8 ratios, regardless of cirrhosis.¹⁷ Given these discrepancies and short-term follow-up, our goal was to explore the immunological responses of IFN-free DAA therapy in a cohort of PWH with HCV coinfection over longer follow-up.

Similarly, we sought to address the gap in existing literature by evaluating longer-term liver outcomes. Perez-Is and coauthors followed PWH/HCV coinfection after DAA treatment for 24 months and showed that within the first month of starting DAA therapy, noninvasive liver fibrosis scores [aspartate transaminase (AST) to Platelet Ratio Index (APRI), fibrosis-4 (FIB-4)] decreased and remained sustained after treatment for at least 24 months of follow-

up after starting DAA therapy and did not improve further as time proceeded.¹⁸ The authors suggested that rapid declines in liver fibrosis scores were due to the removal of the chronic viral antigenic stimulation from HCV infection, which may underlie ongoing inflammation and immune activation.¹⁸ Other studies with shorter follow-up time periods also demonstrated rapid improvements of the FIB-4 scores, but these improvements did not seem to be influenced by HIV coinfection.¹⁹ Therefore, there remains a knowledge gap regarding the long-term FIB-4 scores among PWH who received DAA treatments.

In this study of PWH/HCV infection enrolled in the multisite U.S. HOPS cohort, we explored longitudinally the effects of DAA treatment on liver-related outcomes, immunological outcomes, and estimates of severe liver disease through 48 months.

Materials and Methods

The HIV Outpatient Study

Established in 1993, the HOPS is an ongoing, open, prospective U.S. cohort study of $\geq 10,000$ adults with HIV (≥ 18 years old) cared for in HIV specialty clinics. Currently, the HOPS consists of eight total clinical sites, with the following six sites contributing data for this analysis: Chicago, IL; Denver, CO; Philadelphia, PA; Stony Brook, NY; Tampa, FL; and Washington, DC. The HOPS protocol is approved annually by institutional review boards at each participating institution and at the CDC. All study participants provided written informed consent. Sociodemographic, clinical (including comorbidities, medications, etc.), and laboratory data from each clinical encounter of enrolled participants are abstracted from the medical record and entered into an electronic database by trained study coordinators. For this analysis, we used the HOPS datasets that were available as of June 30, 2020.

Study criteria, definitions, and outcomes

HOPS participants were included if they had a chronic HCV infection as evidenced by at least one detectable HCV RNA viral load (VL) or an HCV genotype test (VL or genotype obtained June 30, 2010, or after to account for participants awaiting initial DAA approval), or presence of DAA prescription on/after January 1, 2014, in the absence of available HCV RNA or genotype result (Fig. 1). DAA agents included sofosbuvir, daclatasvir, simeprevir, ledipasvir, velpatasvir, voxilaprevir, grazoprevir, elbasvir, glecaprevir, pibrentasvir, paritaprevir, ombitasvir, and dasabuvir. Participants treated with IFN/RBV were excluded from the analyses to focus on the contemporary care patterns and the effect of DAA-specific treatment. Participants without an available FIB-4 index were also excluded, given this biomarker served as the primary variable in propensity matching as described below (Supplementary Fig. S1).

Participants included were classified as having been prescribed or not prescribed DAA (DAA-treated and DAA-naïve, respectively) based on medication prescription data. The participant's first DAA prescription date, ascertained by the prescription records, was assumed to be the therapy initiation date and was used as the temporal reference point ("index date") to contrast changes in longitudinal trajectories of immune and hepatic clinical biomarkers before and after the DAA prescription date. Given the routine immunological

and hepatic lab tests along with HIV- and/or HCV-related outcomes including mortality among HOPS participants, the following markers were evaluated: CD4 count, CD4%, CD8 count, CD8%, and CD4/CD8 ratio (immune) and AST, alanine transaminase (ALT), platelet count, and FIB-4 index (hepatic). For FIB-4 index not already documented in the HOPS database, we calculated it with laboratory values by using the following equation: $\left(\text{Age at time of lab test (year)} \times \text{AST} \left(\frac{U}{L} \right) \right) / \left(\text{Platelet count} (10^9) \times \sqrt{\left(\text{ALT} \left(\frac{U}{L} \right) \right)} \right)$. Markers were assessed longitudinally over study observation from June 30, 2010, to June 30, 2020, before and after the first DAA prescription date.

Propensity score matching

To evaluate the longitudinal impact of DAA treatment on clinical marker trajectories in this observational cohort, we implemented propensity score matching. DAA-naïve participants were matched with DAA-treated participants on FIB-4 index score (nearest to the initial DAA prescription date), time (nearest year and date) of FIB-4 measurement, age at time of FIB-4 measurement, and sex, with the largest weight given to FIB-4 score. Multiple rounds of matching were pursued so that all DAA-naïve participants who met study criteria were matched with one participant from the DAA-treated group. Once matched, a pseudo-DAA prescription date was assigned to the DAA-naïve participant based on the same date of the matched DAA-treated participants, each representing an “index date” for these respective participants. Our purpose in propensity score matching was to line up participants (using index date) mainly on liver pathology (FIB-4) and then on age at time of HCV infection and sex, across the two treatment groups (DAA-naïve and DAA-treated) after a documented HCV infection. Consequently, comparison of longitudinal trajectory for clinical markers based on DAA prescription/pseudo-prescription date as the index date (time 0) could be established at similar level of liver pathology between DAA-treated and DAA-naïve groups. Unlike with conventional propensity score matched analyses, our approach allowed one participant in the DAA-treated group to be matched with more than one participant in the DAA-naïve group. Once the propensity score matching process was completed, all participants were subsequently included in multivariable analyses modeling the trajectory of immune and hepatic markers before and after the propensity score matched index date.

