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MAJOR ARTICLE

Risk of Hepatocellular Carcinoma After Direct-Acting Antiviral Treatment for Hepatitis C Virus Infection in People With HIV

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Background. To inform hepatocellular carcinoma (HCC) surveillance after hepatitis C virus (HCV) cure with direct-acting antivirals (DAA), we estimated HCC risk post-DAA in people with human immunodeficiency virus (HIV) with advanced liver fibrosis or cirrhosis under universal DAA.

Methods. We used data from HepCAUSAL, a collaboration of cohorts of HIV–HCV coinfection from Europe and North America. Eligibility criteria were HIV–HCV coinfection, advanced liver fibrosis or cirrhosis, DAA naïve, HIV-RNA < 50 copies/mL, on antiretroviral therapy, no HBV coinfection, and no prior HCC diagnosis or liver transplant. Follow-up started when eligibility was met and ended at HCC diagnosis, death, loss to follow-up, 6 years, or database closure, whichever came first. We estimated the 6-year risk and annual probability of HCC if all eligible individuals had initiated DAA at baseline using a weighted pooled logistic model for the monthly HCC risk among DAA initiators.

Results. Of 3824 eligible individuals (92% males, median age 60 years [IQR: 54, 64]), 2373 (62%) who initiated DAA, 43 had an HCC diagnosis during follow-up. The estimated 6-year HCC risk (95% CI) under universal DAA was 2.5% (1.6, 3.9). Annual HCC probability was 0.81% (0.34, 1.54) between baseline and month 12 after DAA initiation, 0.64% (0.28, 1.19) between years 1 and 2, 0.50% (0.27, 0.84) between years 2 and 3, 0.34% (0.13, 0.63) between years 3 and 4, 0.19% (0.07, 0.33) between years 4 and 5, and 0.10% (0.01, 0.24) between years 5 and 6.

Conclusions. An estimated 2.5% of people with HIV and advanced liver fibrosis or cirrhosis are diagnosed with HCC by 6 years post-DAA. Annual probability of HCC declines over time and falls below 0.4% after 3 years.

Keywords. annual risk; advanced liver fibrosis; cirrhosis.

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Hepatocellular carcinoma (HCC) is a leading cause of death in individuals with hepatitis C virus (HCV) infection [1–4]. People with HCV and human immunodeficiency virus (HIV) coinfection may be at higher risk of HCC because they have a high prevalence of risk factors for liver disease and experience more rapid liver disease progression than people with HCV alone [5–7].

Regardless of HIV status, treatment with direct-acting antivirals (DAA) cures HCV infection in about 95% of people [8–10], improves liver function, and reduces HCC risk [11–13]. After DAA treatment, European and Asian Pacific clinical guidelines recommend lifelong HCC surveillance beginning at the advanced liver fibrosis stage, whereas US guidelines recommend surveillance only for people with cirrhosis [14–16].

These recommendations are based on unadjusted HCC risk estimates for people receiving HCV treatment in the interferon era and the early DAA era, when treatment was prioritized for patients at higher risk of liver disease progression and were predominantly derived from studies among people without HIV who were well-engaged in care [11, 17–25]. Therefore, individuals included in these studies who did initiate DAA may not be representative of the broader population eligible for DAA treatment. As a result, previous estimates might not be applicable to the current practice of universal DAA for all individuals with HCV–HIV coinfection.

To help inform HCC surveillance strategies in people with HIV, we estimated 6-year and annual HCC probabilities as if all people with HIV–HCV coinfection and advanced liver fibrosis or cirrhosis had initiated DAA (universal DAA treatment) using data from an international collaboration of cohorts in high-income countries.

METHODS

Data Source

The HepCAUSAL Collaboration is a consortium of cohorts of people with HIV–1 and HCV coinfection in Europe and North America, most of them attending HIV and infectious disease clinics [26] (Supplementary Table 1). Data were prospectively collected and/or extracted from electronic health records or medical chart reviews, prepared in a standardized format [27], and harmonized across cohorts [28]. Data include demographics, medications (including antiretroviral therapy and DAAs), laboratory measurements (blood panels, HIV and viral hepatitis serologies and viral loads), mortality, comorbidities, and substance use (smoking, alcohol, and other drugs).

Study Design

Individuals were eligible if they could receive DAAs within their health system (Supplementary Table 1) and met the following criteria between November 2013 and March 2023: HIV–HCV coinfection (serological or virological evidence of HIV and chronic HCV infection, defined by a detectable HCV-RNA, HCV antigen, or HCV genotype test result; the most recent detectable HCV test could not be followed by interferon treatment without a subsequent HCV RNA test to determine whether sustained virological response [SVR] was achieved), advanced liver fibrosis or cirrhosis (definition below), DAA-naive, HIV virological suppression (HIV-RNA <50 copies/mL) confirmed within the previous 12 months, on antiretroviral therapy, and no history of a positive hepatitis B surface antigen result, HCC diagnosis, or liver transplant. We excluded individuals with a Veterans Aging Cohort Study (VACS) index >100—a predictor for all-cause mortality among people with HIV—because people with a short life expectancy are not expected to benefit from treatment and are usually not offered DAA treatment [29]. Individuals could meet the eligible criteria at several months before DAA initiation. To improve the efficiency of our estimates, we allowed them to be included as eligible individuals in multiple months, but once they initiated DAA, they were no longer eligible [30].

