HBV Treatment as Prevention – Scientific Support

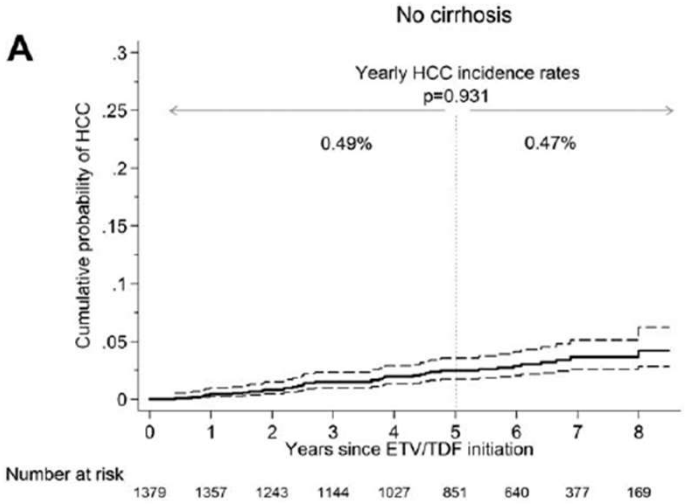
H. Razavi

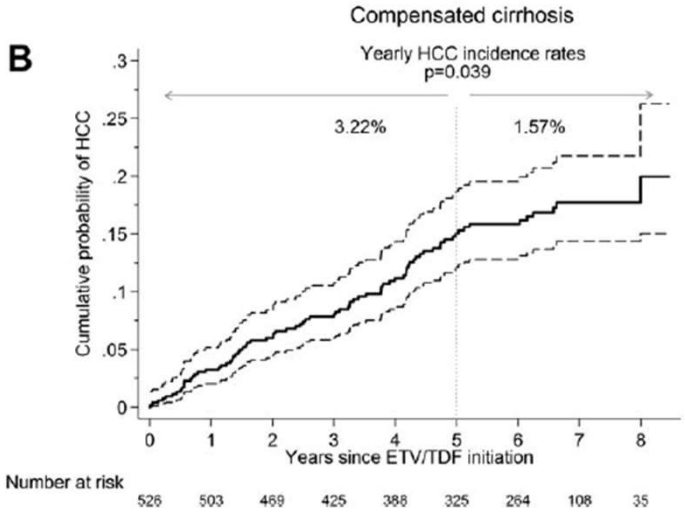
22 October 2020

@CDAFound

CDA FOUNDATION

Studies in the European HBV cohorts have shown that long term suppression of HBV replication may reduce HCC risk over time

