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Direct-Acting Antivirals and Risk of Hepatocellular Carcinoma in People With HIV/HCV Coinfection

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Background

- Hepatitis C virus (HCV) infection is a leading cause of hepatocellular carcinoma (HCC) and people with HIV/HCV have faster HCV disease progression
- Direct-acting antivirals (DAA) cure ~95% of people with HCV, but a residual HCC risk remains; evidence is limited for people with HIV
- To inform HCC monitoring guidelines post-DAA, we estimated HCC risk and risk trends among people with HIV/HCV co-infection and advanced liver fibrosis/cirrhosis.

Methods

- Data on individuals with HIV/HCV from HepCAUSAL, a collaboration of 12 cohorts from Europe and North America.
- Target trial emulation. Below an overview.

Target trial	Emulated trial
Eligibility: HIV/HCV co-infection, advanced liver fibrosis (F3) or cirrhosis (F4) (based on: clinical cirrhosis diagnosis, biopsy, liver stiffness ≥9.5 kPa, or two FIB-4 ≥3.25), DAA naïve, HIV-RNA <200 copies/mL, on antiretroviral therapy, no hepatitis B virus co-infection, and no previous HCC diagnosis or liver transplant	Same
Intervention 1) Immediate DAA initiation with a DAA containing regimen for 8 to 12 weeks 2) No DAA treatment during follow up	Same
Outcome: Incident (de novo) HCC	Same
Assignment procedure: Participants are randomly assigned and are aware of the strategy they are assigned to at baseline	Randomization is assumed conditional on baseline covariates
Causal contrast: intention-to-treat (ITT) and per-protocol	Observational analog of the per-protocol effect
Analyses: ITT: survival analysis to estimate 4-year HCC risk by DAA strategy, risk differences and risk ratios. **Per-protocol,** same, with adjustment for baseline and time-varying covariates associated with loss to follow-up and treatment adherence via inverse probability weighting. As death is a competing event, we estimate the total effect of DAA on HCC.	Same per-protocol analysis with sequential emulation

Key Findings

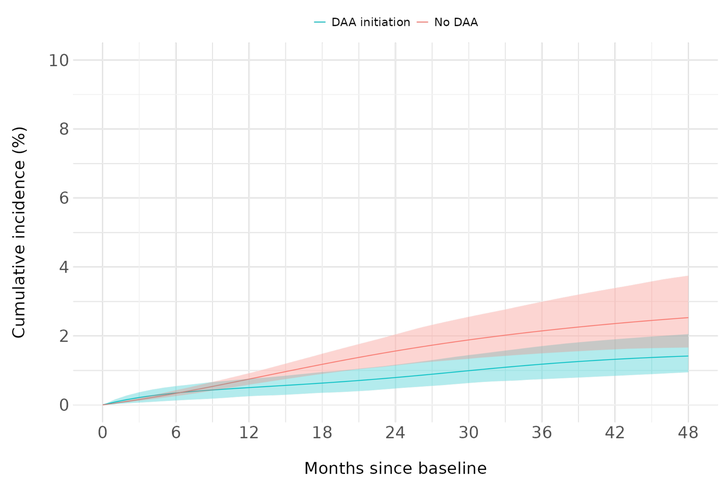
- 3,906 eligible individuals
  - 60% initiated DAAs
  - 94 incident HCC during follow-up
  - 835 died (21%)
  - 1,452 with F3 and 2,822 with F4

Age	Previous treatment	Males	History of injection drug use	End stage liver disease	Ever AIDS
58 years	16%	87%	46%	10%	29%

Table 1: Risk of hepatocellular carcinoma among people with HIV and HCV co-infection and advanced liver fibrosis or cirrhosis, overall and by liver fibrosis stage

