HIV and the Liver

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Outline

1. Viral Hepatitis Coinfections
2. Metabolic Liver Disease and HIV
3. Hepatocellular carcinoma (HCC) and HIV
4. ART and PrEP in People with Hepatitis B

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Symptoms: losing weight, difficulty swallowing

Exam: thrush, cervical lymphadenopathy, splenomegaly

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ALT 122, AST 98, Bilirubin 1.4mg/dL (24µmol/L),
WBC 3300, Hematocrit 38%, Platelets 144

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What are the next steps in testing and treatment?

What is the most important next step in management?

A. Test for viral hepatitis B and C
B. Screen for alcohol use disorder
C. No further testing. Recheck ALT/AST in 6 months
D. Screen for steatosis (aka NAFLD or NASH) with imaging or biopsy
E. Screen for cirrhosis with imaging or biopsy
F. Multiple options above

Elevated Aminotransferases in People Living with HIV

1. Screen for coinfections: hepatitis B and C are most important
2. Screen and counsel on alcohol use
3. Screen for medication and drug use
4. Screen for steatosis (NASH, NAFLD) with imaging
5. Consider other causes of liver disease: autoimmune hepatitis, etc.

Non-invasive estimates of fibrosis:

$$\textbf{FIB-4} = \frac{\text{Age } x \text{ AST}}{\text{Platelets } x \sqrt{\text{ALT}}}$$

*Best when age 35- 65yo

$$\textbf{APRI} = \frac{\text{AST}/\text{ULN}_{\text{AST}}}{\text{Platelets}} x\ 100$$

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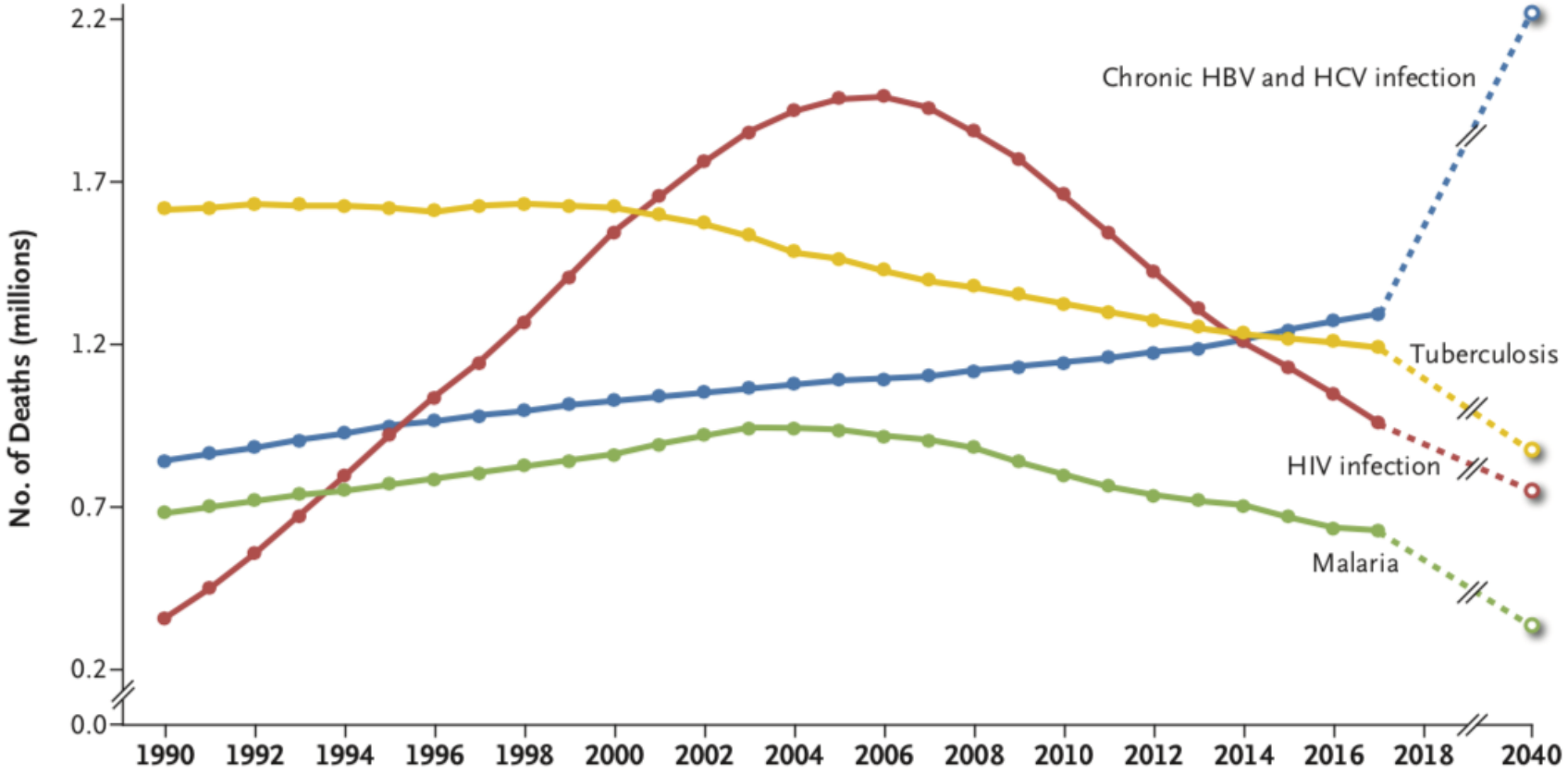
WBC 3300, Hematocrit 38%, **Platelets 144**

HAV IgG – positive
HCV Ab – negative
HBsAg positive, HBcAb positive, HBsAb negative
HBeAg positive, HBV DNA 4.2 x 10^6