A detectable HCV-RNA was defined as a positive qualitative RNA test or a quantitative test with a viral load above the detection limit or >15 copies/mL when the detection limit was not specified. Advanced liver fibrosis or cirrhosis was defined according to the following diagnostic hierarchy: a diagnosis of cirrhosis based on medical chart review or International Classification of Diseases (ICD)-9/10 diagnostic codes, a liver biopsy indicating a Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) score ≥F3, a liver stiffness measurement (LSM) ≥9.5 kPa by FibroScan, or 2 fibrosis-4 scores (FIB-4) ≥3.25 between 6 and 24 months of each other (Supplementary Figure 1).

Outcome and Follow-up

The outcome was an incident HCC diagnosis, defined by ICD-9/10 diagnostic codes or a recorded diagnosis in medical charts. Post-DAA HCC surveillance consisted of biannual abdominal ultrasound with or without and alfa-fetoprotein in people with F4 in the United States and in people with ≥F3 in European countries as per clinical guidelines [14, 16]. In 5 cohorts (23% of eligible individuals) without data on the type of liver cancer, we assumed their primary liver cancer diagnosis to be HCC (Supplementary Table 2). Follow-up started when all eligibility criteria were met (baseline) and ended at the earliest date of HCC diagnosis, death, loss to follow-up (ie, no HIV-RNA measurement ≥15 months), 6 years after baseline, or cohort-specific administrative end of follow-up.

DAA Treatment

DAA treatment was defined as initiating sofosbuvir, ledipasvir, daclatasvir, simeprevir, velpatasvir, glecaprevir, pibrentasvir, grazoprevir, ombitasvir, paritaprevir, or voxilaprevir in the

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baseline month. Individuals were classified into the DAA group if they initiated DAA treatment at baseline and into the no DAA group otherwise.

Prognostic Factors

We considered the following prognostic factors at baseline: age, sex, alanine transaminase, aspartate aminotransferase, platelet count, end-stage liver disease (defined as ascites, hepatic encephalopathy, hepatorenal syndrome, or esophageal variceal bleeding), CD4 cell count, month since baseline, geographical region (North America or Europe), calendar month of eligibility, and history of smoking, AIDS, high-risk alcohol consumption/alcohol use disorder (based on an alcohol use disorder identification test (AUDIT) score of more than 3 for females and 4 for males, more than 20 g of alcohol per week for males or 25 g for females, or ICD-9/10 codes for alcohol dependence/abuse), peg-interferon treatment, diabetes, and injection drug use (based on self-reported injection and/or opioid use, ICD codes for opioid abuse/dependency or use of medication for opioid use disorder).

Statistical Analyses

To estimate the 6-year HCC risk under universal DAA initiation, we estimated the risk in the DAA group and standardized it to the distribution of the above prognostic factors in the total eligible population. More specifically, we fitted a pooled logistic regression model for the monthly probability of HCC among eligible individuals in the DAA group, with months since baseline and calendar month of eligibility as covariates. We then applied the Aalen-Johansen estimator [31] to estimate 6-year risk and the probability of HCC in each 12-month period after DAA initiation among those without HCC at the start of the period.

To standardize the risk, eligible individuals received a time-fixed nonstabilized inverse probability (IP) weight (to adjust for confounding) whose denominator was estimated via a pooled logistic regression model for the probability of DAA initiation, including the above baseline prognostic factors. Individuals also received a time-varying nonstabilized IP censoring weight (to account for potential selection bias due to loss to follow-up) whose denominator was estimated among all eligible individuals via a pooled logistic regression for the monthly probability of remaining uncensored, including the above prognostic factors at baseline and their time-varying counterparts. The 2 sets of weights were multiplied and truncated at the 99th percentile [32]. Continuous variables were modeled using restricted cubic splines with 4 knots. We estimated the 95% confidence intervals using percentile-based nonparametric bootstrapping with 500 repetitions.

We performed a subgroup analysis by F3 or F4 fibrosis stage. We classified eligible individuals as having cirrhosis (F4) based on liver biopsy, LSM ≥12.5 kPa, or a clinical diagnosis. For this subgroup analysis, we included an additional criterion: 2 pretreatment AST to Platelet Ratio Index scores ≥2, measured 6–24 months apart [33]. Eligible individuals not identified as having baseline cirrhosis based on this definition were categorized as having advanced liver fibrosis (F3).

Sensitivity Analyses

We performed several sensitivity analyses to assess the robustness of our findings. To explore the impact of some prevalent HCC cases being included at baseline, we (1) backdated the diagnosis date of HCC 6 months (the approximate HCC tumor doubling time [16]) and (2) restricted the analysis to individuals with an abdominal ultrasound within 1 year from baseline in 5 cohorts with ultrasound data. We also (3) censored individuals at 24 months without an HIV-RNA measurement (rather than at 15 months), (4) censored at liver transplantation and (5) at death, (6) excluded one cohort with no data on alcohol use, (7) excluded individuals with evidence of end-stage liver disease at baseline, and (8) excluded individuals who died during the first 6 months after baseline. For the subgroup analysis in persons with cirrhosis, we used alternative operational definitions of cirrhosis by modifying FibroScan cutoffs and altering test criteria (Supplementary Material).