Statistical analysis

We summarized demographic and clinical characteristics for DAA-treated and DAA-naïve groups using mean, standard deviation/median (interquartile range [IQR]) or percent (frequency), as appropriate. To assess differences in cohort characteristics at index date (time 0), we used Pearson’s chi-square tests for categorical variables and Student’s *t*-test, or Kruskal–Wallis tests if variable distribution was skewed, for continuous variables. We assessed longitudinal trajectories in immune markers, including CD4 and CD8 count (log transformed), CD4% and CD8%, and CD4/CD8 ratio, and hepatic markers, including ALT, AST, platelet count, and FIB-4 scores, using linear mixed models (LMM). To assess longitudinal trajectory in HIV and HCV VL results (detectable vs. undetectable), we used generalized linear mixed model (GLMM). For both LMM and GLMM models, we used random intercept terms for each participant to allow for correlation between repeated measures within participants over time. We used splines in these models to allow for and

fit immune and hepatic marker trajectory changes as a function of DAA treatment. For each participant, estimates of longitudinal marker change were centered on the index date, defined earlier as the DAA prescription date (DAA-treated) or the pseudo-DAA prescription date (DAA-naïve). Residual analyses assessed distribution assumptions (quantile–quantile plots and residual histograms). Both LMM models for continuous clinical marker measurements and GLMM models for dichotomized HIV/HCV VL results (detectable vs. undetectable) were evaluated with and without covariate adjustment, including age, race/ethnicity, sex at birth, and time from index date. We used the parameter estimates from the mixed models to compare the longitudinal effect upon clinical marker trajectory, utilizing linear contrasts to compare and test for statistical differences before and after the index date between and within the two participant groups. To examine the longitudinal impact of DAA treatment on liver fibrosis, we conducted survival analyses using Kaplan–Meier curve and Cox regression to assess time to incident advanced liver fibrosis (FIB-4 ≥ 3.25). All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC).

Results

Population characteristics

Of 11,307 HOPS participants enrolled by June 30, 2020, 4,742 had any observation/clinical data from June 30, 2010, onward. Of these, 347 (7.3%) had confirmed HCV coinfection, based on evidence of a detected HCV RNA, having had HCV genotype testing (on/after June 2010), and/or having DAA prescribed (on/after January 2014) (Fig. 1). Of the 347 PWH/HCV coinfection, the median age was 53.8 years (IQR 46.9, 59.6), 106 (30.5%) were women, 233 (67.1%) were publicly insured, 154 (44.4%) reported being of non-Hispanic/Latino Black or African American (NHB) race/ethnicity. A total of 153 (44.1%) persons received DAA therapy during observation. Cohort characteristics by DAA treatment status are depicted in Table 1. The median time from HIV diagnosis to HCV infection confirmation (by HCV RNA, HCV genotype, or prescription of DAA) was 17.8 years (IQR 9.1, 23.5), the median follow-up time from HCV confirmation to the end of observation for the DAA-treated group was 3.55 (1.91, 4.56) years in contrast with 2.38 (0.77, 4.26) years for the DAA-naïve group. Among PWH treated with DAA therapy, median time from HCV infection confirmation to DAA initiation was a median of 2.77 (1.16, 4.18) years. With propensity score matching on FIB-4, the median time from HCV infection confirmation to the pseudo-DAA treatment date for the DAA-naïve group was 1.97 (0.34, 3.57) years.

For our study population, the median values (as of the index date) were CD4 cell count of 530 cells/mm³, CD4% of 29%, ALT of 29 mu/μL, and AST of 33 mu/μL. Proximal to index date, CD4 count and CD4% were slightly higher for the DAA-treated group than for the DAA-naïve group ($p < .01$), while CD8 count and CD4 nadir, along with ALT, AST, were not markedly different from those of the DAA-naïve group. CD4/CD8 ratio, though, for the DAA-treated group was higher ($p < .001$) than that of the DAA-naïve group (Table 1).

Trajectories in immune markers

Changes in markers modeled and summarized as mean (95% confidence interval) spanning 48 months before and after the index date are depicted in Supplementary Figure 2a–c.

Before index date, CD4 count (in log scale) increased with a linear trajectory in slope of 0.04 (0.03, 0.05) for the DAA-treated group, which was comparable with that of the DAA-naïve group 0.03 (0.02, 0.04), while for CD4%, the slope was 0.81 (0.67, 0.94) and 0.39 (0.24, 0.63) for DAA-treated and DAA-naïve groups, respectively. In addition, linear trajectory in slope for CD8 count (in log scale) was -0.02 (-0.03 , 0.01) and -1.07 (-1.23 , -0.91) for CD8% for the DAA-treated group, representing a faster decline than that of the DAA-naïve group for CD8 count and CD8%: -0.01 (-0.02 , 0.01) and -0.49 (-0.67 , -0.30), respectively (Table 2, Supplementary Fig. S2a and b). Collectively, linear trajectory for CD4/CD8 ratio of the DAA-treated group decreased faster after treatment than that of the DAA-naïve group, which followed a more similar longitudinal trajectory over time (Supplementary Fig. S2c). Changes in CD4 ($p < .0001$) count and CD8 ($p < .001$) count after index date were significantly faster in the DAA-treated group, while changes in CD4% ($p = .59$), CD8% ($p = .45$), and CD4/CD8 ratio ($p = .36$) were all comparable with that of the DAA-naïve group (Table 3).

Trajectories in hepatic, virologic, and other markers

For the hepatic markers, the longitudinal trajectory in slope for ALT before index date was -2.15 (-4.42 , 0.11) and -3.14 (-5.67 , -0.63) for DAA-treated and DAA-naïve groups, respectively. After treatment started, the slope for the DAA-treated group decreased sharply to -9.70 (-13.25 , -6.15). For the DAA-naïve group, the slope changed to -2.83 (-7.18 , 1.53) after index date, which remained similar to that of before index date (Table 2, Supplementary Fig. S4a).

