Hepatitis B in HIV: Augmenting Therapy and HCC Screening

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Disclosures

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Disclaimer

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AETC AIDS Education & Training Center Program Mountain West

Data Considerations

Data in this presentation offer a limited perspective of how systemic, social, and economic factors impact health. We recognize that racism, not race, creates and perpetuates health disparities.

To Learn More:
https://www.cdc.gov/minorityhealth/racism-disparities

FAQ #1: Persistent HBV viremia

54-year-old man presents after reestablishing HIV care after some loss to follow-up. Diagnosed with HIV and chronic hepatitis B (eAg+) in 2010. Was previously on emtricitabine-tenofovir DF-efavirenz but had a history of treatment interruption. History of type 2 diabetes, cryptococcal meningitis in 2012 (nadir CD4 80) with subsequent renal injury on amphotericin B – now has chronic kidney disease with baseline creatinine of 1.8. Resumed emtricitabine-tenofovir AF-bictegravir in March 2022.

Date	HIV RNA level (copies/mL)	HBV DNA level (IU/mL)
March 2022	560,000	33,450,000
June 2022	<40	546,000
Oct 2022	Not detected	340,000
Mar 2023	Not detected	125,000
July 2023	Not detected	57,000

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FAQ #1: Persistent HBV viremia

Which of the following would you do next?

A. Send HBV DNA genotypic resistance testing.

B. Review adherence.

C. Add entecavir 1 mg PO once daily.

D. Add entecavir 0.5 mg PO once daily.

Table 1.

Key Characteristics of Oral Antiviral Agents Used to Treat HBV*

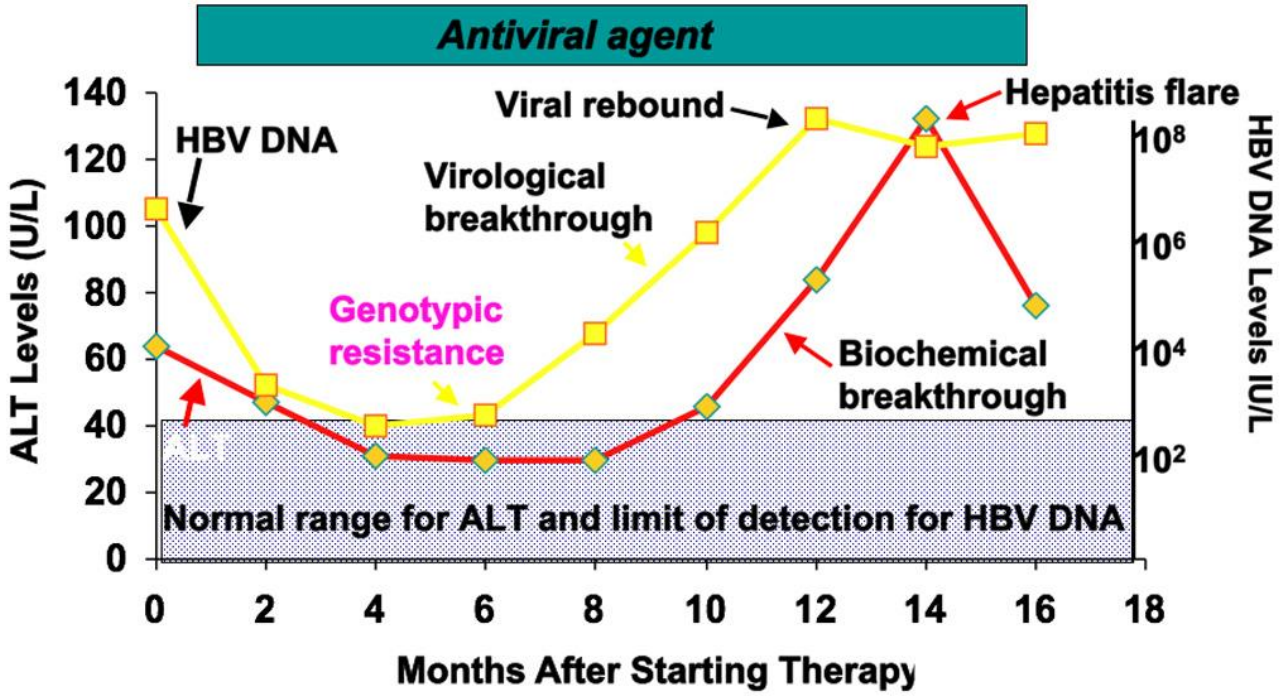
Medications	Trade Name	Category	Oral Dosing (Adults)	Potency	Barrier to Resistance
Adefovir	*Hepsera*	Nucleotide analogue	10 mg once daily	Low	Moderate
Entecavir	*Baraclude*	Nucleoside analogue	0.5 mg once daily^	High	High
Lamivudine	*Epivir-HB*	Nucleoside analogue	100 mg once daily	Moderate	Low
Tenofovir alafenamide	*Vemlidy*	Nucleotide analogue	25 mg once daily	High	High
Tenofovir DF	*Viread*	Nucleotide analogue	300 mg once daily	High	High