Viral hepatitis is a leading cause of infectious disease death around the world



*Before COVID

Thomas DL, NEJM 2019; Foreman KJ, Lancet 2018

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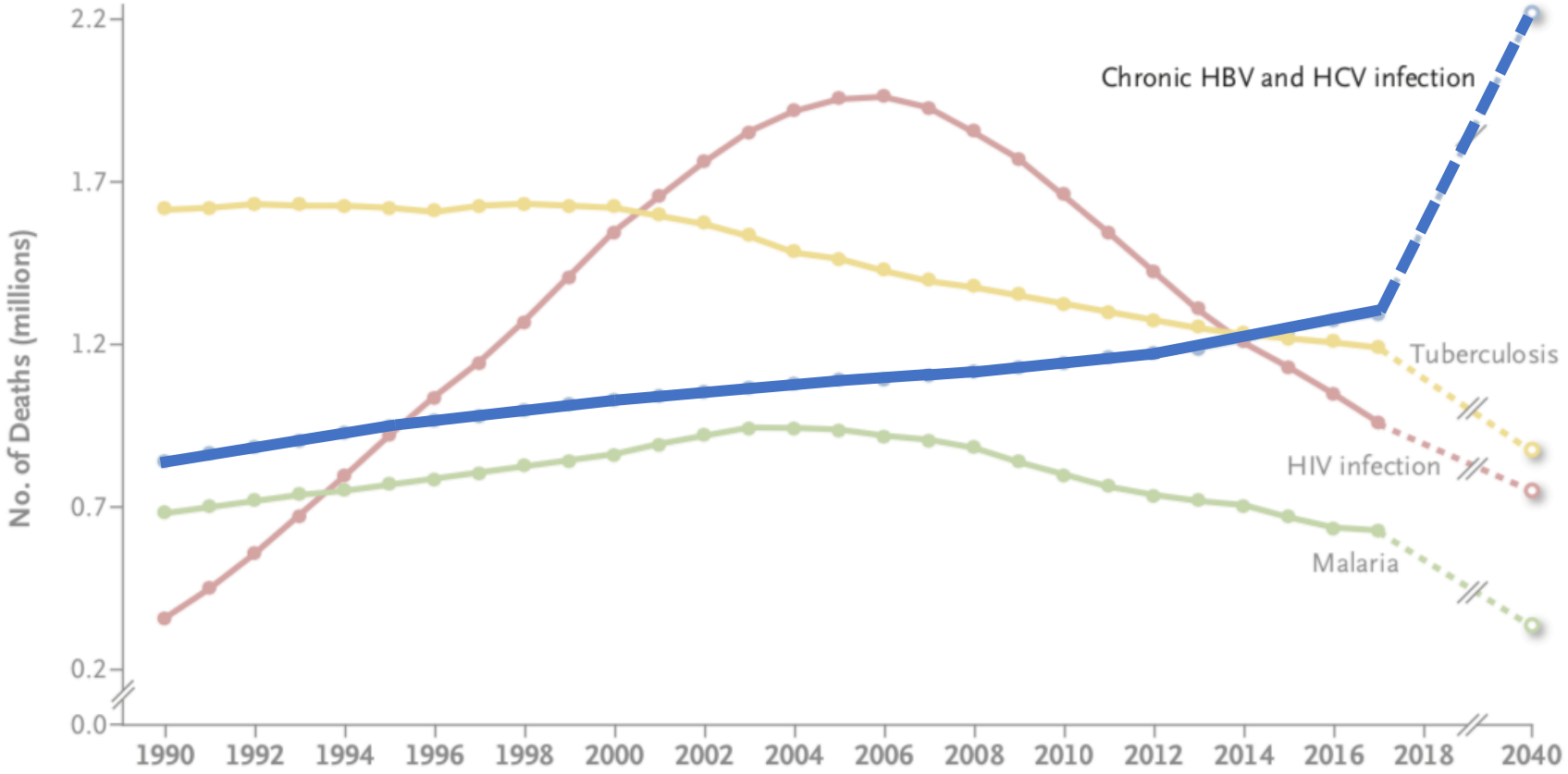
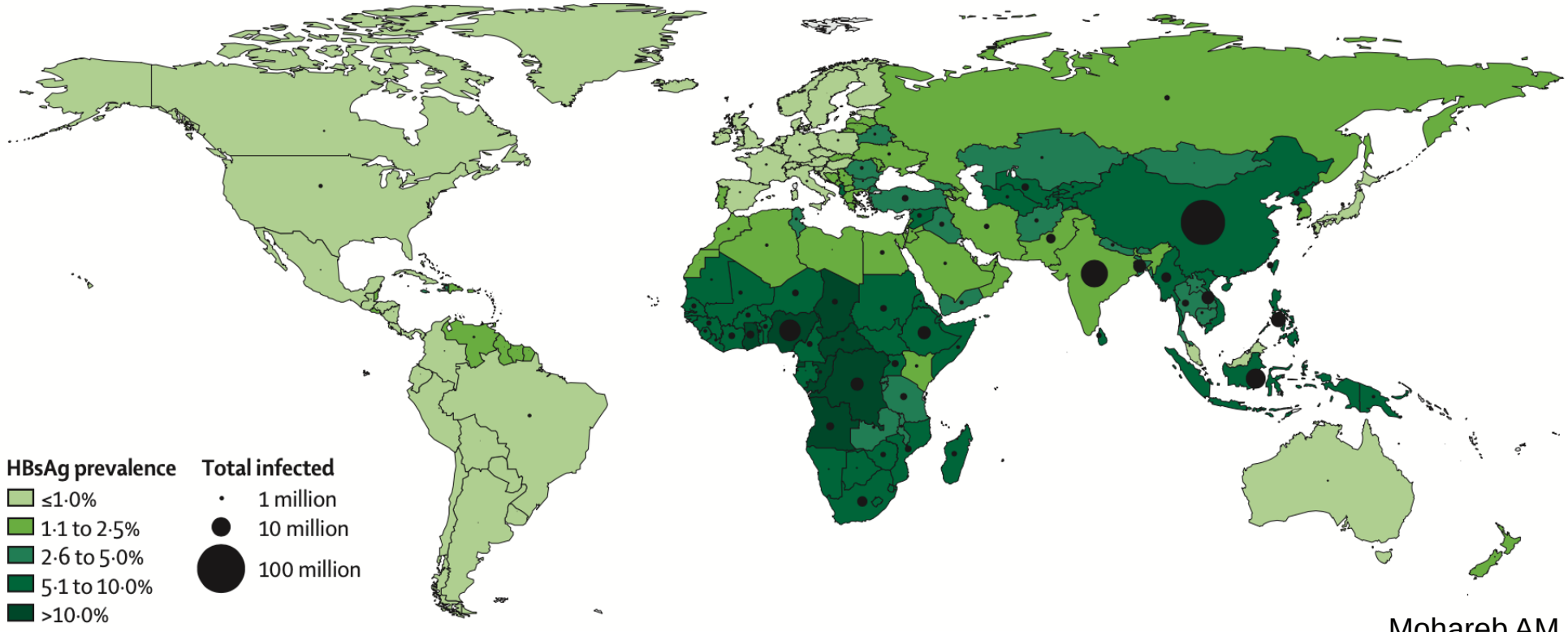


*Before COVID

Thomas DL, NEJM 2019; Foreman KJ, Lancet 2018

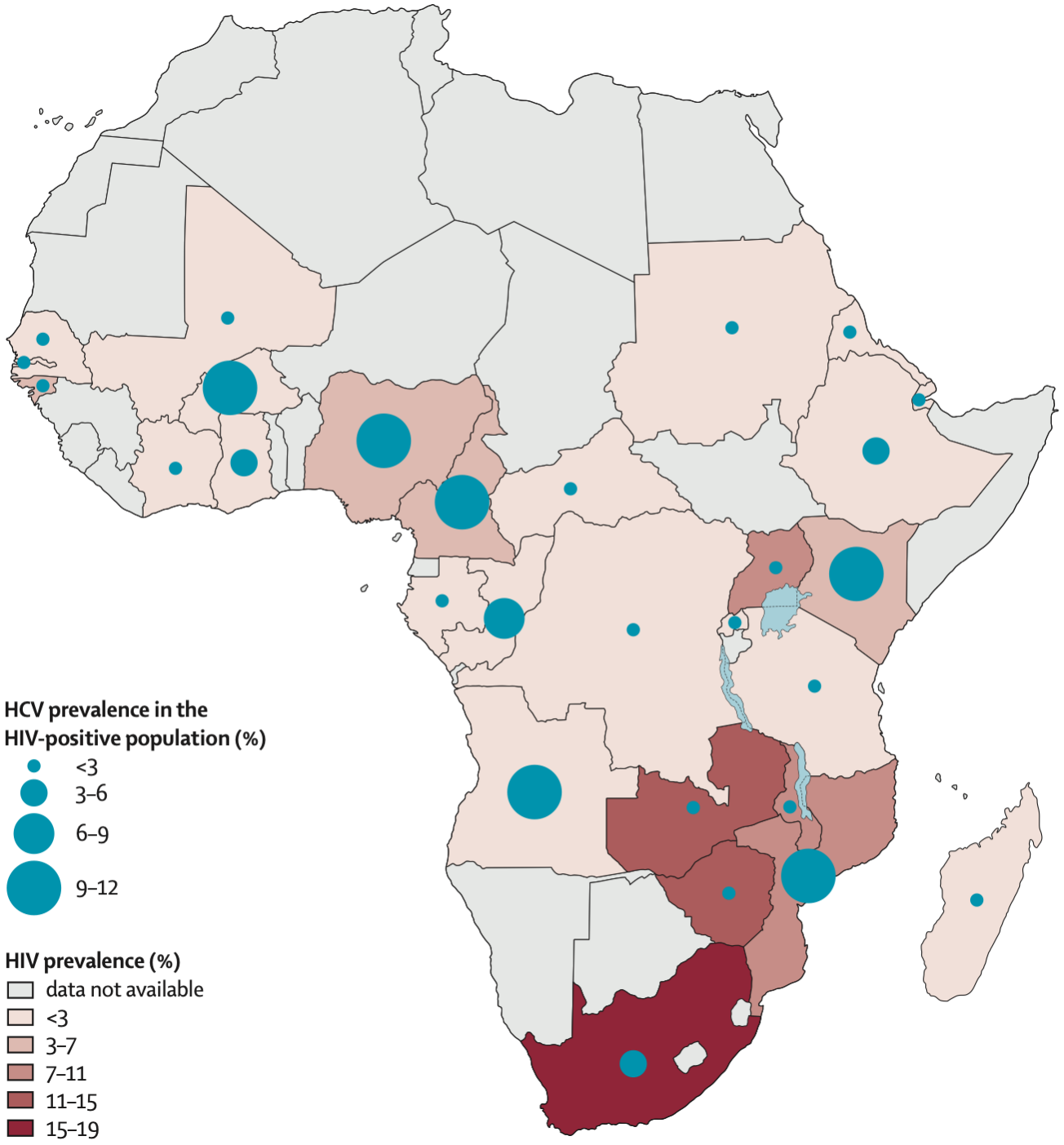
Global Epidemiology of HBV

- 300 million people with active infection
- 1.5 million new infections; 820,000 deaths each year
- 3- 4 million with HIV-HBV coinfection



Mohareb AM, Lancet HIV 2022

HCV prevalence among people living with HIV



- 150 million people with active infection around the world
- 3% pooled HCV prevalence among people living with HIV in Africa, with regional variation
- 300 000 annual deaths worldwide

Bhargavi Rao, Lancet Infect Dis 2015

HBV and HCV Coinfection with HIV

- Increased risk of cirrhosis and hepatocellular carcinoma (HCC)
- Increased risk of mortality
- Can complicate management of other coinfections (e.g., TB)
- Management
    - Screen for liver-related complications: cirrhosis and HCC
    - HCV – treat with direct acting antivirals
    - HBV – treat with dually active ART

Which drugs are active against both HIV and HBV?