Trajectories in longitudinal AST, however, slope change after index date -6.95 (-13.34 , -0.57) from that of before index date for DAA-treated group was similar to that of the DAA-naïve group -7.95 (-15.17 , -0.73) (Table 2, Supplementary Fig. S4a).

After DAA treatment, the longitudinal trajectory in platelet substantially increased at a rate of 4.27 (1.64, 6.90) for the DAA-treated group, while for the DAA-naïve group, the longitudinal trajectory in blood platelet decreased by -2.72 (-5.87 , 0.44) after index date (Table 2). With DAA treatment, platelet slope trajectory showed a steeper upward trend in clear contrast to that for the DAA-naïve group after index date (Table 2, Supplementary Fig. S4b).

For all participants with HIV/HCV coinfection ($n = 347$), 80% had detectable HCV VL before DAA treatment. DAA treatment effectively reduced HCV VL to undetectable level within 20 months of DAA treatment. Without DAA treatment, probability of detectable HCV VL remained over 80% and continuously increased after index date. Overall, for HIV VL test closest to index date, 94 (27.1%) participants had detectable HIV VL (VL above the lower limit of the test used), with 64 of them having been DAA-treated and 29 for DAA-naïve ($p \leq .001$). GLMM estimated probability of having detectable HIV VL in DAA-treated group after DAA treatment date, and DAA-naïve group remained relatively unchanged (Supplementary Fig. S3).

Longitudinal trajectory in participants' FIB-4 score reflected changes in ATL, AST, and platelet trajectories. For those on DAA therapy, FIB-4 score dropped by 0.26 (0.41, 0.11) in

contrast to an increase by 0.02 (0.16, -0.20) for persons without DAA treatment (Table 2, Supplementary Fig. S4c).

Additional modeling analyses

After adjusting for age, sex, and race/ethnicity, DAA treatment had a similar effect on the longitudinal trajectory of HIV immune markers in CD4, CD8, and CD4/CD8 ratio and liver functionality measures in ALT, AST, platelet, and FIB-4 score (Tables 2 and 3).

Probability of reaching a FIB-4 score ≥ 3.25 with Kaplan–Meier estimate showed a consistent longitudinal DAA treatment effect of not reaching advanced fibrosis ($p < .01$). By year 6 after HCV infection, over 80% of persons on DAA treatment had FIB-4 less than 3.25, in contrast with 60% for persons without the treatment (not shown). Results from Cox regression show DAA's positive impact on maintaining normal liver functionality remained statistically significant after adjusting for age, sex, and FIB-4 score at index (Fig. 2).

Discussion

In our multisite cohort of 347 adults with HIV/HCV coinfection, we evaluated the effect of treatment with DAAs from 2010 to 2020 with treated participants' follow-up of up to 3 years. Women (30.5%) and NHB persons were well represented (30.5% and 44.4%, respectively) in this analysis. We were able to evaluate the trajectories of immune, virologic, and hepatic biomarkers. The beneficial effects of DAAs on liver function and fibrosis have been well established in persons with HCV monoinfection and HIV/HCV coinfection; however, our study adds to this body of literature substantially by assessing longer-term longitudinal effects of DAAs on clinically measurable and relevant biomarkers for this participant group; it also compares DAA-treated and DAA-naïve PWH/HCV coinfection in the same U.S.-based cohort.

In our study, participants treated with DAAs had more favorable changes in hepatic markers and variable changes in immunological markers, as compared with their counterparts not treated with DAAs. For instance, the speed of decline of CD8⁺ cell count, a marker of T cell activation, was faster among persons on DAA therapy than those who remained untreated, with a similar trajectory favoring improved CD4/CD8 ratio. The modeled results indicated more precipitous decreases in ALT/AST through 48 months and a steeper increase in platelet count among people on DAA therapy as compared with those not treated. FIB-4 scores continuously declined for DAA-treated group (Supplementary Fig. S4c), with the likelihood of progressing to advanced fibrosis (FIB-4 > 3.25) being consistently lower than that of the DAA-naïve group 3 months after DAA treatment initiation (Fig. 2).

HIV is a state of chronic inflammation even persisting during stable antiretrovirals therapy. Chronic HCV infection is associated with naïve CD4⁺ T cell lymphopenia and long-standing/persistent elevation of cellular and soluble immune activation parameters, the latter heightened in the setting of HIV coinfection.²⁰ HCV coinfection can potentially further enhance immune activation in those with HIV, demonstrated by higher levels of markers of inflammation, including higher levels of CD4⁺ and CD8⁺ T cell activation compared with PWH who do not have HCV. HCV eradication appears to be associated with significant

reductions in markers of activation that correlate with reductions in measures of hepatic fibrosis.²¹

Several studies address immune activation and changes in T cell lymphocytes and ratios in those treated with DAAs. In a group of 51 coinfecting and 161 HCV mono-infected persons followed for 1 year post-SVR, both groups had a significant mean decrease from pre-DAA therapy to post-SVR year 1 for activated CD4⁺ T cells and activated CD8⁺ T cells. This suggests continued improvements in immunological recovery in T cell activation during DAA therapy and after achievement of SVR, as HCV clearance normalizes activated T cell phenotype.²² In another study of 33 PWH/HCV coinfection followed from baseline until 36 weeks after SVR, investigators found a decrease in liver severity markers (plasma markers and gene expression related to antiviral/inflammatory response along with improvement in liver disease markers) and no change in CD4⁺ or CD8⁺ T cells.²³ In 97 HIV/HCV-coinfecting participants assessed at end of therapy and 1 month later, there was a significant decrease in immune activation (i.e., human leukocyte antigen -DR isotype and CD38 on CD4⁺ and CD8⁺ cells), HIV DNA, microbial translocation markers, and D-dimer, and no changes in CD4⁺ or CD8⁺ T cell counts were found.¹⁵ Finally, in a large ICONA study of 939 PWH/HCV coinfection who achieved sustained viral response after DAA treatment, Bandera and colleagues found no differences in CD4 and CD4/CD8 cell profiles in a pre-versus post-comparison through 1 year but observed a fast decline in CD8 cells among those treated with RBV-free DAA therapy.¹⁶