We used SAS version 9.4 and R version 4.2.3 for the statistical analyses.

RESULTS

Of 20 289 individuals with HIV–HCV coinfection, 3824 met the eligibility criteria at least once and, on average, at 20 months during the study period (Figure 1). Of the resulting 31 317 eligible individuals, 2373 initiated DAA and 28 944 (3586 unique individuals) did not; with 2135 individuals contributing follow-up to both DAA groups. Median baseline (interquartile range [IQR]) age and CD4 cell count were 60 years [54, 64] and 473 cells/mm^3 [298, 681], respectively, 91.7% were male, 48.3% had a history of injection drug use, 69.7% had HCV genotype 1, 16.8% had a history of interferon treatment, and 65.3% had cirrhosis (Table 1).

Compared with the no DAA group, individuals in the DAA group were more likely to have cirrhosis (71.5% vs 64.8%) and a history of interferon treatment (28.4% vs 15.9%) and were less likely to have a history of end-stage liver disease (6.4% vs 8.2%) and diabetes (27.7% vs 38.3%) (Table 1) at baseline. Standardized mean differences were <0.1 for most prognostic factors (Supplementary Figures 2 and 3). Of the 1451 individuals who never initiated DAA during the 6-year study period, 471 (32.4%) died, and 503 (34.6%) were lost to follow-up. Among 2373 DAA initiators, 35.7% were classified as having ≥F3 by FIB-4 score, 28.7% by a clinical diagnosis, and 35.5% by FibroScan/biopsy.

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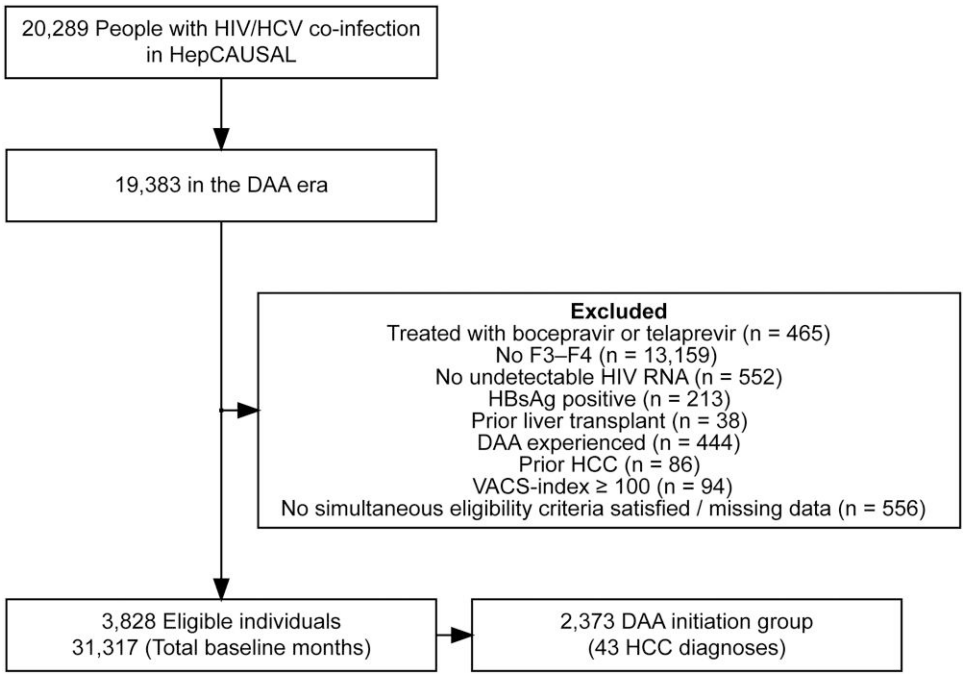


Figure 1. Selection of eligible people with HIV and HCV coinfection initiating DAA in HepCAUSAL, 2013–2023. Abbreviations: DAA, direct-acting antivirals; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; VACS index, Veterans Aging Cohort Study index; F3–F4, advanced fibrosis or cirrhosis based on the METAVIR score.

Over a median [IQR] follow-up of 4.3 years [2.4, 5.8] after DAA initiation, there were 43 HCC diagnoses and 301 deaths. The proportion of individuals with treatment failure ranged between 6.3% and 7.7% depending on the definition of HCV cure (Supplementary Table 3). Among those achieving SVR 12 weeks after the end of treatment (SVR12+), 2.4% had evidence of HCV reinfection, with a reinfection rate of 0.85 (95% CI: .64, 1.10) per 100 person-years. Seven out of 43 HCC diagnoses occurred in individuals with evidence of treatment failure, and one occurred in an individual with evidence of HCV reinfection. Only 4 individuals received a liver transplant during follow-up.

In 5 cohorts with abdominal ultrasound data (including 59.1% of all individuals from the DAA group), 1404 individuals (90%) had ≥1 abdominal ultrasound before DAA initiation, with a median [IQR] time between the last ultrasound and DAA treatment of 7 [2, 22] months, and 802 (57.1%) had an ultrasound 1 year before baseline.