A. Tenofovir disoproxil fumarate
B. Tenofovir alafenamide
C. Dolutegravir
D. Rilpivirine
E. Cabotegravir
F. Emtricitabine
G. Lamivudine

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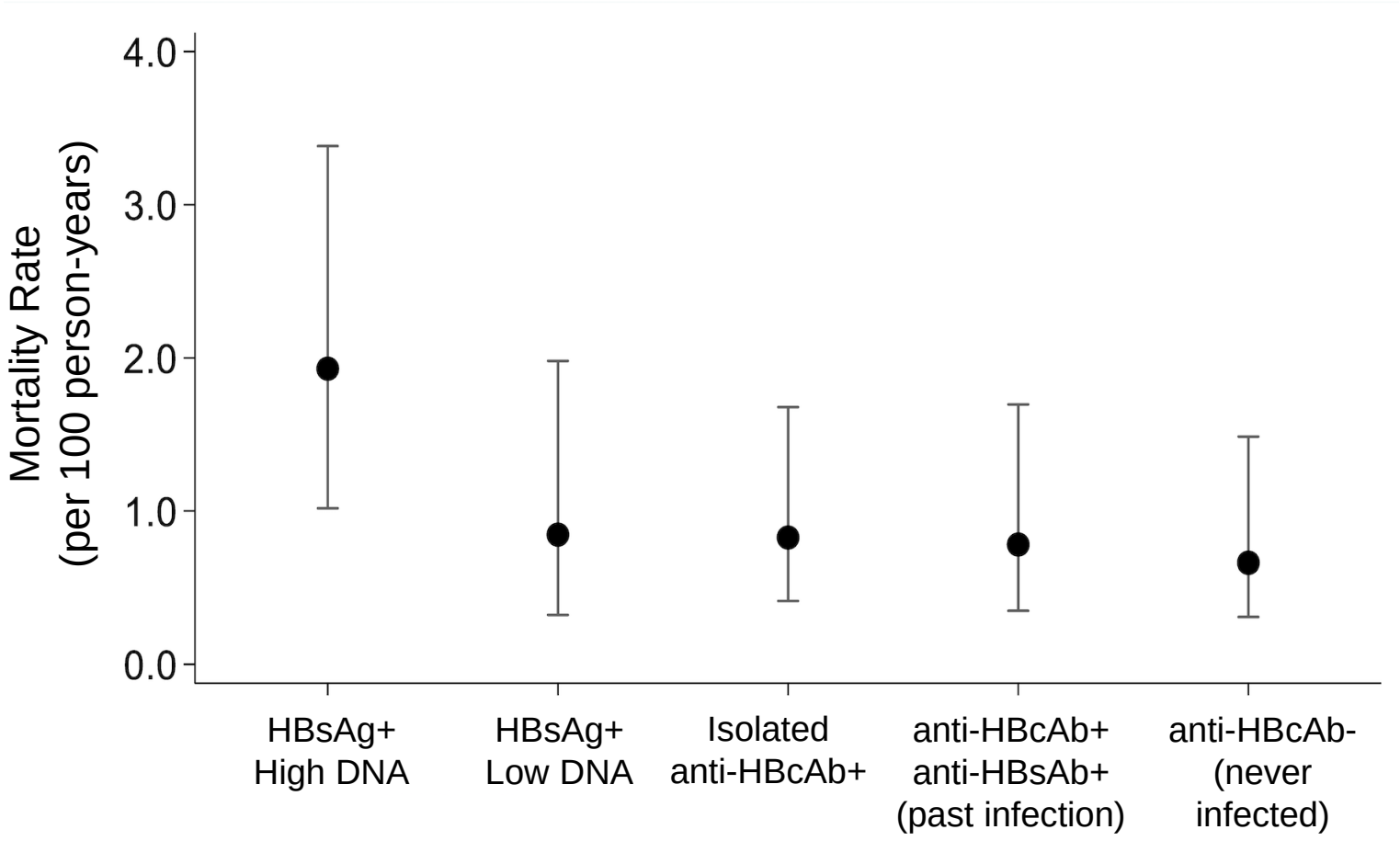
Mortality associated with HIV-HBV coinfection in Multicenter AIDS Cohort Study (MACS)

HIV-1	HBsAg	Person years	Deaths from liver disease (n)	Liver mortality per 1000 person years	p
–	–	31 366	0	0·0	Reference
–	+	1318	1	0·8	0·04
+	–	20 605	35	1·7	<0·0001
+	+	1834	26	14·2	<0·0001
Overall		55 123	62	1·1	..

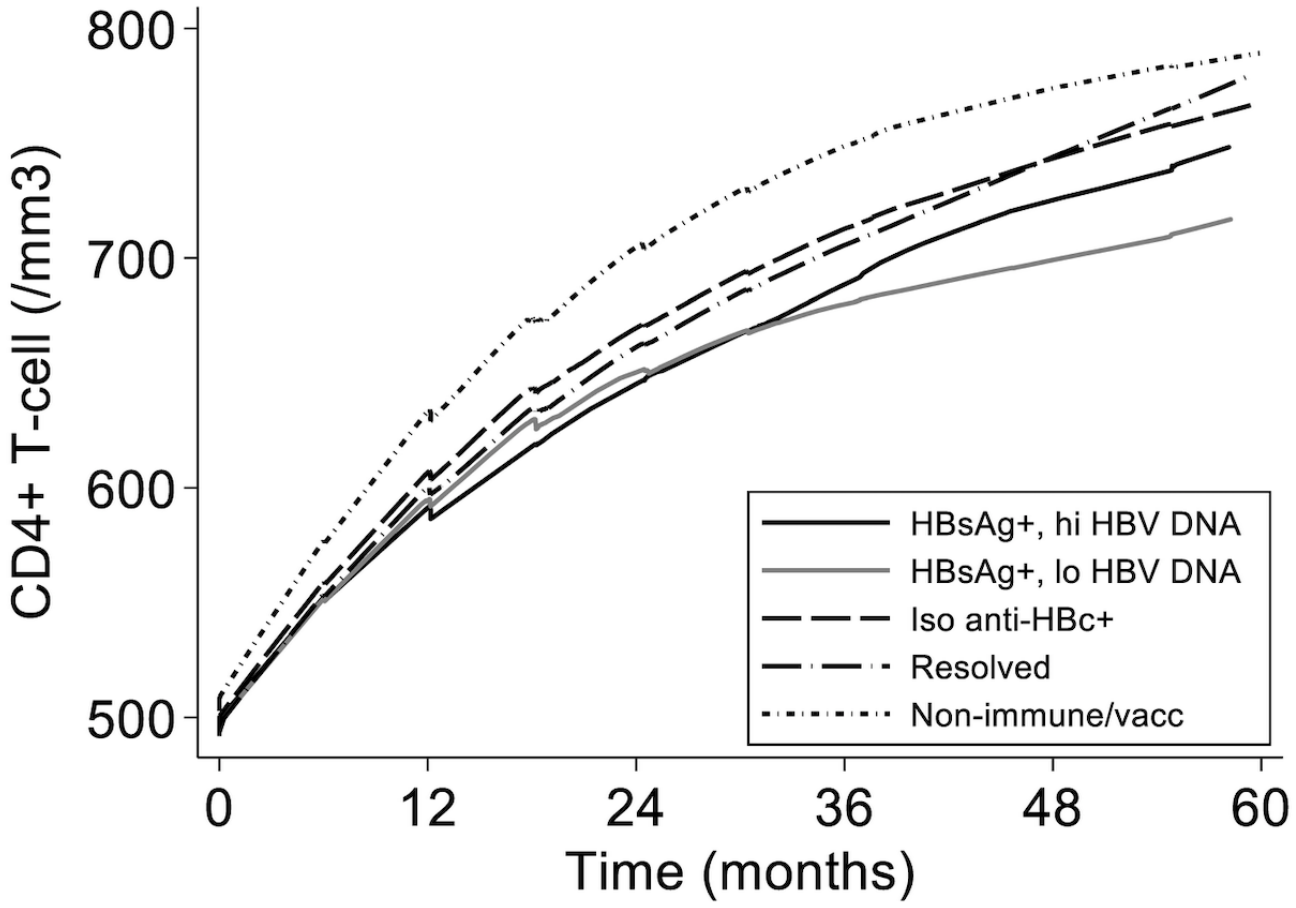
Thio CL, Lancet 2002

Mortality associated with HIV-HBV coinfection after immediate initiation of ART



Mohareb AM, J Viral Hepatitis 2021

CD4+ recovery in HIV-HBV coinfection after immediate initiation of ART (TEMPRANO)



Mohareb AM, J Viral Hepatitis 2021

Preventing and Managing HIV-HBV Coinfection

People Living with HIV

33 million

HBV Vaccination, dual active ART

People Living with HBV

250-300 million

PrEP, HBV treatment

People Living with HIV-HBV

3- 4 million

Dual active ART

Mohareb AM, JAMA Netw Open 2021

Outline

1. Viral Hepatitis Coinfections
2. Metabolic Liver Disease and HIV
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4. ART and PrEP in People with Hepatitis B

Case Continued, 8 years later

35yo M treated with TDF/3TC/DTG for HIV-HBV coinfection

- He has had a continually suppressed HIV viral load
- His HBV DNA took 24 months to decline and has since had sporadic rises (“blips”)
- HCV Ab continues to be negative
- ALT and AST initially improved to normal levels but over the past 2 years they have been >3 x upper limit of normal

What are possible causes of elevated aminotransferases in this person?

What are possible causes of elevated aminotransferases in this person?