Various studies also explored the effects of DAAs on liver stiffness and serum liver fibrosis scores. Lledo and colleagues reported on results from 260 participants (105 with HIV infection) who had hepatic elastography performed at baseline and SVR, noting a significant fibrosis regression in 40%, which was more frequent in persons with baseline advanced fibrosis, and no significant difference in liver fibrosis changes comparing coinfecting and mono-infected.¹⁹ In another study among 78 HIV/HCV-coinfecting persons who were followed for 12 months, both liver stiffness and serum liver fibrosis scores decreased after DAA treatment.²⁴ Improvement was significantly correlated with higher severity of pretreatment liver disease. Another study of 112 PWH/HCV coinfection, where 35% had cirrhosis, who were followed from the beginning of anti-HCV therapy to 12 months later showed a significant decrease in liver stiffness in those with cirrhosis. A significant increase in CD4 count and percentages and CD8 count was only seen in persons without cirrhosis, but not in CD4/CD8 ratios, whether cirrhosis was present or not.¹⁷ A multicenter prospective cohort in Spain of 178 HIV/HCV-coinfecting persons, who were followed for 16 months, showed an improvement in liver stiffness that was greater in those with advanced liver disease (fibrosis stages F3–F4) but reached statistical significance in both groups. Lab-based APRI and FIB-4 scores improved; only the decline between baseline and end of treatment (EOT) measures achieved statistical significance; that observed between EOT and SVR did not. It was suggested that this might be correlated with inflammation improvement.²⁵ Consequently, the findings from our cohort extend those from clinical trials of DAAs, especially in terms of improvement in serum fibrosis scores and serum hepatic markers.

In addition, we were able to compare the trajectories in CD4 and CD8 counts, percentages, and CD4/CD8 ratios between treated and untreated persons (Supplementary Fig. S2a–

2c), observing improved CD4/CD8 ratios and a faster rate of decline in CD8 cells. We also showed that the improvements in blood ALT/AST and platelets continued to trend in a favorable direction through 48 months (Supplementary Fig. S4a and b). FIB-4 scores significantly declined in the treated group, while it trended slightly upward in the untreated group (Tables 1 and 2). The probability of maintaining a FIB-4 score <3.25 was significantly better in the treated group post-treatment, as shown both with covariate adjustment in Cox regression analyses (Fig. 2) and Kaplan–Meier analyses without covariate adjustment (not shown in figure). To our knowledge, this is the first cohort of PWH/HCV coinfection comparing these parameters in DAA-treated versus untreated individuals with such substantial length of follow-up.

Our analyses and findings from the observational cohort are subject to some limitations. Hepatic, immunological, and virologic laboratory results were obtained as part of routine HIV care and not at study-prescribed fixed intervals; therefore, there could be some information bias. The HOPS providers obtain medical records information from specialty and outside care, whenever possible; however, the HOPS database may not have captured some out-of-network prescriptions or care received at sites external to the HOPS clinics, which could have led to misclassification of DAA treatment status. Because of the observational nature of this analysis, and some differences in HOPS participants who did versus did not receive DAA therapy (also see Simoncini¹³), we employed a propensity score matching strategy, but residual confounding by indication is possible. In the GLMMs, after applying quality controls by setting the upper/lower limits for out-of-range values and visually inspecting the data, we proceeded with models assuming linear rather than nonlinear marker trajectories, which could potentially lead to some simplified inferences. We did not have data on some important characteristics of participants, such as HCV genotype, transient elastography, hepatitis B status. Finally, HOPS participants represent a convenience sample of persons seen at select HIV urban specialty clinics, and therefore, findings may not be generalizable to those for people seen in other care settings.