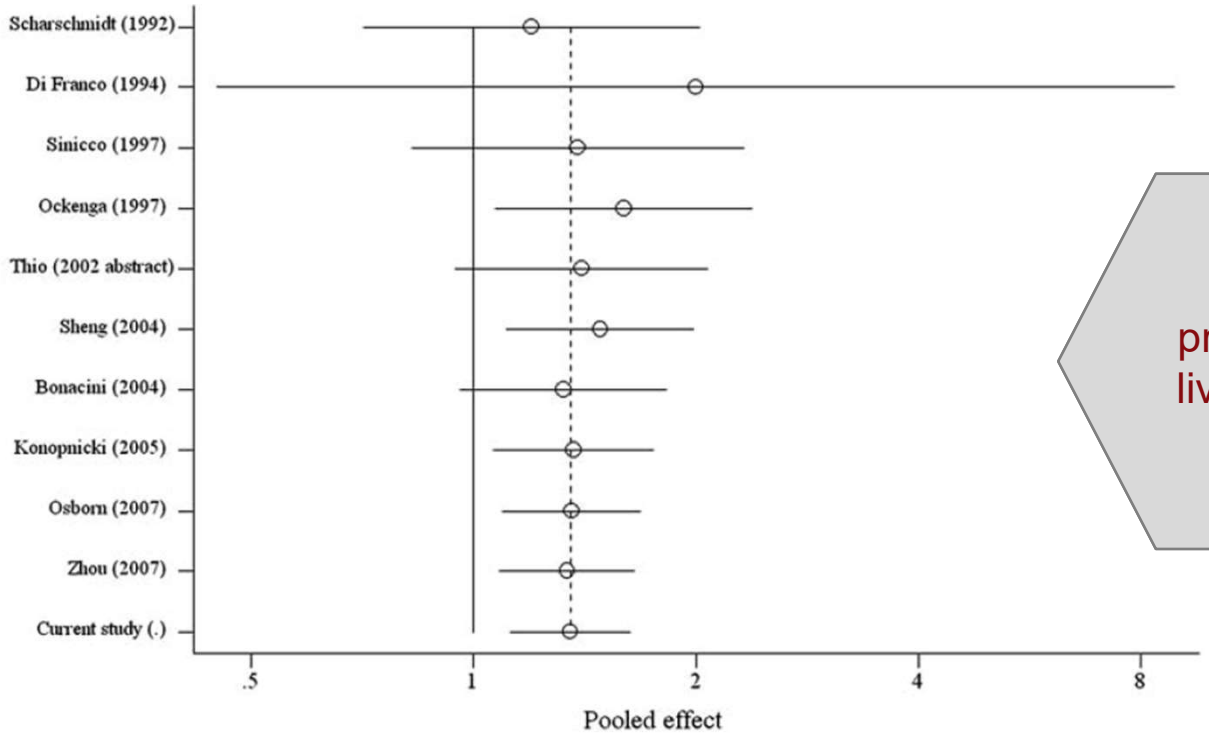




Unlike HCV, HCC also develops in non-cirrhotic HBV patients making surveillance strategies more complex

Papatheodoridis GV, Idilman R, Dalekos GN, et al. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology. 2017;66(5):1444-1453. doi:10.1002/hep.29320

Most of the existing data supporting HBV treatment as prevention are reported in HIV cohorts which have a higher mortality than mono-infected cases



Plot of cumulative meta-analysis for the effect of hepatitis B virus infection on overall mortality among HIV+ patients

Keep in mind that HIV infection accelerates progression of HBV related liver diseases & mortality is higher among HIV/HBV coinfection individuals

Nikolopoulos GK, Paraskevis D, Hatzitheodorou E, et al. Impact of hepatitis B virus infection on the progression of AIDS and mortality in HIV-infected individuals: a cohort study and meta-analysis. Clin Infect Dis. 2009;48(12):1763-1771. doi:10.1086/599110

Prospective analysis of 4 European HIV cohorts showed that TDF treatment has a large impact on reducing HCC incidence over time

	No TDF	TDF	*p* value
	n = 1,032	n = 2,593	
Median age in years (IQR)	35 [29, 42]	37 [31, 44]	0.5
Female sex (%)	179 (17)	414 (16)	0.4
Non-caucasian (%)	136 (13)	588 (23)	<0.001
HIV transmission group (%)			<0.001
Heterosexual	235 (23)	726 (28)	
IDU	289 (28)	299 (12)	
MSM	422 (41)	1401 (54)	
Other	25 (2)	51 (2)	
Missing	*61 (6)*	*116 (4)*	
HCV coinfection (%)	352 (34)	490 (19)	<0.001
Liver cirrhosis (%)	145 (14)	620 (24)	<0.001
Median baseline CD4 count in cells/μl (IQR)	310 (159–503)	332 (190–498)	0.02
Cohort (%)			<0.001
Aquitaine	291 (28)	319 (12)	
Athena	236 (23)	1146 (44)	
EuroSIDA	276 (27)	553 (21)	
SHCS	229 (22)	575 (22)	
Median follow-up in years (IQR)	5.0 (1.9–9.0)	9.8 (5.7–14.5)	<0.001
Calendar year of last visit (IQR)	2008 (2002–2014)	2014 (2014–2015)	<0.001

P value from Chi-square or Mann-Whitney *U* tests. ART, antiretroviral therapy; HCV, hepatitis C virus; IDU, injection drug use; IQR, interquartile range; MSM, men who have sex with men; SHCS, Swiss HIV Cohort Study; TDF, tenofovir disoproxil fumarate.

The two arms had similar median age and sex. The TDF arm had more cirrhotic patients.