The estimated 6-year HCC risk (95% CI) under universal DAA was 2.54% (1.59, 3.90) (Figure 2). The estimated annual probability of HCC among HCC-free individuals at the start of each period was 0.81% (0.34, 1.54) between baseline and month 12 after DAA initiation, 0.64% (0.28, 1.19) between years 1 and 2, 0.50% (0.27, 0.84) between years 2 and 3, 0.34% (0.13, 0.63) between years 3 and 4, 0.19% (0.07, 0.33) between year 4–5, and 0.10% (0.01, 0.24) between years 5 and 6 (Figure 3).

Subgroup Analyses by Liver Disease Stage

Among 20 458 eligible individuals (2701 unique)with F4 at baseline, 1679 initiated DAA, and 35 HCC diagnoses occurred after DAA initiation (Supplementary Table 4). The estimated 6-year HCC risk had all eligible individuals who initiated DAA at baseline was 2.38% (1.40, 3.76), and the overall crude HCC incidence rate after DAA was 0.52 (0.36, 0.72) cases per 100 person-years. The estimated annual probability of HCC was 0.78% (0.32, 1.53) between baseline and month 12 after DAA initiation, 0.72% (0.30, 1.30) between years 1 and 2, 0.46% (0.24, 0.77) between years 2 and 3, 0.25% (0.08, 0.51) between years 3 and 4, 0.13% (0.02, 0.28) between years 4 and 5, and 0.07% (0.001, 0.26) between years 5 and 6.

Among 10 859 eligible individuals (1440 unique) with F3 at baseline, 676 initiated DAA, and 8 HCC diagnoses occurred after DAA initiation. The estimated 6-year HCC risk was 1.59% (0.78, 3.23), and the overall crude incidence rate after DAA was 0.30 (0.13, 0.59) cases per 100 person-years (because the low number of events prevented fitting a regression model, we estimated the risk nonparametrically and without weights).

Sensitivity Analyses

The 6-year risk of HCC ranged between 2.11% and 2.72% under different assumptions (Supplementary Figures 4 and 5).

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Table 1. Baseline Characteristics of Eligible Individuals With HIV and Advanced Liver Fibrosis or Cirrhosis, HepCAUSAL Collaboration 2013–2023

Characteristic[a]	All (n = 31 317)	No DAA[b] (n = 28 944)	DAA[b] (n = 2373)	Standardized Mean Difference
Age (years)	60.0 (54.0, 64.0)	60.0 (55.0, 64.0)	57.0 (51.0, 63.0)	0.30
Sex				0.19
Male	28 707 (91.7%)	26 663 (92.1%)	2044 (86.1%)	
Female	2610 (8.3%)	2281 (7.9%)	329 (13.9%)	
Mode of HIV transmission[c]				0.50
Heterosexual	1305 (4.2%)	1133 (3.9%)	172 (7.2%)	
Homo/bisexual	1144 (3.7%)	976 (3.4%)	168 (7.1%)	
Injection drug use	5730 (18.3%)	4957 (17.1%)	773 (32.6%)	
Other	22 498 (71.8%)	21 308 (73.6%)	1190 (50.1%)	
Unknown	640 (2.0%)	570 (2.0%)	70 (2.9%)	
Behavioral				
History of injection drug use	15 122 (48.3%)	13 888 (48.0%)	1234 (52.0%)	−0.08
History of cigarette smoking				0.13
No	3557 (11.4%)	3255 (11.2%)	302 (12.7%)	
Yes	25 520 (81.5%)	23 689 (81.8%)	1831 (77.2%)	
Unknown	2240 (7.2%)	2000 (6.9%)	240 (10.1%)	
HIV related				
CD4 T-cell count (cells/mm^3)	473 (298, 681)	471 (296, 679)	502 (320, 710)	−0.09
History of AIDS	6190 (19.8%)	5649 (19.5%)	541 (22.8%)	−0.08
HCV related				
Known duration of HCV diagnosis (years)	10.7 (4.6, 14.4)	10.7 (4.7, 14.4)	10.4 (3.3, 15.2)	−0.01
Hepatitis C virus genotype				0.23
1	21 813 (69.7%)	20 272 (70.0%)	1541 (64.9%)	
2	1242 (4.0%)	1163 (4.0%)	79 (3.3%)	
3	2212 (7.1%)	1958 (6.8%)	254 (10.7%)	
4	1010 (3.2%)	856 (3.0%)	154 (6.5%)	
6	1 (0.0%)	0 (0.0%)	1 (0.0%)	
Unknown	5039 (16.1%)	4695 (16.2%)	344 (14.5%)	
Previous pegylated interferon treatment	5265 (16.8%)	4592 (15.9%)	673 (28.4%)	−0.30
Fibrosis-4 Index value	3.4 (2.4, 5.1)	3.4 (2.4, 5.0)	3.3 (2.2, 5.2)	−0.01
Liver fibrosis stage				0.14
F3	10 859 (34.7%)	10 183 (35.2%)	676 (28.5%)	
F4	20 458 (65.3%)	18 761 (64.8%)	1697 (71.5%)	
History of end-stage liver disease	2515 (8.0%)	2364 (8.2%)	151 (6.4%)	0.07
Model for end-stage liver disease (MELD) score				
No complete tests to determine MELD	8627 (27.5%)	7855 (27.1%)	772 (32.5%)	7855 (27.1%)
<15	19 783 (63.2%)	18 280 (63.2%)	1503 (63.3%)	18 280 (63.2%)
≥15–<20	1282 (4.1%)	1233 (4.3%)	49 (2.1%)	1233 (4.3%)
≥20–30	1344 (4.3%)	1301 (4.5%)	43 (1.8%)	1301 (4.5%)
≥30	281 (0.9%)	275 (1.0%)	6 (0.3%)	275 (1.0%)
Other				
HBV core antibody positive	20 010 (63.9%)	18 563 (64.1%)	1447 (61.0%)	0.07
History of diabetes	11 746 (37.5%)	11 088 (38.3%)	658 (27.7%)	0.23
Estimated glomerular filtration rate (mL/min/1.73 m^2)	85.1 (64.7, 100.6)	84.6 (64.1, 100.2)	90.5 (71.2, 103.4)	−0.25
Hemoglobin (g/dL)	13.7 (12.4, 14.9)	13.7 (12.3, 14.8)	14.1 (13.0, 15.2)	−0.21
VACS index	48.0 (35.0, 63.0)	48.0 (36.0, 63.0)	42.0 (29.0, 58.0)	0.31
Year of first eligible visit	2015 (2014, 2017)	2015 (2014, 2016)	2015 (2015, 2016)	−0.21

Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus; VACS, Veterans Aging Cohort Study.

[a]Median (Q1, Q3) for continuous variables; n (%) for categorical variables.

[b]Because being DAA-naïve at the beginning of the month was an eligibility criterion, individuals became ineligible after the month they initiated DAA. Therefore, individuals could contribute to the "no DAA" group in multiple months during the study period (December 2013 to March 2023) if they remained eligible over subsequent visits but could contribute to the DAA group only once, the month they initiated a DAA.

[c]"Other" category includes hemophilia, perinatal transmission, and unspecified sexual contact.

Excluding individuals with end-stage liver disease and censoring at death resulted in the greatest difference in point estimates compared to the main analysis. In analyses restricted to individuals with cirrhosis, the 6-year risk of HCC was similar under alternative definitions of cirrhosis (Supplementary Figure 6).

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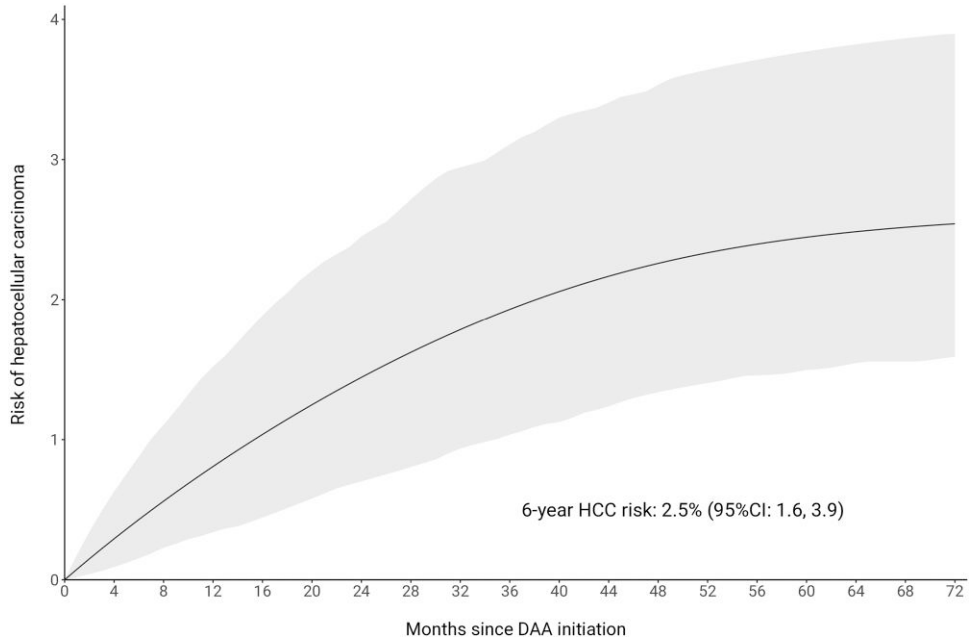


Figure 2. Estimated HCC risk after universal DAA initiation in people with HIV and advanced liver fibrosis or cirrhosis, HepCAUSAL Collaboration 2013–2023. Shaded area is the pointwise 95% confidence interval.