Conclusions

In conclusion, in our large heterogeneous cohort of U.S. PWH/HCV coinfection treated with DAAs, we found modest changes in immunological markers (CD4, CD8) and substantial improvements in hepatic markers in the 3–4 years following DAA treatment. Findings from our cohort extend those from clinical trials of DAAs, especially in terms of improvement in serum fibrosis scores and serum hepatic markers. Additional studies with even longer follow-up would be useful to evaluate the longevity of marker improvements and how these may relate to liver and nonliver health, such as cardiometabolic disease, in aging PWH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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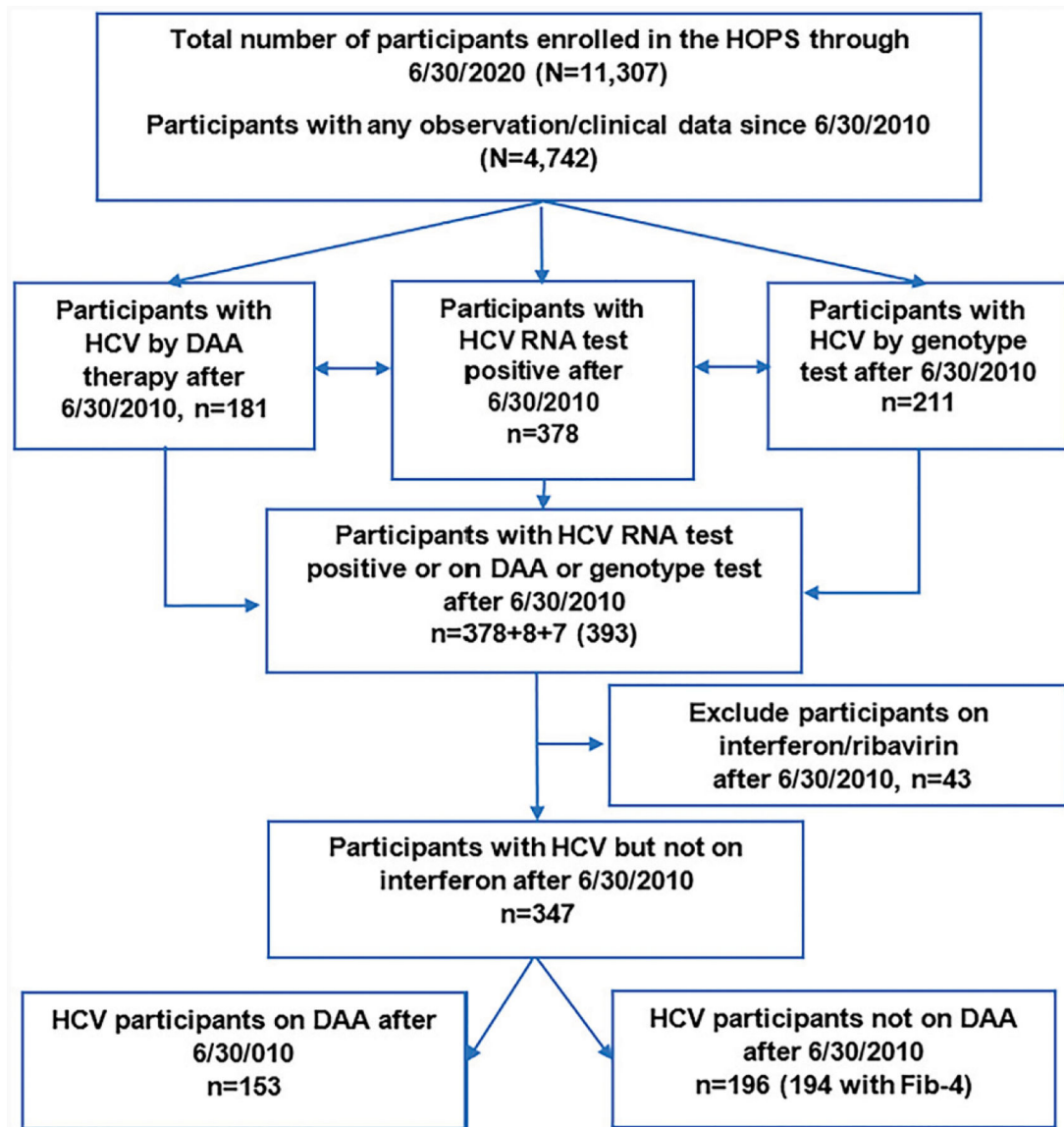
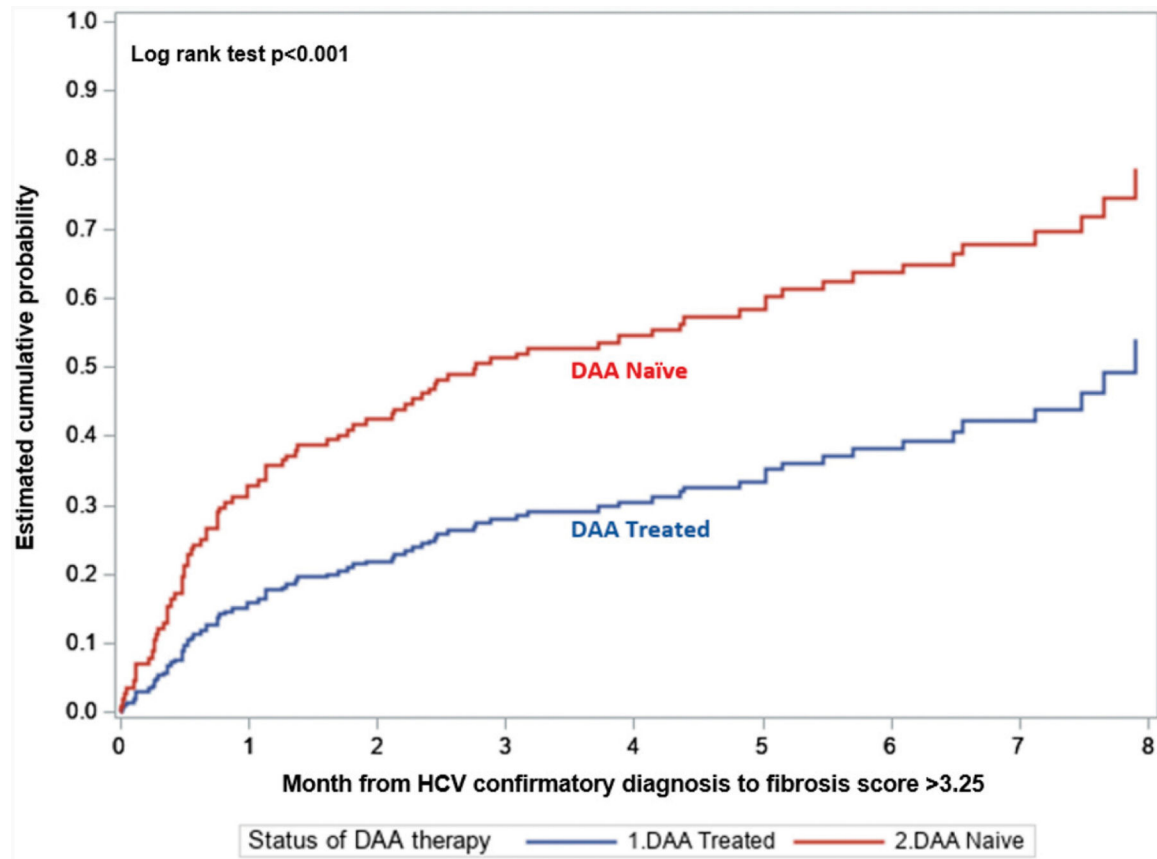


FIG. 1.