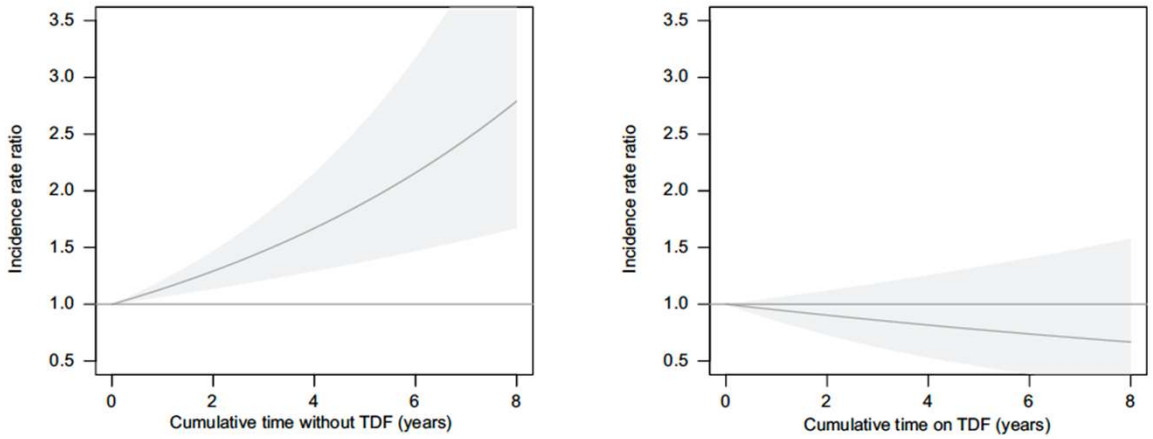
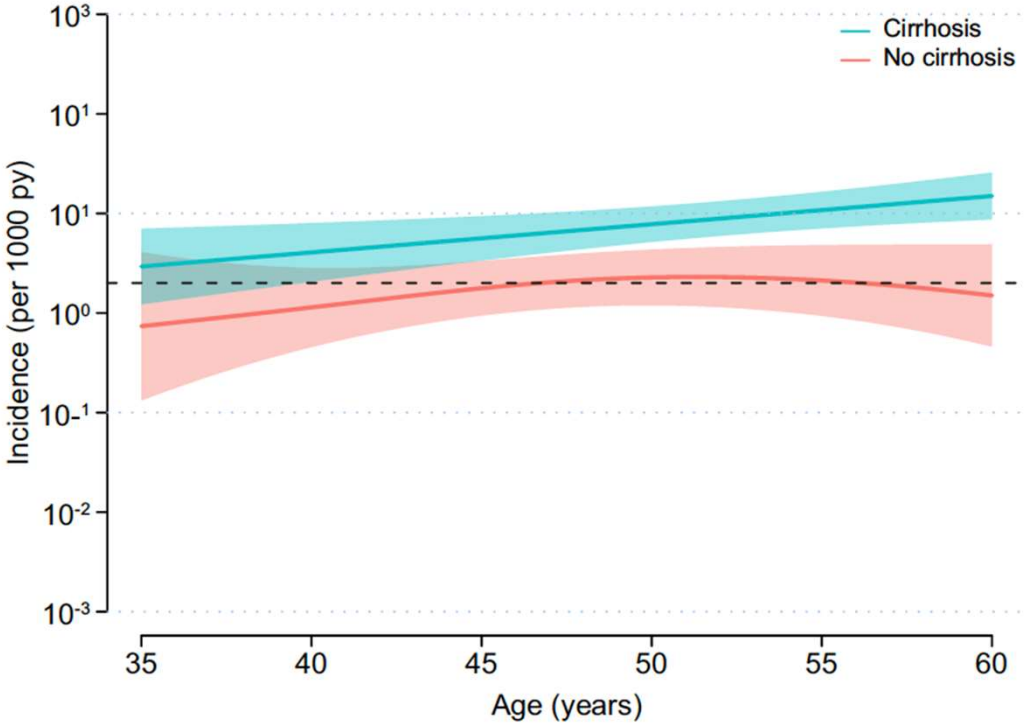


Fig. 1. HCC incidence rate ratio, stratified by cumulative time on HBV therapy regimens. Left panel: without TDF; right panel: with TDF. HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TDF, tenofovir disoproxil fumarate.