*Telbivudine is not included as it is no longer manufactured in the United States

^Increase entecavir to 1.0 mg once daily in persons with: a history of 1) hepatitis B viremia while receiving lamivudine, 2) known lamivudine or telbivudine resistance substitutions rtM204I/V (with or without rtL180M, rtL80I/V, or rtV173L, or 3)decompensated cirrhosis.

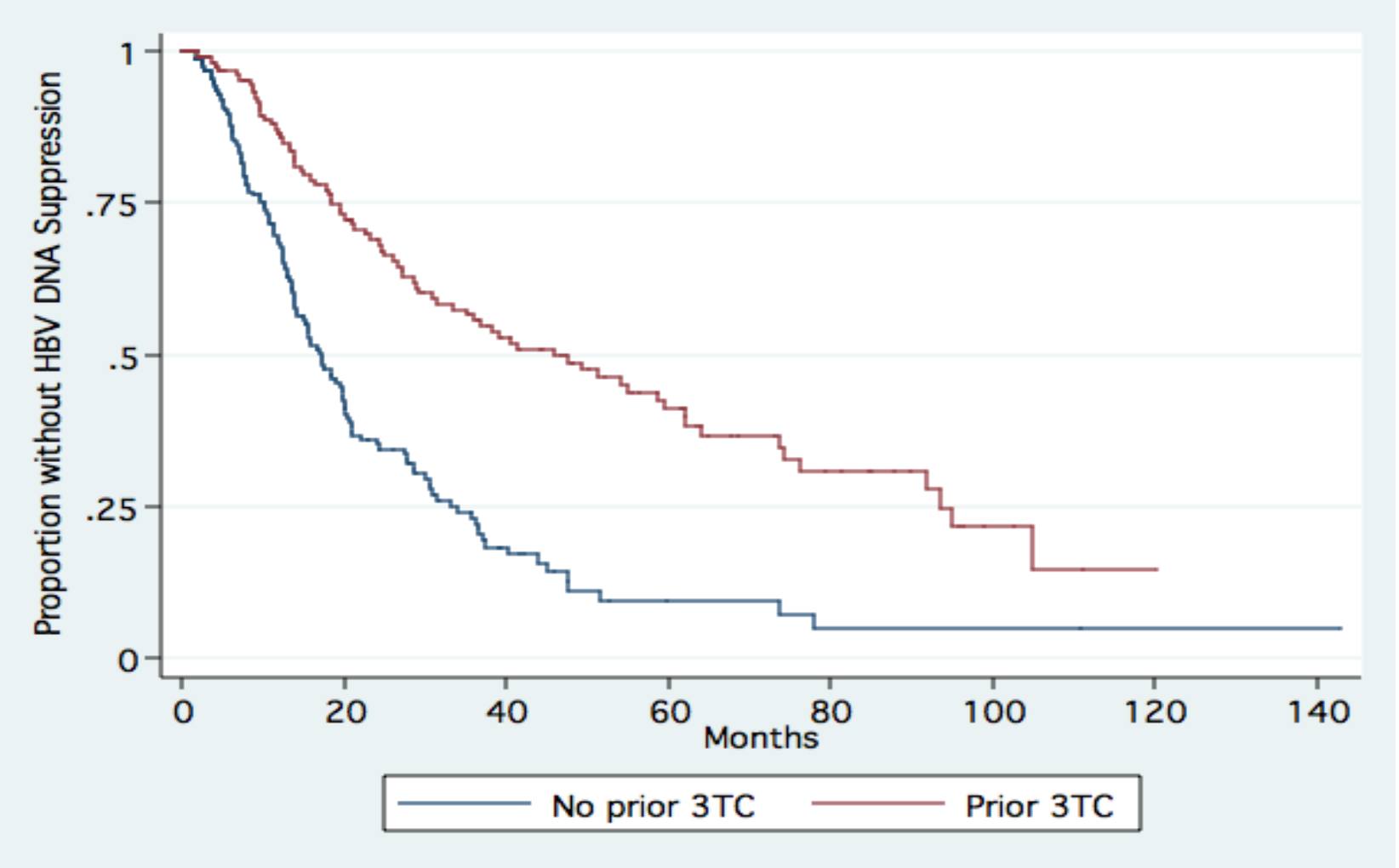
HBV Genotypic Resistance Testing