A. Complication of ART
B. Sporadic elevations in HBV DNA (“blips”) cause liver disease
C. Other coinfections affecting the liver
D. Metabolic disease affecting the liver
E. Other causes

Many factors promote liver disease in people living with HIV

HIV

- Bacterial translocation
- Depleted intestinal CD4
- Systemic increase in oxidative stress

Coinfections

- Chronic Hepatitis B, C
- Acute Hepatitis
- HSV, VZV, CMV, EBV
- Syphilis
- Hemorrhagic fevers

Steatotic Liver Disease

- Metabolic factors
- Alcohol intake
- Aging

Medications, Drugs

- Hepato-toxicity, metabolic effects
  - ART
  - Antibiotics
  - Analgesics
  - Herbal medicines
  - Alcohol

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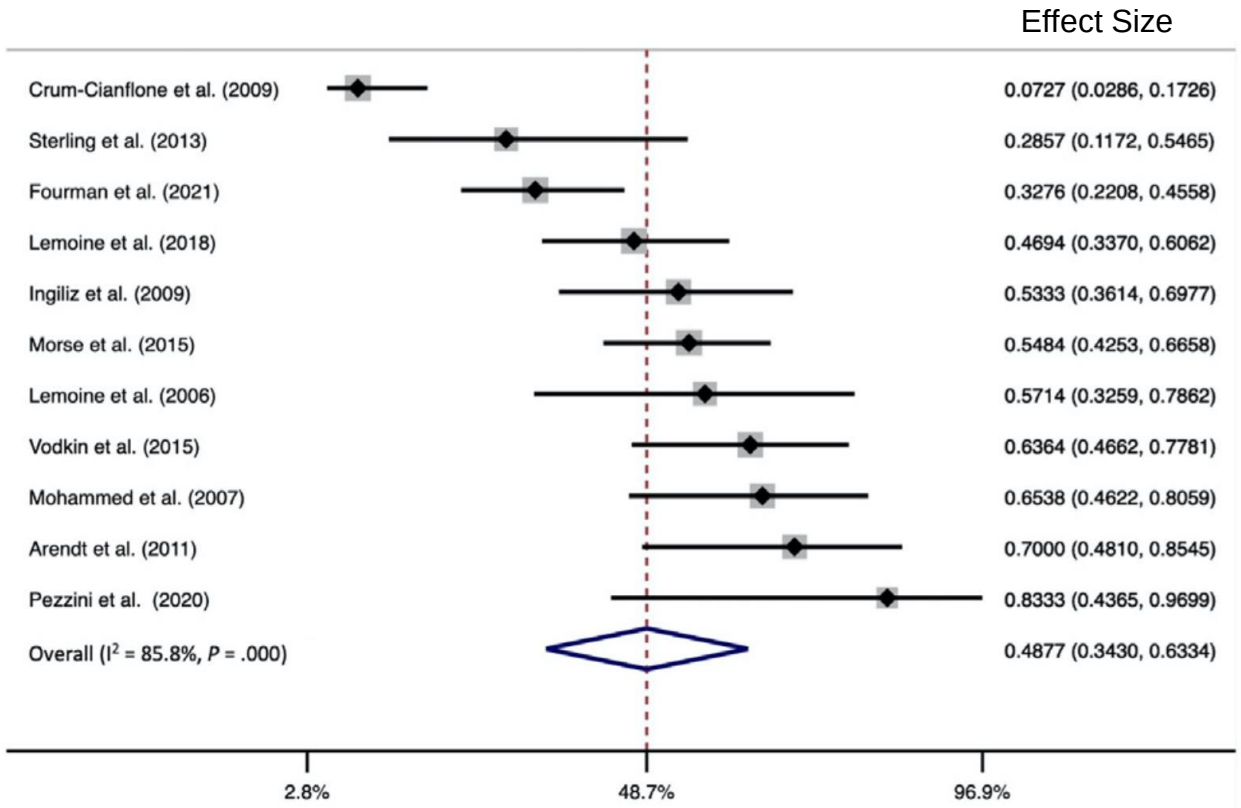
Nomenclature Change (2023)

Steatotic Liver Disease (SLD)

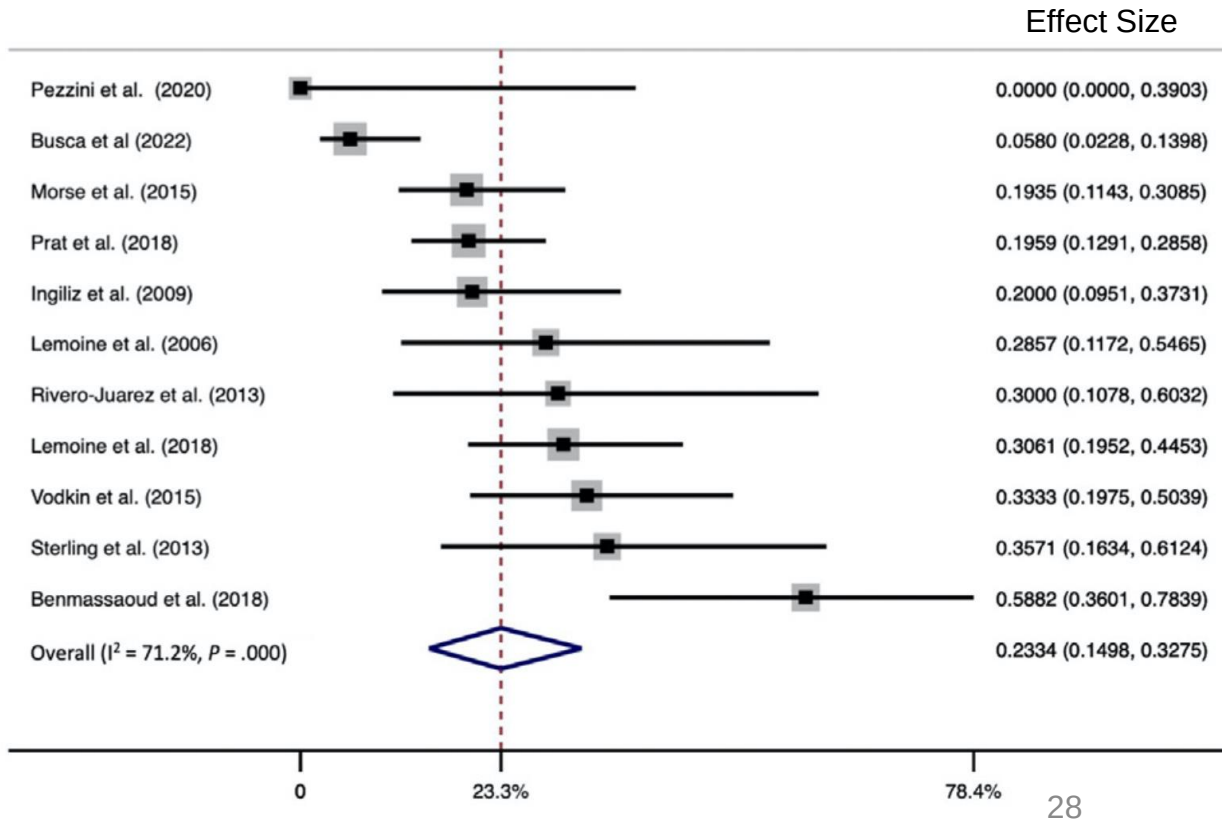
- **M**etabolic Dysfunction-**A**ssociated **S**teatotic **L**iver **D**isease **(MASLD)**
  - **M**etabolic Dysfunction-**A**ssociated **S**teato**h**epatitis **(MASH)**
- **MASLD and increased alcohol intake* (MetALD)**
  - MASLD predominant … ALD predominant
  - 140/210 — 210 — 280 — 350/420
  - Weekly alcohol intake (g)
  - MASLD predominant … ALD predominant
  - 20/30 — 30 — 40 — 50/60
  - Average daily alcohol intake (g)
- **Alcohol-Associated (Alcohol-related) Liver Disease (ALD)**
- **Specific aetiology SLD**
  - **Drug-Induced Liver Injury (DILI)**
  - **Monogenic diseases****
  - **Miscellaneous*****
- **Cryptogenic SLD**

Prevalence of Steatosis and Fibrosis in People with HIV who underwent Liver Biopsy