Over 3,393 py, HCC incidence was 5.90 per 1,000 py among cirrhotic case on TDF and 1.17 per 1,000 py in non-cirrhotic cases on TDF.

Wandeler G, Mauron E, Atkinson A, et al. Incidence of hepatocellular carcinoma in HIV/HBV-coinfected patients on tenofovir therapy: Relevance for screening strategies. J Hepatol. 2019;71(2):274-280. doi:10.1016/j.jhep.2019.03.032

The study found that screening (using a cutoff of 2 cases per 1,000py) may not be necessary if non-cirrhotic patients start treatment before age 45



Adjusted incidence of hepatocellular carcinoma among HIV/HBV coinfected individuals at initiation of TDF-containing ART (n = 2,537). Dotted line represents the recommended screening threshold; shaded area represents the 95% CI.

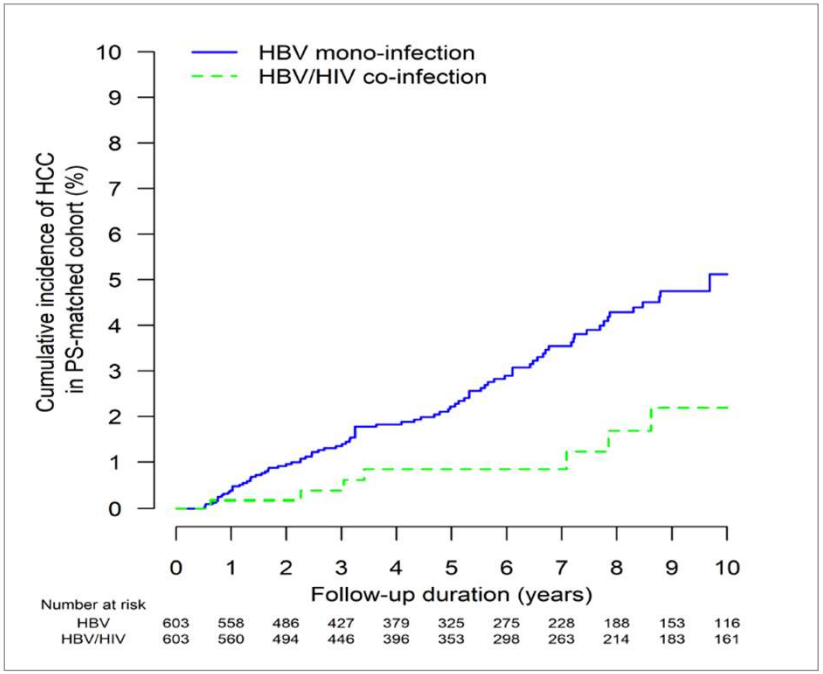
Once the patients are cirrhotic, they need to be screened for HCC even if on treatment.

After the initiation of TDF, the incidence of HCC remained stable over time, suggesting that an assessment of HCC risk at TDF start would be adequate to inform long term individual HCC screening strategies.

Wandeler G, Mauron E, Atkinson A, et al. Incidence of hepatocellular carcinoma in HIV/HBV-coinfected patients on tenofovir therapy: Relevance for screening strategies. J Hepatol. 2019;71(2):274-280. doi:10.1016/j.jhep.2019.03.032

A matched cohort study in Hong Kong (n= 692 HBV/HIV+, n= 2,380 HBV+) found HIV/HBV co-infected patients had lower risk of HCC compared with antiviral therapy treated HBV mono-infected patients.

- Inclusion criteria:
  - All patients with HBV/HIV co infection
  - All HBV mono infected patients treated with antiviral therapy
  - All patients identified from an electronic database involving all public hospitals in Hong Kong from 2000 to 2017
- Exclusion criteria:
  - Hepatitis C virus (HCV) infection
  - HCC diagnosed within six months
  - follow up less than 6 months
- Primary outcome was HCC
- A propensity score (PS) for each patient was defined as the conditional probability of having HIV infection given the baseline characteristics (including age, sex, cirrhosis, bilirubin, alanine transaminase/ALT, platelet, albumin, and prothrombin time).
- HBV/HIV coinfected and HBV mono-infected patients were matched in a 1:5 ratio by PS matching.
- 85% were male, mean (± SD) age was 42±12 years, and 4.5% had cirrhosis at baseline.
- Weighted Fine Gray model showed that HIV infection was associated with a lower risk of HCC (sub-distribution hazard ratio 0.39, 95% confidence interval 0.16 0.94, p=0.036)



Conclusion: This observation can be explained by a lower threshold, in terms of severity of liver disease, to start antiviral treatment in HBV/HIV coinfected compared to HBV mono-infected patients.