Flowchart of study cohort selection, the HIV Outpatient Study, 2010–2020.

**FIG. 2.**

Estimated cumulative probability for incident advanced liver fibrosis (fibrosis-4 > 3.25) among persons with HIV/hepatitis C virus coinfection stratified by direct-acting antiviral treatment status, the HIV Outpatient Study, 2010–2020.

Note: Cox regression with covariates adjustment for age, sex, and Fib-4 score at index date for patients with no Fib-4 score > 3.25 one year prior to index date ($n=235$). Index date is the DAA prescription date for the DAA-treated group and propensity score matched pseudo date of DAA prescription for DAA-naïve group, respectively.

Table 1.

Description of Persons with HIV/Hepatitis C Virus Coinfection by Direct-Acting Antiviral (DAA) Treatment Status at Time of DAA Prescription, the HIV Outpatient Study, 2010–2020

	Total	DAA-treated group	DAA-naïve group	p value ^a
Total	347 (100%)	153 (44.1%)	194 (55.9%)	
Age (years)				
Mean (SD)	52.7 (9.7)	54.8 (8.8)	51.9 (10.4)	<.01
Median (IQR)	53.8 (46.9, 59.6)	55 (49, 62)	54 (46, 59)	
Sex at birth				.24
Female	106 (30.5)	51 (33.3)	53 (27.3)	
Male	243 (69.5)	102 (66.7)	141 (72.7)	
Race at enrollment				.06
Hispanic	62 (17.9)	34 (22.2)	28 (14.4)	
Non-Hispanic Black	154 (44.4)	59 (38.6)	95 (48.9)	
Non-Hispanic White	122 (35.2)	58 (37.9)	64 (33.0)	
Unknown/other	5 (1.4)	2 (1.4)	7 (3.7)	
Insurance				.02
Private	87 (25.1)	42 (27.5)	45 (23.2)	
Public	233 (67.1)	107 (69.9)	126 (65.0)	
None/unknown	27 (7.8)	4 (2.6)	23 (11.8)	
Smoking				.35
Yes	256 (73.3)	116 (75.8)	140 (71.4)	
No	93 (26.7)	37 (24.2)	56 (28.6)	
Alcohol use				.55
Current	149 (42.9)	60 (39.2)	89 (45.9)	
Never	146 (42.1)	67 (43.8)	79 (40.7)	
Previously	26 (7.5)	14 (9.2)	12 (6.2)	
Unknown	26 (7.5)	12 (7.8)	14 (7.2)	
BMI				<.001
≤25	157 (45.2)	50 (32.7)	107 (55.2)	
26–30	113 (32.6)	62 (40.5)	51 (26.3)	
31–35	51 (14.7)	29 (19.0)	22 (11.3)	

	Total	DAA-treated group	DAA-naïve group	p value ^d
≥35	26 (7.5)	12 (7.8)	14 (7.2)	
Patients with ≥1 FIB-4 after index (n, %)	275 (79.25)	131 (85.62)	144 (74.22)	<.01
Patients FIB-4 missing after index (n, %)	72 (20.75)	22 (14.38)	50 (25.78)	
Mean (SD)	2.73 (3.29)	2.71 (2.37)	2.74 (3.87)	.92
Median (IQR)	1.68 (1.18, 2.74)	1.87 (1.25, 3.01)	1.55 (1.06, 2.50)	
<1.45	137 (39.5)	51 (33.3)	86 (44.3)	.08
1.45–3.25	139 (40.1)	65 (42.5)	74 (38.1)	
>3.25	71 (20.5)	37 (24.2)	34 (17.5)	
CD4 count (cells/mL), median (IQR) at index date	530 (325, 767)	581 (400, 786)	487 (270, 745)	<.01
CD4 count at index date				.04
≥200 cells/mL	319 (91.4)	145 (94.8)	174 (88.8)	
<200 cells/mL	30 (8.6)	8 (5.2)	22 (11.2)	
CD4 nadir at index date				.79
≥200 cells/mL	273 (78.6)	119 (77.8)	154 (79.4)	
<200 cells/mL	74 (21.3)	34 (22.2)	40 (20.6)	
CD4%	29 (22, 37)	32 (25, 38)	28 (19, 37)	<.01
CD8 count (cells/mL)	755 (533, 1029)	757 (536, 1033)	752 (531, 1020)	.71
CD8%	43 (36.2, 54)	41 (35, 51)	45 (38, 56)	<.01
CD4/CD8 ratio	0.64 (0.42, 0.95)	0.70 (0.44, 0.98)	0.60 (0.37, 0.91)	<.001
Last HIV VL test before index date				
VL over low limit, N(%)	94 (27.1)	25 (16.4)	69 (35.6)	<.001
ALT (mu/pL)	29 (18, 52)	31.5 (17.5, 51.5)	28 (19, 52)	.29
AST (mu/pL)	33 (23, 52)	30.5 (21, 44.5)	35 (24, 56)	.08
Platelet (counts/pL)	202 (142, 251)	194 (136, 240)	206 (151, 258)	.11
Chronic HBV infection				.29
Yes	75 (21.6)	29 (18.9)	46 (23.7)	
No	272 (78.4)	124 (81.1)	148 (76.3)	
Observation window (months)				<.001
Overall, median (IQR)	146 (73, 226)	193 (114, 249)	124 (46, 193)	
Before index date	110 (36, 190)	157 (68, 211)	69 (13, 161)	
After index date	35 (12, 55)	43 (23, 55)	25 (9, 51)	