Metabolic Dysfunction-Associated Steatohepatitis (MASH) / NASH

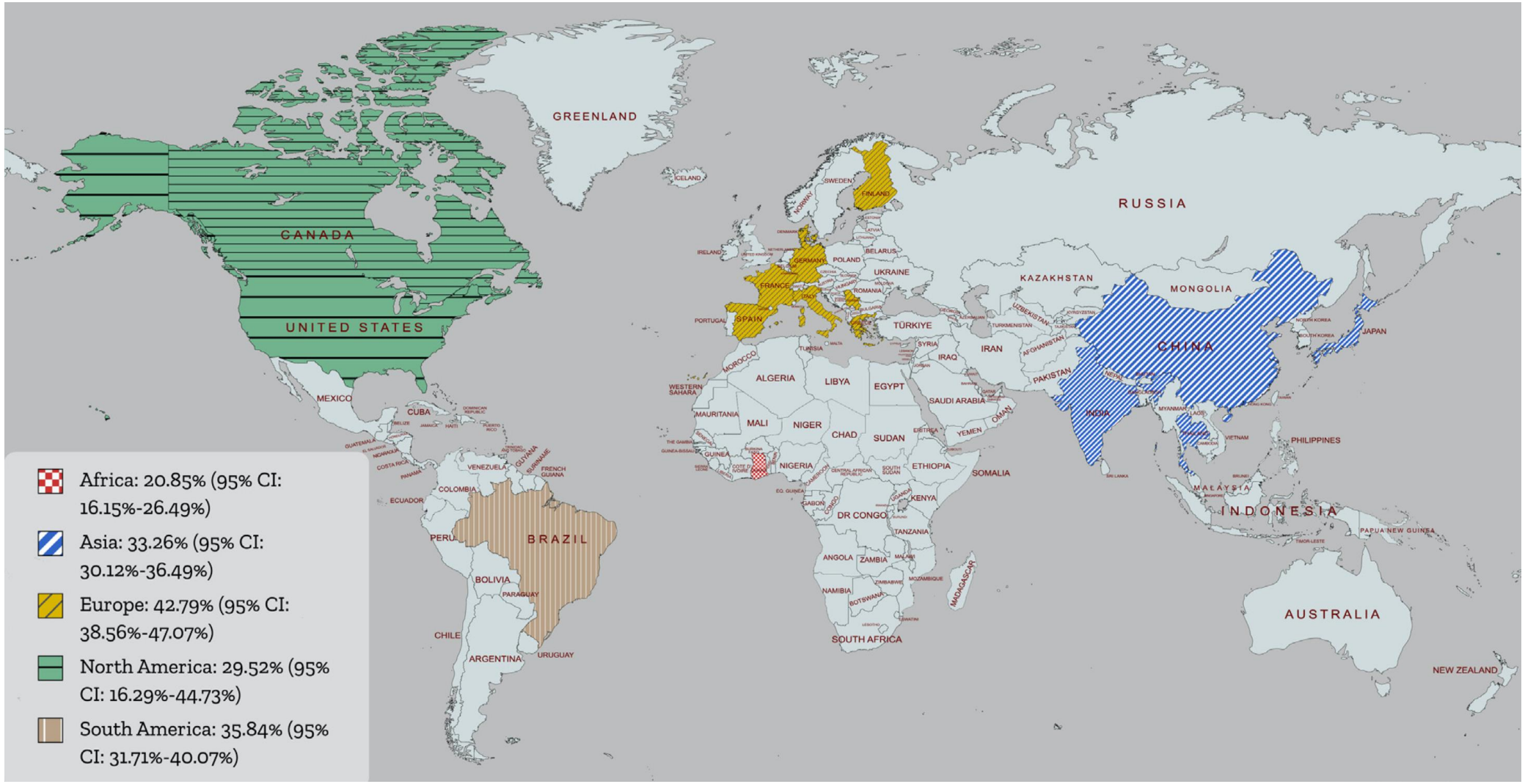


Fibrosis (≥F2)



Kalligeros, Clin Gastroentreol Hepatol 2023.

Data sources on Steatosis/Fibrosis in people with HIV monoinfection



Kalligeros, Clin Gastroentreol Hepatol 2023.

Is HIV independently associated with SLD?

Compared to people living with HIV without NAFLD (MASLD), those living with HIV with NAFLD were more likely to have:

- Diabetes
- Hypertension
- Hyperlipidemia
- Metabolic Syndrome
- Higher BMI
- More years since HIV diagnosis
- Longer exposure to ART

Kalligeros, Clin Gastroentreol Hepatol 2023.

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ART and SLD

- Older NRTIs, some PIs
- Didanosine, zidovudine, stavudine, zalcitabine
- TAF, some INSTIs via weight gain?

Kalligeros, Clin Gastroentreol Hepatol 2023.

Hepatitis B and Steatotic Liver Disease

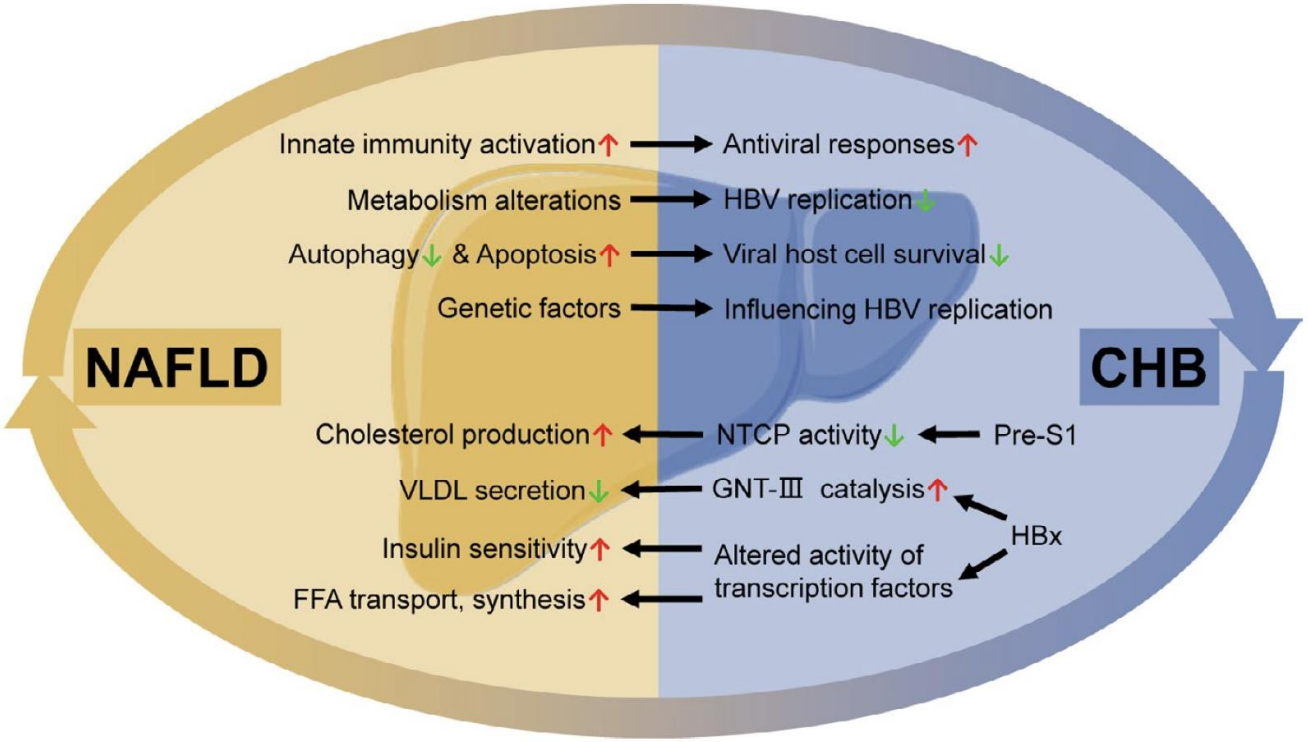
Complex and poorly understood interaction between HBV and SLD.

Is there a decreased incidence of SLD among people with HBV?

SLD may accelerate fibrosis and cirrhosis among people with HBV,

BUT there appears to be a negative correlation with HCC.

Does SLD promote HBsAg loss?



Zhang, Liver Intl 2020
Yang, Liver Intl 2022
Shi, World J Gastroenterol 2021

Outline

1. Viral Hepatitis Coinfections
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Case Continued, 5 years later

40yo M treated with TDF/3TC/DTG for HIV-HBV coinfection

- He has had a continually suppressed HIV viral load.
- He remains HBsAg-positive with undetectable HBV DNA.
- He occasionally has elevated ALT.
- He was started on a statin.
- He has a family history of colon cancer and cancer of unknown primary.

Should we screen for hepatocellular carcinoma in this person?

Should we screen for HCC in people living with HIV?

A. Screen all people with HIV, even without HBV
B. Screen all people with HBV, even without HIV
C. Screen all people with HIV-HBV coinfection, but not either infection alone
D. Screen people with HIV-HBV coinfection above age 40yo
E. Screen all people only if they have cirrhosis
F. No need to screen for HCC if they take ART
G. No need to screen for HCC at all