Lui G, Yip T, Yuen B, et al. 358. HIV Infection and the Risk of Hepatocellular Carcinoma in Patients with Hepatitis B Virus (HBV) Co-infection: a Propensity Score-matched Cohort Study, Open Forum Infectious Diseases, Volume 6, Issue Supplement_2, October 2019, Page S188, https://doi.org/10.1093/ofid/ofz360.431

An economic analysis from France showed that a test and treat all HBV patients was the most cost-effective strategy in France

Table 3. Treatment eligibility according to the four strategies and cost-effectiveness baseline analysis

Strategy	Treatment eligibility																Cost-effectiveness baseline analysis			
	HBeAg+ chronic Infection				HBeAg+ chronic hepatitis				HBeAg- chronic infection				HBeAg- chronic hepatitis				Life years	QALY	Lifetime costs	ICER €/QALY
	F0/F1	F2	F3	F4	F0/F1	F2	F3	F4	F0/F1	F2	F3	F4	F0/F1	F2	F3	F4				
S1	*	*	*	✓	†	✓	✓	✓				✓	†	✓	✓	✓	26.26	21.30	43,581	
S2	*	*	*	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓	26.26	21.30	43,816	Dominated‡
S3	*	✓	✓	✓	†	✓	✓	✓		✓	✓	✓	†	✓	✓	✓	26.47	21.47	46,543	17,051
S4	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	26.53	21.51	49,249	26,569

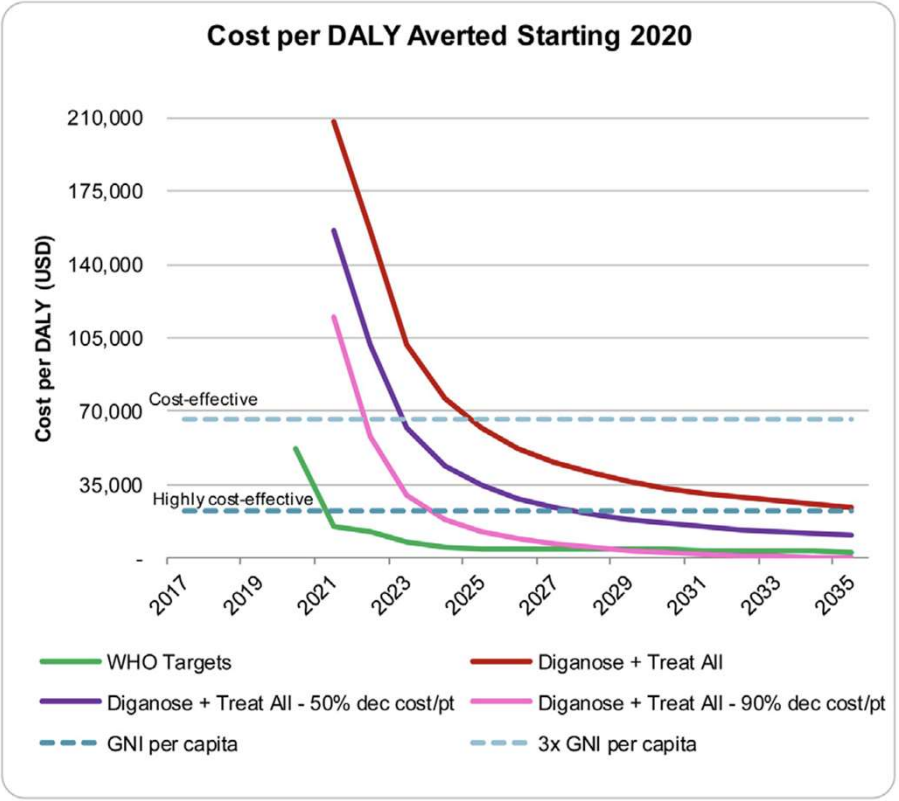
✓ All patients treated * Patients treated if ≥ 30 y-o † Patients treated if ALT ≥ 2 times upper level of the normal