- Same methodology as HIV resistance testing (consensus based sequencing)
- May not be successful when HBV DNA level < 500 IU/mL
- Data: resistance mutations, genotype, precore/core promoter mutations
- Indications:
  - Suboptimal response in a patient on antiviral medication
  - Virologic +/- biochemical breakthrough
  - Not at baseline (even if treatment experienced)



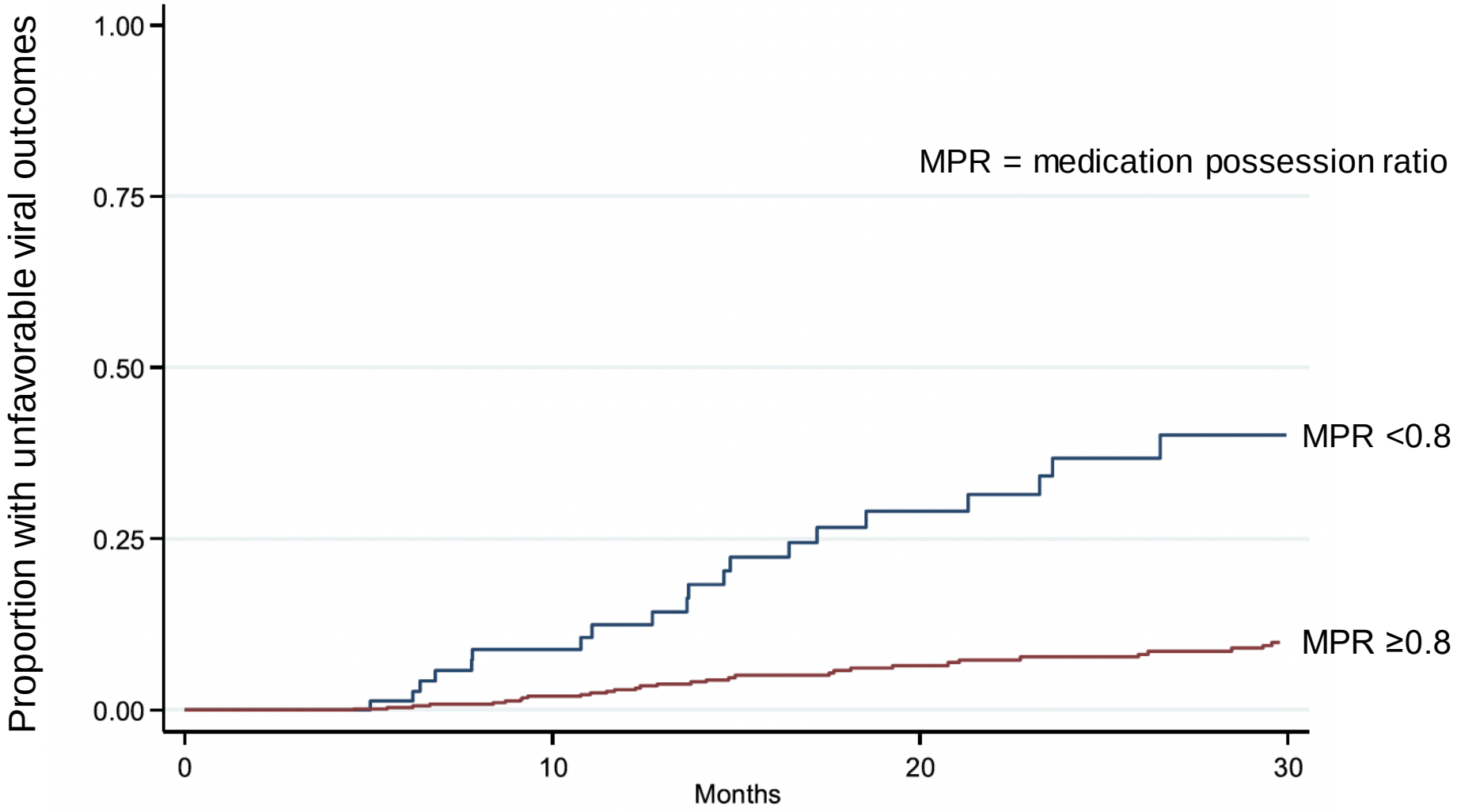
Ghany et al, *Hepatology* 2009;49(5 supplement):S174-S184.