Screening for HCC in HBV monoinfection

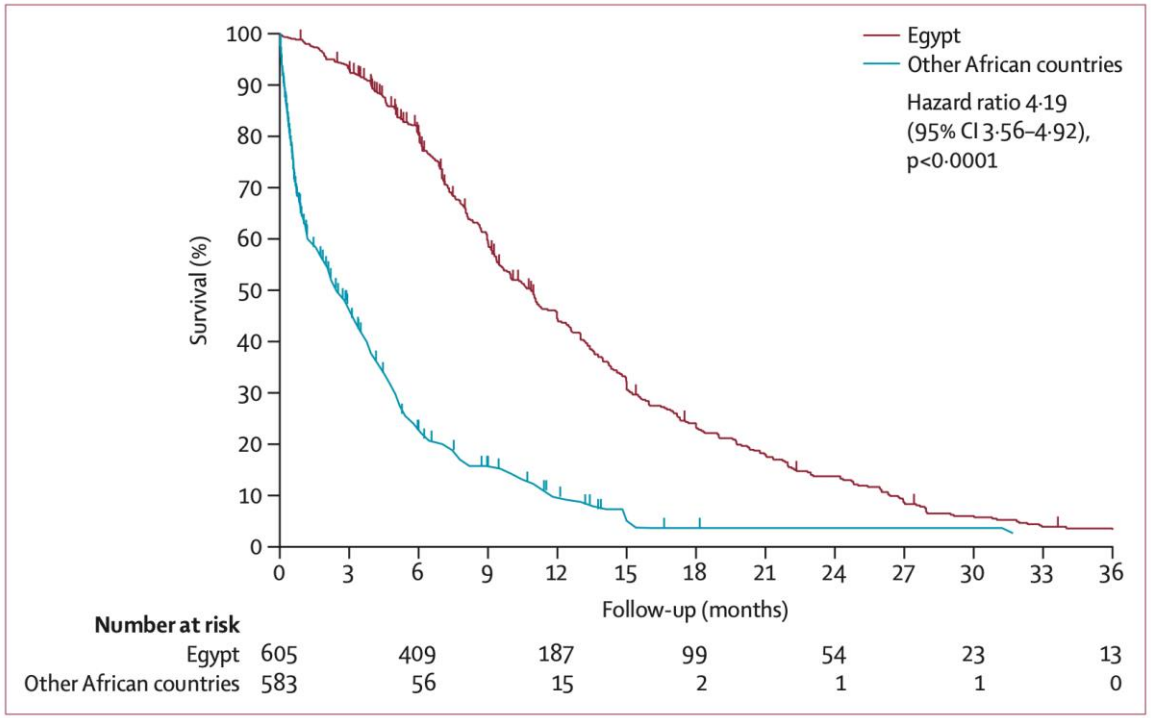
HCC screening is thought to be cost-effective in people whose risk exceeds 0.2% per year (i.e., 2 per 1000 person-years).

Europe/North American guidelines recommend HCC screening for people with HBV monoinfection:

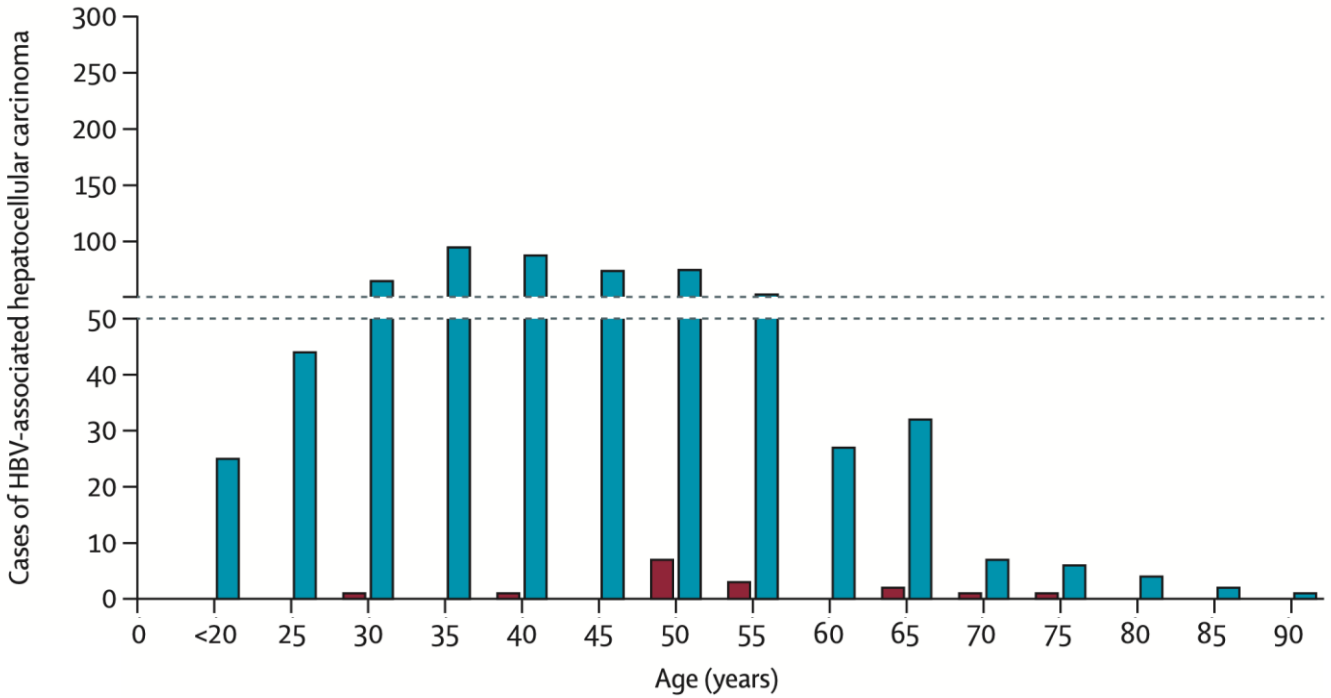
- Anyone with cirrhosis
- Asian or Black males >40yo
- Asian females >50yo
- Other demographics based on risk scores (PAGE-B, REACH-B)

HCC is an important cause of early death in Africa

Survival after HCC Diagnosis (all cause)



Age at HCC Diagnosis (HBV-monoinfection)



Yang, Lancet Gastroenterol Hepatol 2017

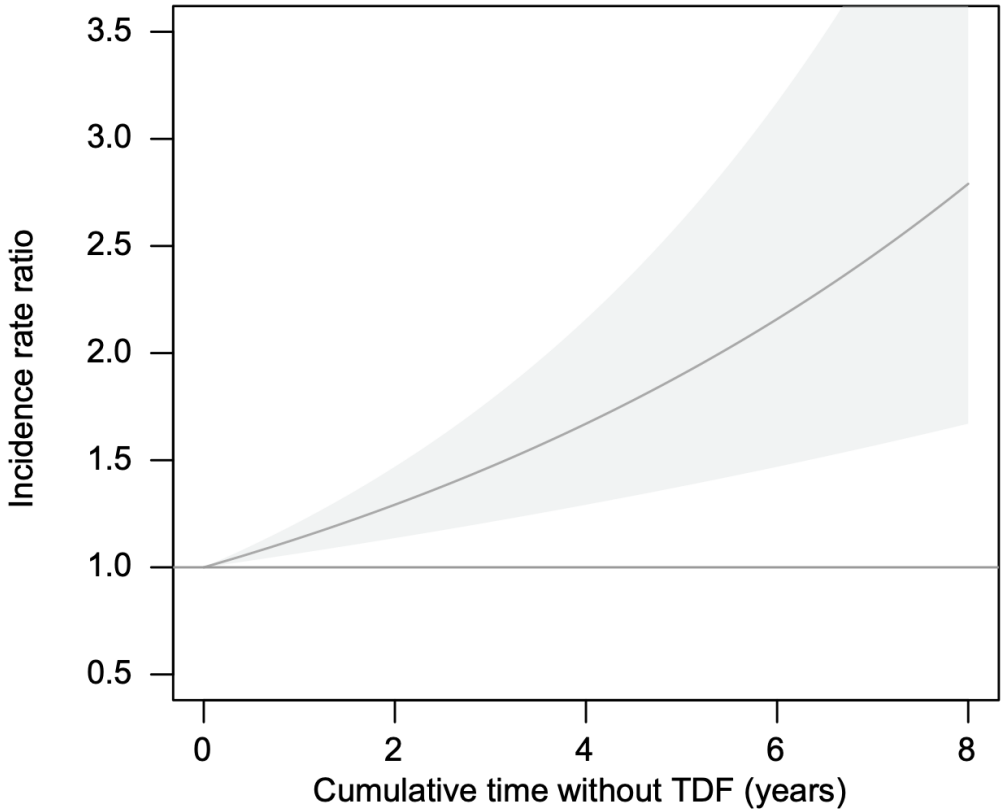
Screening for HCC in people with HIV-HBV