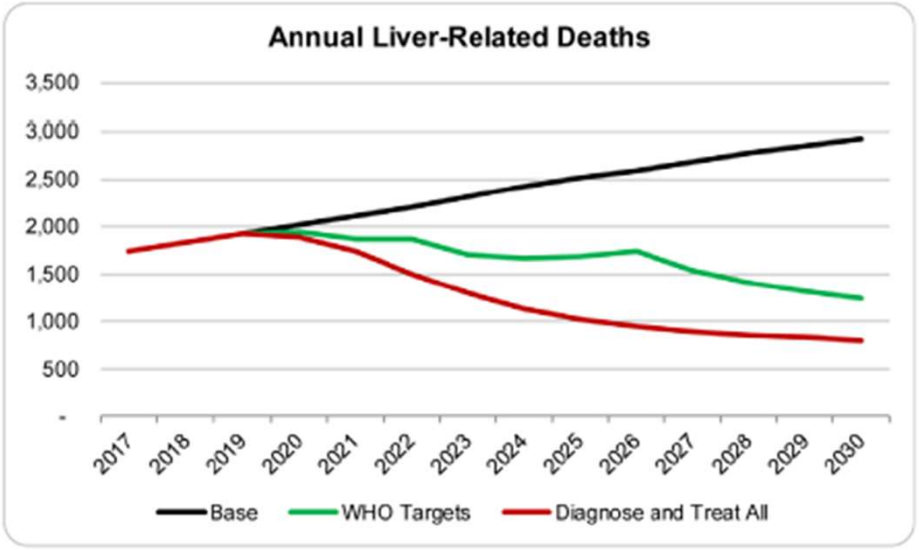
‡ Weakly dominated strategy: higher ICER than that of a more effective alternative strategy

- Treating all patients (S4) was the most expensive but also the most effective strategy (with a lifetime mean gain of 0.04, 0.21, 0.21 QALYs compared with S3, St and S1 respectively) and was cost effective compared to S3 (ICER = 26,569Euros /QALY)

Lepers C, Fontaine H, Carrat F, Mathurin P, Pol S, Zoulim F, Yazsanpanah Y, Deuffic-Burban S, Toward a simplification of chronic hepatitis B treatment recommendations – cost effectiveness of scaling up treatment with nucleoside analogue, EASL 2020 Poster

Our study in Saudi Arabia also showed that testing & treating all HBV patients becomes highly cost effective after 2036





Similar economic analyses were conducted for Brazil, Philippines, Uganda, Uzbekistan with the same conclusions.

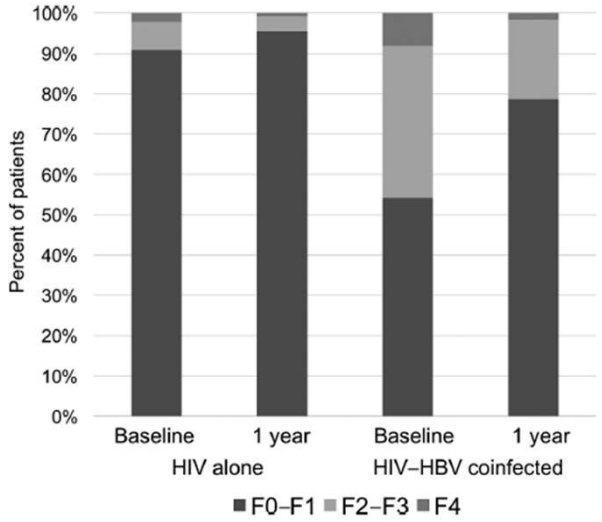
The study also highlighted that 90% diagnosis and 80% treatment of eligible patients (WHO targets) does not achieve the WHO mortality targets (65% reduction in mortality) → we need to switch to test & treat

Sanai FM, Alghamdi M, Dugan E, et al. A tool to measure the economic impact of Hepatitis B elimination: A case study in Saudi Arabia [published online ahead of print, 2020 Sep 25]. J Infect Public Health. 2020;S1876-0341(20)30640-7. doi:10.1016/j.jiph.2020.09.004

Appendix

We know that antiviral treatment will result in fibrosis regression among HBV patients

- A Zambia cohort of 463 HIV patients (61 HIV/HBV) on TDF containing ART – observed a reduction in liver stiffness measurement after one year.