HBV DNA suppression in CNICS cohort



Kim et al, *JAIDS* 2015; 66(1):96-101.

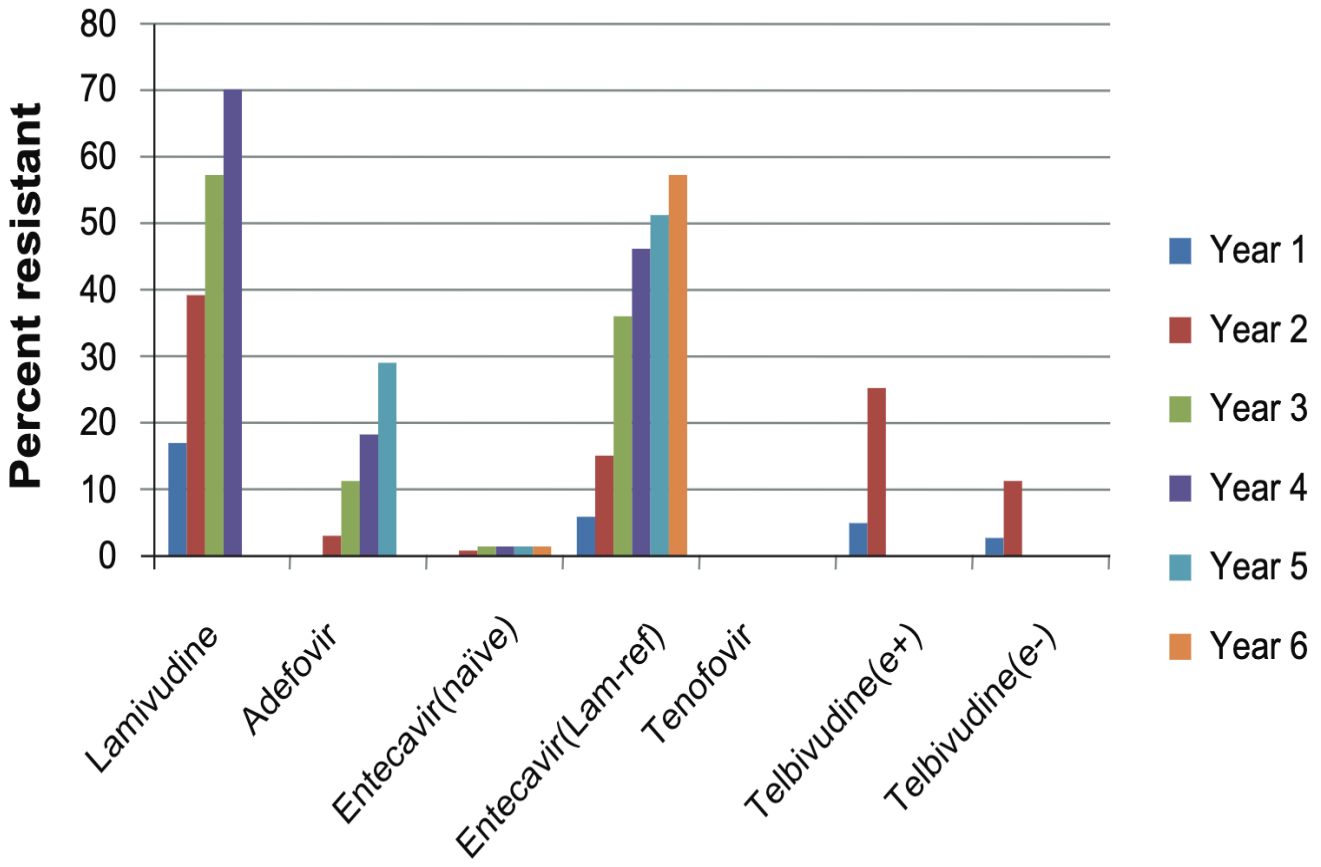
HBV DNA suppression sensitive to lapses in adherence