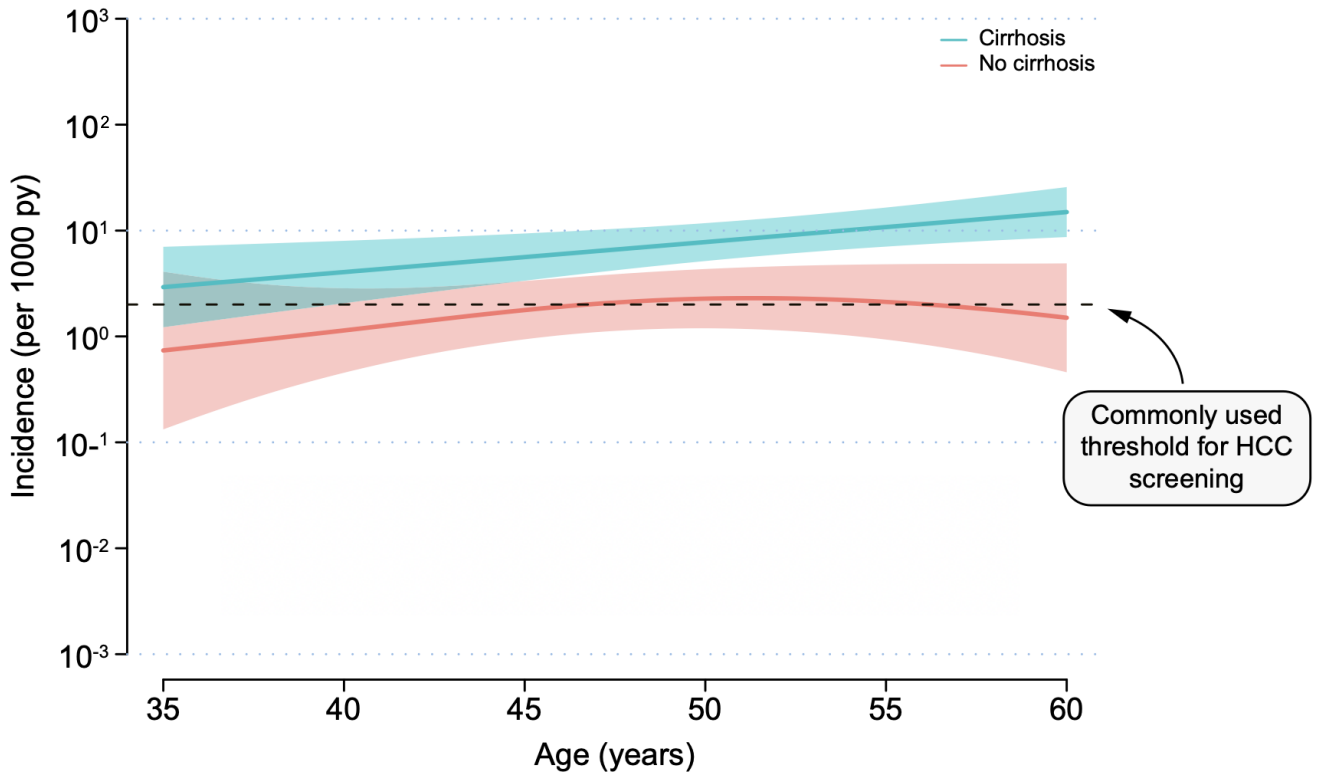
Analysis of HCC in 4 prospective European cohorts of PLWH

Major findings:

Increasing risk of HCC for a longer time off tenofovir

For people without cirrhosis, HCC risk was low until >45yo





Wandeler, J Hepatol 2019

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Case Continued, 2 years later

42yo M treated with TDF/3TC/DTG for HIV-HBV coinfection

- He has had a continually suppressed HIV viral load.
- He remains HBsAg-positive.
- He has started a statin.
- He has gained some weight.
- He expresses a strong preference for ART simplification because of perceived side effects, convenience, and general disdain for 3-drug therapy.

How do we counsel this person?

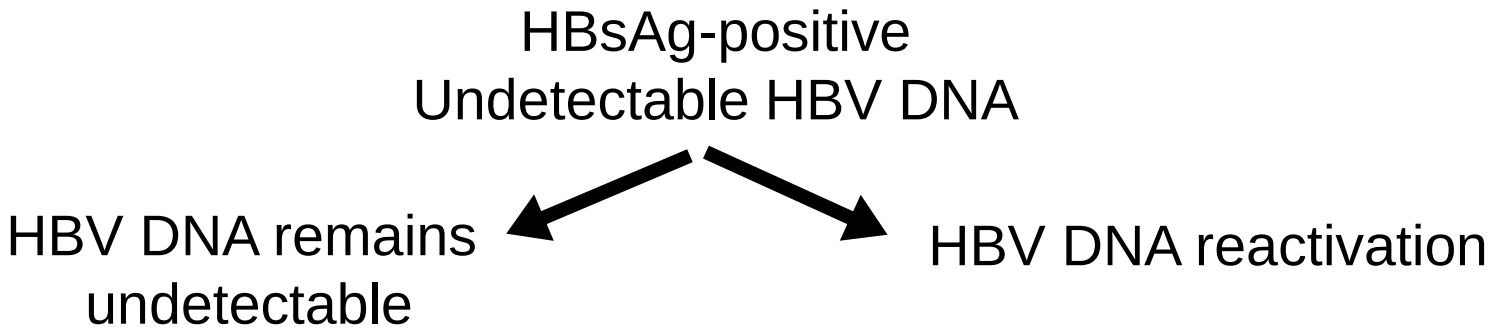
How would you approach “ART simplification” for a person with HIV-HBV coinfection who is currently taking TDF/3TC/DTG?

A. Switch to 3TC/DTG (lamivudine/dolutegravir)
B. Switch to 3TC/DTC and add entecavir for the HBV
C. Switch to long-acting injectible (tenofovir-free) ART
D. Switch to DTG/RPV (dolutegravir/rilpivirine)
E. Do not switch off from TDF/3TC/DTG

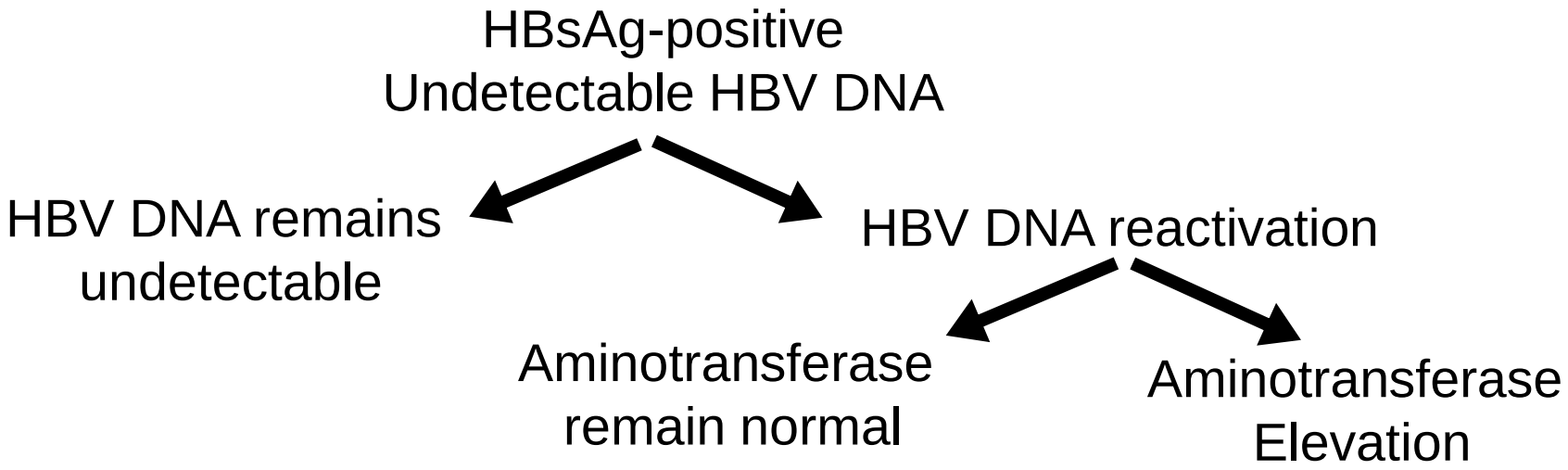
Stopping Therapy in Chronic HBV: Possible Outcomes

HBsAg-positive
Undetectable HBV DNA

Stopping Therapy in Chronic HBV: Possible Outcomes



Stopping Therapy in Chronic HBV: Possible Outcomes



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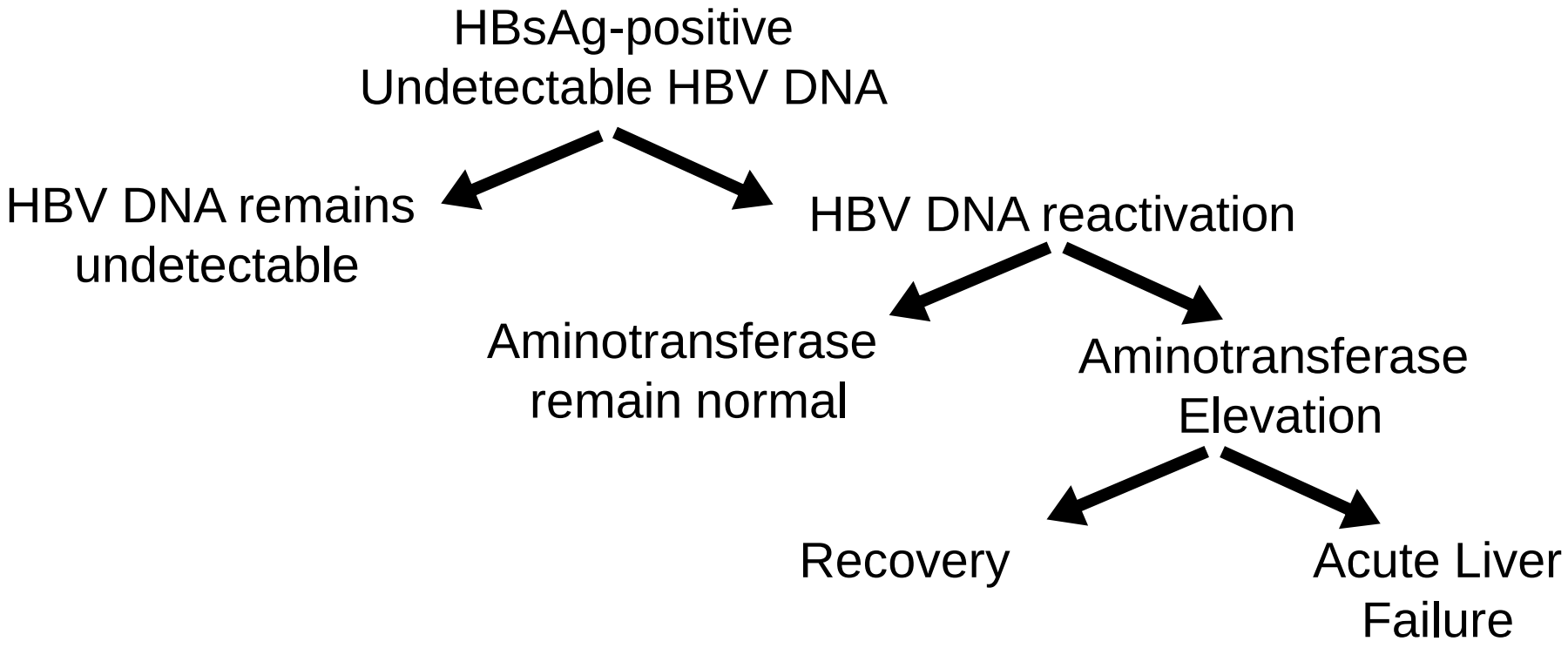