- A Nigeria cohort of 106 HIV+ and 71 HIV/HBV saw a reduction in liver stiffness measurement after 3 years

Characteristic	All, *n*=177	HIV, *n*=106	HIV/HBV, *n*=71	*P*
Baseline LSM (kPa), median (IQR)	5.5 (4.4–6.8)	5.1 (4.2–5.8)	6.4 (4.7–9.0)	<0.001
LSM at follow-up (kPa), median (IQR)	4.9 (4.2–6.1)	4.9 (4.2–5.8)	5.2 (4.1–6.6)	0.163
Change (kPa), median (IQR)	−0.4 (−1.5–0.6)	−0.2 (−1.2–0.8)	−1.1 (−2.7–0.3)	<0.001
Baseline LSM ≥9.4 kPa, *n* (%)	19 (10.7)	2 (1.9)	17 (23.9)	<0.001
LSM ≥9.4 kPa at follow-up, *n* (%)	9 (5.1)	1 (0.9)	8 (11.3)	0.002
Decrease in LSM ≥1 stage[b], *n* (%)	47 (26.6)	18 (17)	29 (40.8)	<0.001
ALT ≥2× ULN at follow-up[c], *n* (%)	3 (2)	1 (1.1)	2 (3.6)	0.285

[a]Includes 17 patients who did not initiate ART.
[b]Decrease of at least one stage (i.e. F3 to F2) in patients with at least F2 at baseline.
[c]ULN=31 IU/mL.

Vinikoor MJ, Sinkala E, Chilengi , et al. Impact of Antiretroviral Therapy on Liver Fibrosis Among Human Immunodeficiency Virus-Infected Adults With and Without HBV Coinfection in Zambia. Clin Infect Dis. 2017 May 15;64(10):1343-1349. doi: 10.1093/cid/cix122. Erratum in: Clin Infect Dis. 2017 Oct 15;65(8):1431-1433. PMID: 28158504; PMCID: PMC5411400.

Grant JL, Agaba P, Ugoagwu P, et al. Changes in liver stiffness after ART initiation in HIV-infected Nigerian adults with and without chronic HBV. *J Antimicrob Chemother*. 2019;74(7):2003-2008. doi:10.1093/jac/dkz145

A retrospective cohort study in Brazil compared HCV or HBV (n=405) and HIV/HBV+ or HIV/HCV+ (n=399) between 2007-2014

- Coinfected patients were younger (36.7 ± 10 vs 46.3 ± 12.5, p < 0.001)
- Liver cirrhosis was observed in 31.3% of HIV-negative patients and in 16.5% of coinfected (p < 0.001)
- The incidence density of HCC in coinfected and mono-infected patients was 0.25 and 0.72 cases per 100 patient-years (95%CI: 0.12-0.46 vs 0.47-1.05) (long-rank p = 0.002)
- **When adjusting for age or when only cirrhotic are analyzed, the absence of HIV lost statistical significance for the development of HCC**

HIV	*n*	HCC	%	Patient-years	Rate × 100 patient-years	RR	95%CI	*P* value
+	399	10	2.5	3963.80	0.25	-	-	-
-	405	26	6.4	3624.50	0.72	2.98	1.43-6.18	0.003
Model 2: adjusted for age						1.29	0.58-2.87	0.529
Model 3: adjusted for age and DM						1.27	0.56-2.88	0.571
Model 4: adjusted for age, DM and alcohol						1.23	0.52-2.95	0.638

Marcon PDS, Tovo CV, Kliemann DA, Fisch P, de Mattos AA. Incidence of hepatocellular carcinoma in patients with chronic liver disease due to hepatitis B or C and coinfected with the human immunodeficiency virus: A retrospective cohort study. World J Gastroenterol. 2018;24(5):613-622. doi:10.3748/wjg.v24.i5.613