	Total	DAA-treated group	DAA-naïve group	p value ^d
Years from HIV diagnosis to index date				
Mean (SD)	16.45 (8.9)	18.43 (8.0)	14.91 (9.2)	<.001
Median (IQR)	17.8 (9.1, 23.5)	20.2 (13.0, 24.6)	15.0 (7.8, 23.5)	
Months from HCV diagnosis to index date				
Mean (SD)	21.47 (30.18)	33.95 (25.0)	11.81 (30.3)	<.001
Median (IQR)	21.00 (1.3, 41.6)	33.2 (13.9, 50.1)	7.49 (1.4, 31.4)	
Deceased by the end of observation				.003
Yes	39 (11.2)	9 (5.9)	30 (15.5)	
No	308 (88.8)	144 (94.1)	164 (84.5)	
Years from index date to death	2.16 (1.0, 3.9)	2.16 (1.9, 3.4)	2.38 (0.9, 4.0)	.90

Index date refers to DAA prescription date for the DAA group and pseudo-DAA prescription for the comparison group. Age, BMI, ALT, AST, platelet, FIB-4 score, CD4 count, and CD4 nadir are all measures at time closest to index date. Other demographic characteristics refer to time of enrollment in the HOPS cohort. Smoking refers to a patient who has ever smoked. Observation windows start from participants' first HOPS visit to participants' last visit, patient death date, or the end of 2020, whichever came earlier.

^dChi-square test for categorical; t-test or nonparametric Wilcoxon rank-sum test for continuous variables.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CD, cluster of differentiation; FIB-4, fibrosis-4; IQR, interquartile range; HBV, hepatitis B virus; HCV, hepatitis C virus; SD, standard deviation; VL, viral load.

Table 2.

General Linear Mixed Model Estimated Clinical Marker Linear Trajectory Assessing Impact of Direct-Acting Antiviral (DAA) Therapy (Post- vs. Pre-DAA Treatment Comparison) Among Persons with HIV/Hepatitis C Virus Coinfection Adjusted for Age, Sex, and Race, the HIV Outpatient Study, 2010–2020

Markers	DAA-treated (n = 153)			DAA-naïve (n = 194)			Linear trajectory
	Pre-DAA ^a	Post-DAA ^b	Post versus pre ^c	Pre-pseudo ^d	Post-pseudo ^e	Post versus pre ^c	Treated versus naïve ^f (post vs. pre)
Log (CD4 cells/mL) ^g	0.04 (0.03, 0.05) ^j	-0.01 (-0.03, 0.00)	-0.05 (-0.08, -0.03)	0.03 (0.02, 0.04)	0.04 (0.02, 0.06)	0.01 (-0.02, 0.04)	-0.06 (-0.10, -0.03)
Log (CD8 cells/mL)	-0.02 (-0.03, -0.01)	-0.01 (-0.01, 0.02)	0.02 (0.01, 0.04)	-0.01 (-0.02, 0.01)	0.05 (0.03, 0.07)	0.05 (0.03, 0.08)	-0.03 (-0.06, -0.01)
CD4%	0.81 (0.67, 0.94)	-0.05 (-0.24, 0.14)	-0.85 (-1.12, -0.56)	0.39 (0.24, 0.53)	0.04 (-0.23, 0.32)	-0.34 (-0.69, 0.01)	-0.51 (-0.96, -0.06)
CD8%	-1.07 (-1.23, -0.91)	0.48 (0.24, 0.71)	1.55 (1.21, 1.89)	-0.49 (-0.67, -0.30)	0.32 (-0.03, 0.66)	0.80 (0.36, 1.24)	0.75 (0.19, 1.31)
CD4/CD8 (ratio)	0.04 (0.04, 0.05)	-0.04 (-0.01, 0.01)	-0.05 (-0.06, -0.03)	0.02 (0.02, 0.03)	0.00 (-0.01, 0.02)	-0.02 (-0.04, -0.00)	-0.03 (-0.05, 0.00)
ALT (mu/pL)	-2.15 (-4.41, 0.11)	-9.7 (-13.25, -6.15)	-7.55 (-12.45, -2.64)	-3.14 (-5.67, -0.63)	-2.83 (-7.18, 1.53)	0.31 (-5.41, 6.03)	-7.86 (-15.39, -0.33)
AST (mu/pL)	-1.30 (-4.17, 1.56)	-8.26 (-12.9, -3.61)	-6.95 (-13.34, -0.57)	0.92 (-2.18, 4.02)	-7.03 (-12.56, -1.49)	-7.95 (-15.17, -0.73)	0.99 (-8.65, 10.64)
Platelets (count/pL)	-0.74 (-1.97, 0.49)	3.53 (1.63, 5.43)	4.27 (1.64, 6.90)	3.14 (1.73, 4.54)	0.41 (-1.97, 2.80)	-2.72 (-5.87, 0.43)	6.99 (2.89, 11.09)
FIB-4	0.06 (-0.01, 0.13)	-0.20 (-0.31, -0.09)	-0.26 (-0.41, -0.11)	-0.01 (-0.09, 0.07)	0.01 (-0.13, 0.15)	0.02 (-0.16, 0.20)	-0.28 (-0.51, -0.05)
HIV VL (>200 copies/pL) ^h	-0.36 (-0.45, -0.27)	0.18 (0.03, 0.34)	0.54 (0.33, 0.76)	-0.16 (-0.26, -0.06)	0.02 (-0.13, 0.16)	0.17 (-0.03, 0.38)	0.37 (0.08, 0.66)
HCV VL (greater than the lower range value) ⁱ	-0.23 (-0.27, -0.18)	-2.38 (-2.84, -1.93)	-2.16 (-2.63, -1.69)	-0.01 (-0.06, 0.04)	0.21 (-0.06, 0.47)	0.22 (-0.06, 0.49)	-2.37 (-2.92, -1.83)

^aPre-DAA indicates prior to DAA prescription for the DAA-treated group.