Allard et al, *BMC Gastro* 2020;20:140.

Entecavir as Rescue in People with HIV and HBV

- Beware of the prevalence of HBV lamivudine resistance in HIV/HBV patients.
- Beware of its long half life.
- Beware it also needs renal dose adjustment.
- Beware that the threshold for HBV resistance is lower with entecavir than tenofovir (DF or AF.)
- Beware that it is <u>not</u> more potent than tenofovir and relies on HBV immune response as much as TAF/TDF does.



Osborn, *Infect Drug Resist* 2011;4:55-64.

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FAQ #2: To screen or not for hepatocellular carcinoma?

54-year-old man with HIV, chronic hepatitis B, type 2 diabetes and chronic kidney disease with baseline creatinine of 1.8 on emtricitabine-tenofovir AF-bictegravir after some treatment interruption.

Should this patient undergo HCC screening?

A. Yes, of course.

B. No, as there is no evidence to support this in PWH.

C. It depends.

Background

- Hepatocellular carcinoma (HCC) → leading cause of cancer death
- Chronic HBV infection: predominant cause of HCC worldwide
- Determinants of HBV-associated HCC poorly characterized in HIV
  - Data mainly from Asian chronic HBV cohorts without HIV
- Identification of risk factors → HCC development
  - To guide early HCC identification
  - To help aid preventive measures

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Risk of HCC With Hepatitis B Viremia Among HIV/HBV-Coinfected Persons in North America

H. Nina Kim ,[1] Craig W. Newcomb,[2] Dena M. Carbonari,[2] Jason A. Roy,[3] Jessie Torgersen,[2] Keri N. Althoff,[4] Mari M. Kitahata,[1] K. Rajender Reddy,[2] Joseph K. Lim,[5] Michael J. Silverberg,[6] Angel M. Mayor,[7] Michael A. Horberg,[8] Edward R. Cachay,[9] Gregory D. Kirk,[4] Jing Sun ,[4] Mark Hull,[10] M. John Gill,[11] Timothy R. Sterling,[12] Jay R. Kostman,[13] Marion G. Peters,[14] Richard D. Moore,[4] Marina B. Klein,[15] and Vincent Lo Re, III [2], for the North American AIDS Cohort Collaboration on Research, Design of IeDEA[#]

BACKGROUND AND AIMS: Chronic HBV is the predominant cause of HCC worldwide. Although HBV coinfection is common in HIV, the determinants of HCC in HIV/HBV coinfection are poorly characterized. We examined the predictors of HCC in a multicohort study of individuals coinfected with HIV/HBV.