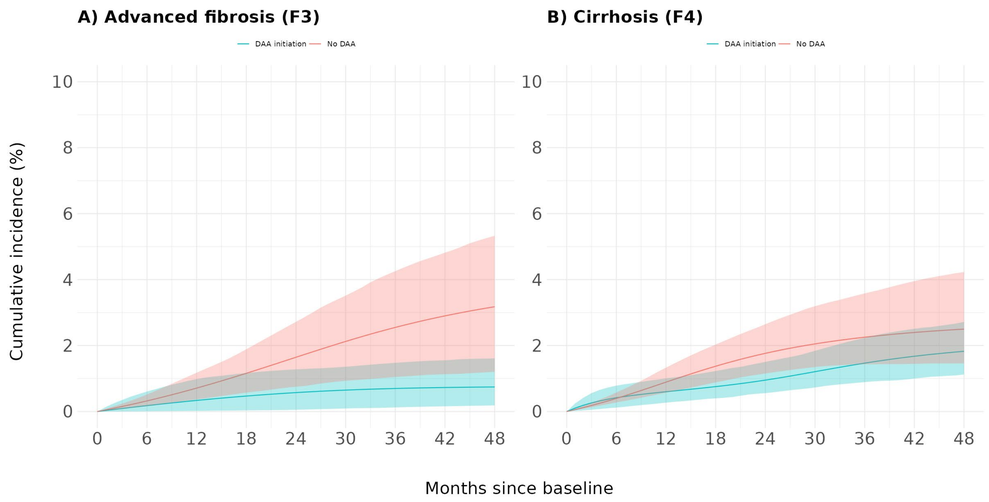
	4-year risk				
Model	**DAA**	**no DAA**	**Risk difference**	**RR (95%CI)**	**Post-DAA annual HCC incidence**
Main	1.42% (0.95, 2.05)	2.53% (1.66, 3.75)	-1.11% (-2.44, -0.03)	0.56 (0.31, 0.99)	0.36% (0.16, 0.58)
		Subgroup Analyses			
F3	0.75% (0.19, 1.61)	3.18% (1.2, 5.33)	-2.43% (-4.56, -0.19)	0.23 (0.06, 0.84)	0.19% (0.01, 0.53)
F4	1.83% (1.12, 2.72)	2.5% (1.46, 4.23)	-0.67% (-2.42, 0.63)	0.73 (0.35, 1.35)	0.46% (0.19, 0.80)

Figure 1: 4-year risk of hepatocellular carcinoma among people with HIV and HCV co-infection and advanced liver fibrosis or cirrhosis



The post-DAA annual HCC risk remained approximately constant over the 4-year period, at an average of 0.36% per year (95%CI: 0.16, 058).

Figure 2: 4-year risk of hepatocellular carcinoma among people with HIV and HCV co-infection by liver fibrosis stage



Panel A) F3 based on a liver biopsy (METAVIR F3), liver stiffness between ≥9.5-12.5 kPa, or APRI<2;
Panel B) F4 based on a clinical diagnosis, liver biopsy (METAVR F4), liver stiffness ≥12.5 kPa, or two APRI scores ≥2.

Conclusion

DAA reduces the 4-year HCC risk by **1.1% on an absolute scale** and **44% on a relative scale** in people with HIV/HCV co-infection and advanced fibrosis or cirrhosis

Discussion

- DAA reduces but does not eliminate HCC risk in people with HIV and advanced liver fibrosis or cirrhosis
- The magnitude of effect of DAA on HCC risk is greater for F3 than F4 fibrosis, as fibrosis regression is more likely for F3
- In patients with F4, the estimated annual HCC risk after DAA was near the 0.4% threshold at which HCC monitoring is deemed cost-effective, suggesting continued monitoring is needed
- In patients with F3, annual HCC risk was below the cost-effectiveness threshold, but the 95% confidence interval was wide and included 0.4%. No or alternative risk-based HCC monitoring strategies could be considered for this group

Acknowledgments

CAUSALab (Mathieu Chalouni, Roger W Logan, Sophia Rein, Daniela K van Santen, Sara Lodi, Miguel A Hernán)
ATHENA (Marc van der Valk, Anders Boyd)
AMACS (Giota Touloumi)
Boston Medical Center HIV cohort (Sara Lodi, Rachel Epstein, David Nunes)
Canadian Co-infection Cohort (Marina B Klein, James Young)
ICONA (Antonella d'Arminio Monforte, Alessandro Tavelli, Massimo Puoti)
CORIS (Inmaculada Jarrín, Juan Berenguer)
Aquitaine (Linda Wittkop)
Austrian HIV Cohort Study (Robert Zangerle)
VACS (Amy C Justice, Christopher T Rentsch, Jessie Torgersen)
South Alberta Cohort (John Gill)
PISCIS (Jose M Miro, Jordi Casabona)
Swiss HIV cohort Study (Andri Rauch, Bernard Surial)

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