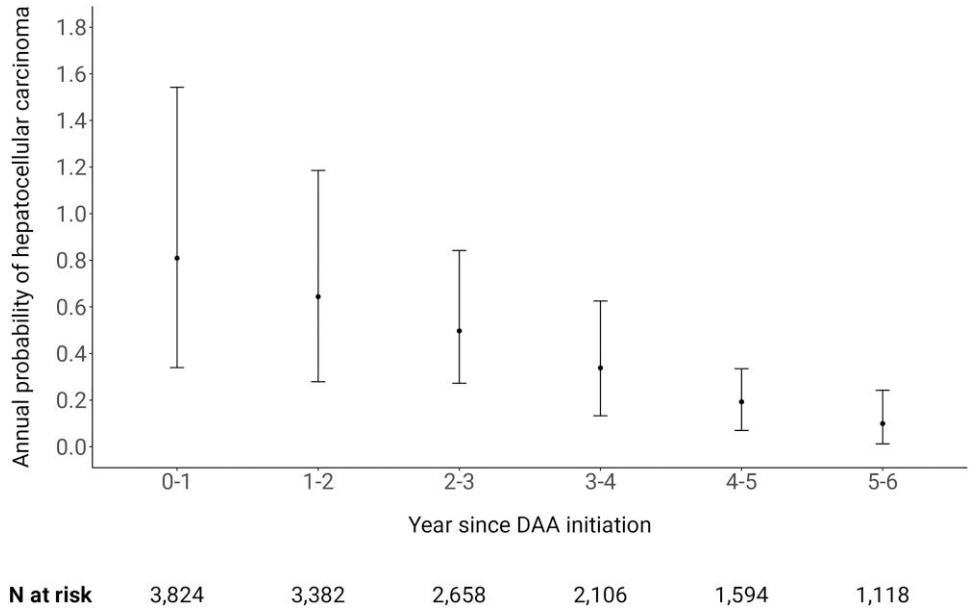


Figure 3. Estimated annual probability of hepatocellular carcinoma after DAA initiation in people with HIV and advanced liver fibrosis or cirrhosis, HepCAUSAL Collaboration 2013–2023. Abbreviation: DAA, direct-acting antiviral.

DISCUSSION

We estimated that 2.5% (95% CI: 1.6, 3.9) of people with HIV and advanced fibrosis or cirrhosis would have been diagnosed with HCC by 6 years post-DAA treatment. The estimated annual probability of HCC declined from 0.81% (95% CI: .34, 1.54) in the year following DAA initiation to 0.10% (95% CI: .01, .24) between 5 and 6 years after DAA initiation.

Most studies in people with HIV have reported post-SVR HCC risks below 1% over periods of 3–4 years [19, 34, 35]; one study reported a 4-year risk of approximately 2% [36], in

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line with our 2% HCC risk by 4 years. These studies were conducted shortly after DAA became available, when individuals at higher risk of liver disease progression and those well-engaged in care were more likely to receive DAAs. Our study updates those estimates for the DAA era for people with HIV eligible for DAA. In studies of people without HIV, the estimated 3-year post-SVR risks vary widely, from <1% to 10% [11, 22, 37–39], but comparisons across studies are complicated by methodological choices (eg, handling of competing events) and differences in study populations.

Post-SVR surveillance may detect HCC at earlier stages when treatment options are most effective [16, 40]. HCC surveillance is deemed cost-effective when annual HCC incidence is above a certain threshold, which varies across HCC clinical guidelines and ranges from 0.4% to 1.5%; but few studies in the DAA era or in people with HIV have reported annual incidence estimates [21, 41]. While a stable annual incidence over 2% for up to 10 years was reported during the interferon era [16, 42], this is the first study to provide information to determine whether these thresholds are reached after DAA in people with HIV. Our estimated annual probability of HCC fell between the 0.4% and 1.5% thresholds during the first 3 years post-DAA and gradually fell below 0.4% afterward. This suggests that HCC surveillance is particularly critical in the first few years after DAA initiation. However, disengagement in HCC surveillance post-SVR could result in missed or delayed HCC diagnoses after DAA initiation [43], which may limit our ability to accurately estimate the annual probability of HCC.

Post-SVR HCC surveillance is currently recommended for people with cirrhosis by all HCC clinical guidelines, while the need for surveillance in patients with advanced fibrosis without cirrhosis remains contentious. Of about 700 eligible individuals with HIV/HCV and advanced fibrosis in our study—to our knowledge the largest to date—only 8 had HCC after DAA, which corresponds to a 6-year risk of 1.6% (0.8, 3.2) and an incidence rate of 0.30 per 100 person-years (0.13, 0.59), which is lower than a meta-analysis of 4 smaller early DAA studies [13] (0.63 per 100 person-years) and similar to a study in people with HIV [36] (0.37 per 100 person-years). Given the low incidence of HCC and the wide HCC risk 95% CI, the necessity for continued HCC surveillance in individuals with pretreatment F3 requires further evaluation.