APPROACH AND RESULTS: We included persons coinfected with HIV/HBV within 22 cohorts of the North American AIDS Cohort Collaboration on Research and Design (1995-2016). First occurrence of HCC was verified by medical record review and/or cancer registry. We used multivariable Cox regression to determine adjusted HRs (aHRs [95% CIs]) of factors assessed at cohort entry (age, sex, race, body mass index), ever during observation (heavy alcohol use, HCV), or time-updated (HIV RNA, CD4+ percentage, diabetes mellitus, HBV DNA). Among 8,354 individuals coinfected with HIV/HBV (median age, 43 years; 93% male; 52.4% non-White), 115 HCC cases were diagnosed over 65,392 person-years (incidence rate, 1.8 [95% CI, 1.5-2.1] events/1,000 person-years). Risk factors for HCC included age 40-49 years (aHR, 1.97 [1.22-3.17]), age ≥50 years (aHR, 2.55 [1.49-4.35]), HCV coinfection (aHR, 1.61 [1.07-2.40]), and heavy alcohol use (aHR, 1.52 [1.04-2.23]), while time-updated HIV RNA >500 copies/mL (aHR, 0.90 [0.56-1.43]) and time-updated CD4+ percentage <14% (aHR, 1.03 [0.56-1.90]) were not. The risk of HCC was increased with time-updated HBV DNA >200 IU/mL (aHR, 2.22 [1.42-3.47]) and was higher with each 1.0 $\log_{10}$ IU/mL increase in time-updated HBV DNA (aHR, 1.18 [1.05-1.34]). HBV suppression with HBV-active antiretroviral therapy (ART) for ≥1 year significantly reduced HCC risk (aHR, 0.42 [0.24-0.73]).

CONCLUSION: Individuals coinfected with HIV/HBV on ART with detectable HBV viremia remain at risk for HCC. To gain maximal benefit from ART for HCC prevention, sustained HBV suppression is necessary. (Hepatology 2021;0:1-13).

Liver cancer is the sixth most common cancer and third leading cause of cancer-related mortality worldwide.(1) Chronic HBV infection, both through inflammation and virally mediated pro-oncogenic mechanisms, is the most common cause of HCC.(2) Coinfection with chronic HBV is common among people

Kim et al, *Hepatology* 2021 Sep;74(3):1190-1202.

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Study Design / Data Source

- **Design**: Cohort study
- **Data Source**:
  - North American AIDS Cohort Collaboration on Research & Design (NA-ACCORD), 22 cohorts
  - Data collection:
    - Demographics, vital status
    - Select diagnoses, medications, alcohol use
    - Laboratory results

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Study Patients

- **Inclusion**:
  - Age ≥18 years, Jan 1995 to Dec 2016
  - Chronic HBV (HBsAg, HBeAg, HBV DNA)
  - HIV RNA, CD4+ cell measurement during this period
- **Exclusions**:
  - HCC prior to start of follow-up
  - ALT/AST >1000 U/L within +/- 30 days of first HBV lab test (acute HBV)

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Main Study Outcome

- Hepatocellular carcinoma – adjudicated event
  - Cancer registry linkage
  - Medical record review using standardized abstraction protocol*
    - Histopathologic diagnosis
    - Supportive radiographic imaging
    - Clinician-confirmed diagnosis

*Silverberg MJ. Ann Intern Med 2015;163:507-18.

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Baseline Demographic, HIV Characteristics

Characteristic	n=8,354
Median age (IQR)	43 (36-49)
Male sex	93.1%
Black	41.0%
Obesity	12.1%
Diabetes mellitus	6.3%
Heavy alcohol use	35.3%
Chronic HCV infection	21.6%
HIV RNA >500 copies/mL	45.3%
CD4+ cell percentage <14%	28.3%

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Baseline HBV-Related Characteristics

Characteristic	n=8,354
HBV DNA tested	64.2%
Median (IQR), log_{10} IU/mL	2.0 (1.3-5.0)
≤200 IU/mL	55.3%
201-2,000 IU/mL	7.0%
>2,000 IU/mL	37.7%
Assessed for qualitative HBV DNA only	27.6%
HBeAg tested (n, %)	46.9%
Positive	26.0%
HBV-active ART*	76.2%
Platelet count <150,000/µL	19.0%