^bPost-DAA indicates after DAA prescription for the DAA-treated group.

^cPre versus post indicates changes after DAA prescription for the DAA-treated group or DAA-naïve group.

^dPre-pseudo indicates prior to propensity score matched FIB-4 date for the DAA-naïve group.

^ePost-pseudo indicates after propensity score matched FIB-4 date for the DAA-naïve group.

^fTreated versus naïve groups represent the difference between post versus pre for DAA-treated and post versus pre for DAA-naïve groups.

^gLogarithmic transformation of CD4 or CD8 counts.

^hLogistic regression for probability of HIV VL >200 copies/mL.

ⁱLogistic regression for probability of HCV VL being detected (greater than the lower range value).

β_j Slope estimates (95% confidence interval) represent the rate of change in marker values per year using all lab results between January 1, 2011, and December 31, 2019.

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Table 3.

General Linear Mixed Model Estimated Clinical Marker Linear Trajectory Assessing Impact of Direct-Acting Antiviral (DAA) Therapy (Post-Treatment Comparison) Among Persons with HIV/ Hepatitis C Virus Coinfection, Adjusted for Age, Sex, and Race, the HIV Outpatient Study, 2010–2020

Markers	DAA-treated (n = 153)			DAA-naïve (n = 194)			Prior to Rx ^e		Post Rx ^f		Post Rx (treated vs. naïve)
	Pre-DAA ^a	Post-DAA ^b	Pre-pseudo ^c	Post-pseudo ^d	Treated versus naïve ^g	Treated versus naïve ^h					
Log (CD4 cells/mL) ^j	0.04 (0.03, 0.05)	-0.01 (-0.03, 0.00)	0.03 (0.02, 0.04)	0.04 (0.02, 0.06)	-0.01 (-0.03, 0.00)	0.05 (0.03, 0.08)					<.0001
Log (CD8 cells/mL) ^j	-0.02 (-0.03, -0.01) ^k	0.00 (-0.01, 0.02)	-0.01 (-0.02, 0.01)	0.05 (0.03, 0.07)	0.01 (0.00, 0.03)	0.04 (0.02, 0.07)					<.001
CD4%	0.81 (0.67, 0.94)	-0.05 (-0.24, 0.14)	0.38 (0.24, 0.53)	0.04 (-0.23, 0.32)	0.42 (-0.62, -0.23)	0.09 (-0.24, 0.42)					.59
CD8%	-1.07 (-1.23, -0.91)	0.48 (0.239, 0.71)	-0.48 (-0.67, -0.30)	0.32 (-0.03, 0.66)	0.59 (0.34, 0.83)	-0.16 (-0.58, 0.25)					.45
CD4/CD8 (ratio)	0.04 (0.04, 0.05)	-0.00 (-0.01, 0.01)	0.02 (0.02, 0.03)	0.00 (-0.01, 0.02)	-0.02 (-0.03, -0.01)	0.01 (-0.01, 0.02)					.36
ALT (mu/pL)	-2.15 (-4.41, 0.11)	-9.7 (-13.25, -6.15)	-3.14 (-5.66, -0.63)	-2.83 (-7.18, 1.53)	0.19 (-2.14, 2.52)	7.49 (3.66, 11.33)					<.001
AST (mu/pL)	-1.30 (-4.17, 1.56)	-8.26 (-12.90, -3.61)	0.92 (-2.18, 4.02)	-7.03 (-12.55, -1.49)	0.17 (-2.41, 2.76)	5.36 (1.09, 9.62)					.01
Platelets (count/pL)	-0.74 (-1.97, 0.49)	3.53 (1.63, 5.43)	3.14 (1.73, 4.54)	0.41 (-1.97, 2.80)	3.88 (2.01, 5.75)	-3.12 (-6.18, -0.07)					.04
FIB-4	0.06 (-0.01, 0.13)	-0.20 (-0.31, -0.09)	-0.01 (-0.09, 0.07)	0.01 (-0.13, 0.15)	-0.07 (-0.17, 0.02)	0.23 (0.07, 0.39)					.004
HIV VL (>200 copies/pL) ^l	-0.36 (-0.45, -0.27)	0.18 (0.03, 0.34)	-0.16 (-0.25, -0.06)	0.02 (-0.13, 0.16)	0.21 (0.08, 0.34)	-0.17 (-0.38, 0.047)					.13
HCV VL (greater than the lower range value) ^m	-0.23 (-0.27, -0.18)	-2.38 (-2.84, -1.93)	-0.01 (-0.06, 0.04)	0.21 (-0.06, 0.47)	0.02 (0.012, 0.02)	0.21 (0.17, 0.256)					<.0001

^aPre-DAA indicates prior to DAA prescription for the DAA-treated group.

^bPost-DAA indicates after DAA prescription for the DAA-treated group.

^cPre-pseudo indicates prior to propensity score matched FIB-4 date for the DAA-naïve group.

^dPost-pseudo indicates after propensity score matched FIB-4 date for the DAA-naïve group.

^ePrior Rx (DAA prescription) refers to before DAA prescription.

^fPost Rx refers to after DAA prescription.

^gTreated versus naïve groups before DAA prescription.

^hTreated versus naïve groups after DAA prescription.

ⁱContrast of treated versus naïve groups before and after DAA prescription.

^jLogarithmic transformation of CD4 or CD8 counts.

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k_i Slope estimates (95% confidence interval) represent the rate of change in marker values per year using all laboratory results between January 1, 2011, and December 31, 2019.

l_i Logistic regression for probability of HIV VL >200 copies/mL.

m_i Logistic regression for probability of HCV VL being positive (greater than the lower range value).