Our study has some limitations. First, our estimates rely on the assumption that DAA adherence and SVR rates in the no DAA group would have been similar to those in the DAA group if all eligible individuals had received DAA treatment, conditional on the measured covariates. Although this assumption cannot be directly tested, it is reassuring that several studies have reported high SVR rates across varying levels of adherence, including among individuals with suboptimal adherence [44, 45]. Second, because DAA treatment is typically not recommended for individuals with a short life expectancy, and the available data may not suffice to assess immediate risk of death, our analysis may include some individuals ineligible for DAA. However, our estimates did not materially change when excluding individuals who died within the first 6 months following DAA. Third, some HCC cases diagnosed shortly after baseline might have been undetected rather than truly new diagnoses. Backdating the dates of HCC diagnoses by 6 months resulted in a lower probability of HCC in the first year post-DAA, indicating delayed screening or that cases may have gone undetected due to the low sensitivity of diagnostic tests during the early stages of HCC. Nevertheless, estimates for subsequent years were similar to those in the main analysis. Fourth, the diagnosis of liver fibrosis or cirrhosis is difficult to make using the available data, given that the positive and negative predictive values for FIB-4 are 65% and 84%, respectively [46]. To reduce misclassification, we used at least 2 FIB-4 values of ≥3.25 spaced 6–24 months apart and excluded laboratory values indicative of acute illness rather than liver fibrosis. HCC risks were consistent across various definitions of cirrhosis. Because there are no specific diagnostic codes for F3 stage, and Fibroscan was not uniformly available across cohorts, we relied primarily on laboratory measurements, which may have overestimated the risk in our population with F3/F4. Fifth, while we included all individuals who initiated DAA, reflecting a real-world population of people with HIV initiating DAA in high-income countries, postcure HCC estimates may be lower given that 8% of eligible individuals did not achieve SVR12+. Last, our estimates rely on correct model specification, but our results were robust to different modeling choices.

In conclusion, people with HIV and advanced liver disease remain at risk for HCC, though the probability of HCC appears to decline over time, falling below current cost-effectiveness thresholds. Our findings suggest that HCC surveillance appears to be most crucial during the initial years post-DAA in people with HIV. Future research is needed to understand if there are populations for whom HCC risk decreases sufficiently that surveillance could be discontinued, and if so, when.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol **2019**; 16:589–604.
2. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. Nat Rev Dis Primers **2021**; 7:6.
3. Calderon-Martinez E, Landazuri-Navas S, Vilchez E, et al. Prognostic scores and survival rates by etiology of hepatocellular carcinoma: a review. J Clin Med Res **2023**; 15:200–7.
4. WHO. Hepatitis C. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c. Accessed 3 January 2025.
5. Ingiliz P, Rockstroh JK. Natural history of liver disease and effect of hepatitis C virus on HIV disease progression. Curr Opin HIV AIDS **2015**; 10:303–8.
6. Kramer JR, Kowalkowski MA, Duan Z, Chiao EY. The effect of HIV viral control on the incidence of hepatocellular carcinoma in veterans with hepatitis C and HIV coinfection. J Acquir Immune Defic Syndr **2015**; 68:456–62.
7. Lin W, Weinberg EM, Chung RT. Pathogenesis of accelerated fibrosis in HIV/HCV co-infection. J Infect Dis **2013**; 207 Suppl 1:S13–8.
8. Lodi S, Klein M, Rauch A, et al. Sustained virological response after treatment with direct antiviral agents in individuals with HIV and hepatitis C co-infection. J Int AIDS Soc **2022**; 25:e26048.
9. Sogni P, Gilbert C, Lacombe K, et al. All-oral direct-acting antiviral regimens in HIV/hepatitis C virus-coinfected patients with cirrhosis are efficient and safe: real-life results from the prospective ANRS CO13-HEPAVIH cohort. Clin Infect Dis **2016**; 63:763–70.
10. Ferreira VL, Tonin FS, Assis Jarek NA, Ramires Y, Pontarolo R. Efficacy of interferon-free therapies for chronic hepatitis C: a systematic review of all randomized clinical trials. Clin Drug Investig **2017**; 37:635–46.
11. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol **2017**: S0168-8278(17)32273-0. doi:10.1016/j.jhep.2017.08.030
12. Celsa C, Stornello C, Giuffrida P, et al. Direct-acting antiviral agents and risk of hepatocellular carcinoma: critical appraisal of the evidence. Ann Hepatol **2022**; 27 Suppl 1:100568.
13. Kim NJ, Vutien P, Cleveland E, Cravero A, Ioannou GN. Fibrosis stage-specific incidence of hepatocellular cancer after hepatitis C cure with direct-acting antivirals: a systematic review and meta-analysis. Clin Gastroenterol Hepatol **2023**; 21: 1723–38.e5.
14. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol **2018**; 69:182–236.
15. Kanda T, Lau GKK, Wei L, et al. APASL HCV guidelines of virus-eradicated patients by DAA on how to monitor HCC occurrence and HBV reactivation. Hepatol Int **2019**; 13:649–61.
16. Singal AG, Llovet JM, Yarchoan M, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology **2023**; 78:1922–65.
17. Leal C, Strogoff-de-Matos J, Theodoro C, et al. Incidence and risk factors of hepatocellular carcinoma in patients with chronic hepatitis C treated with direct-acting antivirals. Viruses **2023**; 15:221.
18. Hong H, Choi WM, Lee D, et al. Prediction of hepatocellular carcinoma development in Korean patients after hepatitis C cure with direct-acting antivirals. Gut Liver **2023**; 18:147–55.
19. Corma-Gómez A, Macías J, Lacalle-Remigio JR, et al. Human immunodeficiency virus (HIV) infection is associated with lower risk of hepatocellular carcinoma after sustained virological response to direct-acting antivirals in hepatitis C infected patients with advanced fibrosis. Clin Infect Dis **2021**; 73:e2109–16.
20. Azzi J, Dorival C, Cagnot C, et al. Prediction of hepatocellular carcinoma in Hepatitis C patients with advanced fibrosis after sustained virologic response. Clin Res Hepatol Gastroenterol **2022**; 46:101923.
21. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology **2017**; 153:996–1005.e1.