*Lamivudine, emtricitabine or tenofovir disoproxil fumarate

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HIV, Traditional Factors Associated with HCC

(n=8,354; 115 HCC events → 1.8 per 1,000 pyrs)

Characteristic	Adjusted* HR (95% CI)
Age (reference: <40 years) 40-49 years ≥50 years	 **1.97 (1.22-3.17)** **2.55 (1.49-4.35)**
Male sex	1.92 (0.60-6.14)
White race (reference: non-white)	1.38 (0.94-2.03)
Obese (BMI ≥30 kg/m^2)	1.00 (0.55-1.83)
Diabetes mellitus†	1.79 (0.95-3.38)
Heavy alcohol use	**1.52 (1.04-2.23)**
Chronic HCV coinfection	**1.61 (1.07-2.40)**
HIV RNA >500 copies/mL†	0.90 (0.56-1.43)
CD4+ percentage† (reference: >28%) 14-28% <14%	 1.47 (0.97-2.21) 1.03 (0.89-1.01)

***Adjusted also for year at start of follow-up**

† Time-updated

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Risk of HCC by Quantitative HBV DNA (n=3,054; 30 HCC events)

HBV DNA level (Time-Updated)	Adjusted HR† (95% CI)
HBV DNA, 200 IU/mL cut-off	
≤200	Reference
>200	2.70 (1.23-5.93)
HBV DNA, 2,000 IU/mL cut-off	
≤200	Reference
201-2,000	2.20 (0.50-9.59)
>2,000	2.85 (1.24-6.57)
HBV DNA, 200,000 IU/mL cut-off	
≤200	Reference
201-200,000	1.77 (0.63-4.94)
>200,000	4.34 (1.72-10.94)

† Adjusted for age and year of start of follow-up

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Risk of HCC by Duration of HBV DNA Suppression (n=4,891; 78 HCC events)

Characteristic (Time-Updated)	Adjusted HR† (95% CI)
Duration of HBV Suppression‡	
Detectable	Reference
Undetectable <1 year	1.12 (0.55-2.28)
Undetectable ≥1 year	0.42 (0.24-0.73)
Duration of HBV Suppression§	
Detectable	Reference
Undetectable <1 year	1.14 (0.56-2.31)
Undetectable 1-4 years	0.55 (0.28-1.07)
Undetectable ≥4 years	0.34 (0.17-0.67)

† Adjusted for age, sex, race, diabetes, HIV RNA, CD4 %, heavy alcohol use, year of follow-up
‡ p-value test for trend = 0.002
§ p-value test for trend = 0.001

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Conclusions

- Any level of HBV viremia increased HCC risk.
- Antiviral therapy reduced but did not eliminate HCC risk.
- HBV DNA surveillance and optimization of HBV suppression are key.
- To gain maximal protective benefit from antiviral therapy for HCC prevention, sustained HBV suppression may be necessary for years.

Shared Decision-making re HCC Screening

- Few studies have examined HCC specifically in PWH with chronic HBV.
- We lack direct evidence for the effectiveness of HCC screening in HIV-HBV coinfection.
- Ultrasound surveillance = standard practice for HCC screening, but it is an imperfect screening modality, and it remains unclear if it helps in this setting.
- HIV-associated immunosuppression has an adverse impact on carcinogenesis and tumorigenesis so we need to examine HCC prevention more rigorously in this population.

Merchante et al, *Current HIV/AIDS Report* 2020;17:6-17.

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FAQ #2: To screen or not for hepatocellular carcinoma?

54-year-old man with HIV, chronic hepatitis B, type 2 diabetes and chronic kidney disease with baseline creatinine of 1.8 on emtricitabine-tenofovir AF-bictegravir after some treatment interruption.

Should this patient undergo HCC screening? And if so, how?

- I would send him for Fibroscan. Cirrhosis is one of the strongest predictors of HCC.
- Given age >50 and diabetes and antiviral history, would consider HCC screening even if not cirrhotic.
- If he had chronic HCV, would prioritize HCV treatment.
- If he were drinking, would talk about reducing/cessation (naltrexone.)
- Abd ultrasound every 6 months (with or without serum aFP.)

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