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22. Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet **2019**; 393:1453–64.
23. Merchante N, Rodríguez-Fernández M, Pineda JA. Screening for hepatocellular carcinoma in HIV-infected patients: current evidence and controversies. Curr HIV/AIDS Rep **2020**; 17:6–17.
24. Semmler G, Meyer EL, Kozbial K, et al. HCC risk stratification after cure of hepatitis C in patients with compensated advanced chronic liver disease. J Hepatol **2022**; 76:812–21.
25. Lockart I, Yeo MGH, Hajarizadeh B, Dore GJ, Danta M. HCC incidence after hepatitis C cure among patients with advanced fibrosis or cirrhosis: a meta-analysis. Hepatology **2022**; 76:139–54.
26. CAUSALab. Hep-CAUSAL. Available at: https://causalab.sph.harvard.edu/hep-causal/. Accessed 9 May 2024.
27. Eurocoord. Enhancing clinical and epidemiological HIV research in Europe through cohort collaboration HIV Cohorts. Data Exchange Protocol (HICDEP) 1.130. Available at: hicdep.org. Accessed 2 January 2025.
28. CAUSALab. What we do. Available at: https://causalab.hsph.harvard.edu/what-we-do/. Accessed 2 January 2025.
29. Tate JP, Justice AC, Hughes MD, et al. An internationally generalizable risk index for mortality after one year of antiretroviral therapy. AIDS **2013**; 27: 563–72.
30. García-Albéniz X, Hsu J, Hernán MA. The value of explicitly emulating a target trial when using real world evidence: an application to colorectal cancer screening. Eur J Epidemiol **2017**; 32:495–500.
31. Young JG, Stensrud MJ, Tchetgen Tchetgen EJ, Hernán MA. A causal framework for classical statistical estimands in failure-time settings with competing events. Stat Med **2020**; 39:1199–236.
32. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol **2008**; 168:656–64.
33. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology **2003**; 38:518–26.
34. Guardigni V, Toschi A, Badia L, et al. Patients with HIV and cirrhosis: the risk for hepatocellular carcinoma after direct-acting antivirals for hepatitis C virus. AIDS **2021**; 35:1967–72.
35. Merchante N, Rivero-Juárez A, Téllez F, et al. Sustained virological response to direct-acting antiviral regimens reduces the risk of hepatocellular carcinoma in HIV/HCV-coinfected patients with cirrhosis. J Antimicrob Chemother **2018**; 73:2435–43.
36. Berenguer J, Aldámiz-Echevarría T, Hontañón V, et al. Clinical outcomes and prognostic factors after HCV clearance with DAA in HIV/HCV coinfected patients with advanced Fibrosis/Cirrhosis. Hepatology **2024**; 81:238–53.
37. Oliveira M, Gaspar R, Santos L, Macedo G. High incidence of hepatocarcinoma in patients with advanced fibrosis treated with direct-acting antiviral agents for hepatitis C: a real-world retrospective study. Clin Res Hepatol Gastroenterol **2024**; 48: 102404.
38. Quaranta MG, Cavalletto L, Russo FP, et al. Reduction of the risk of hepatocellular carcinoma over time using direct-acting antivirals: a propensity score analysis of a real-life cohort (PITER HCV). Viruses **2024**; 16:682.
39. Salama M, Darwesh N, Elsabaawy MM, Abdelsameea E, Gomaa A, Sabry A. Long-term outcomes of patients with liver cirrhosis after eradication of chronic hepatitis C with direct-acting antiviral drugs (DAAs). J Hepatocell Carcinoma **2024**; 11:2115–32.
40. Singal AG, Zhang E, Narasimman M, et al. HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: a meta-analysis. J Hepatol **2022**; 77:128–39.
41. Mezzacappa C, Kim NJ, Vutien P, Kaplan DE, Ioannou GN, Taddei TH. Screening for hepatocellular carcinoma and survival in patients with cirrhosis after hepatitis C virus cure. JAMA Netw Open **2024**; 7:e2420963.
42. Ioannou GN, Beste LA, Green PK, et al. Increased risk for hepatocellular carcinoma persists up to 10 years after HCV eradication in patients with baseline cirrhosis or high FIB-4 scores. Gastroenterology **2019**; 157:1264–78.e4.
43. Willemse S, Smit C, Sogni P, et al. Low compliance with hepatocellular carcinoma screening guidelines in hepatitis B/C virus co-infected HIV patients with cirrhosis. J Viral Hepat **2019**; 26:1224–8.
44. Heo M, Norton BL, Pericot-Valverde I, et al. Optimal hepatitis C treatment adherence patterns and sustained virologic response among people who inject drugs: the HERO study. J Hepatol **2024**; 80:702–13.
45. Norton BL, Akiyama MJ, Agyemang L, Heo M, Pericot-Valverde I, Litwin AH. Low adherence achieves high HCV cure rates among people who inject drugs treated with direct-acting antiviral agents. Open Forum Infect Dis **2020**; 7:ofaa377.
46. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology **2006**; 43:1317–25.

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