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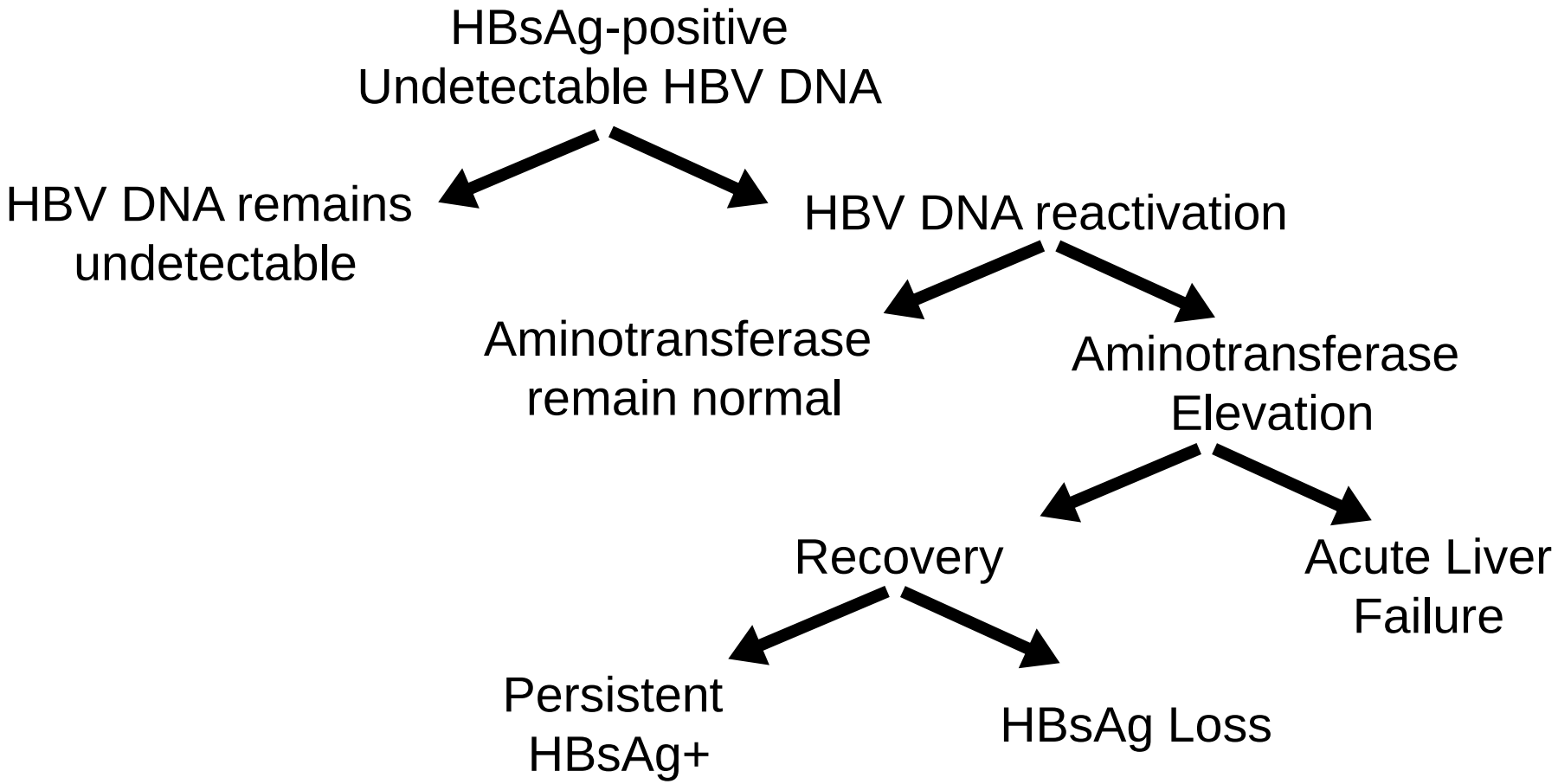

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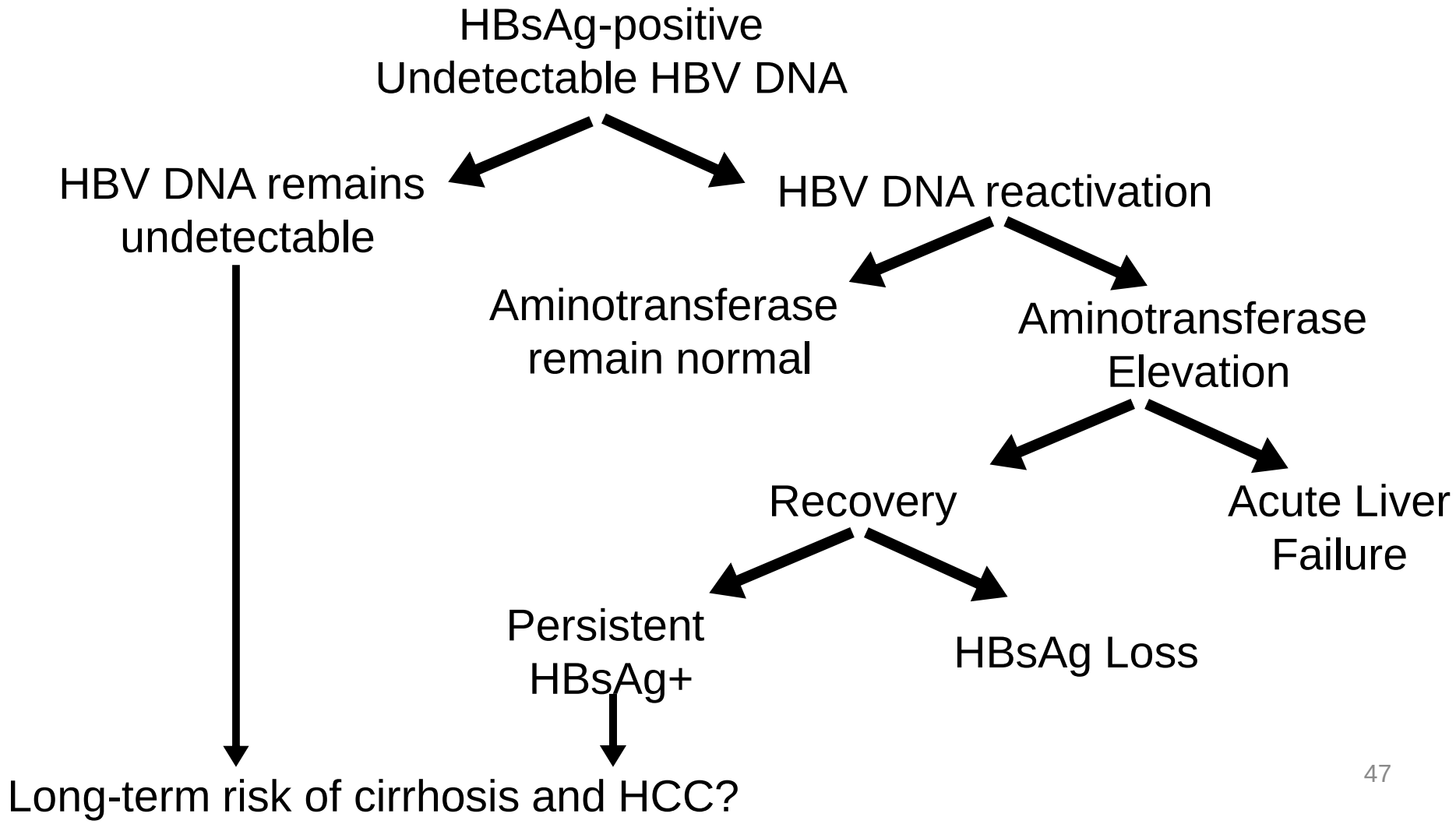
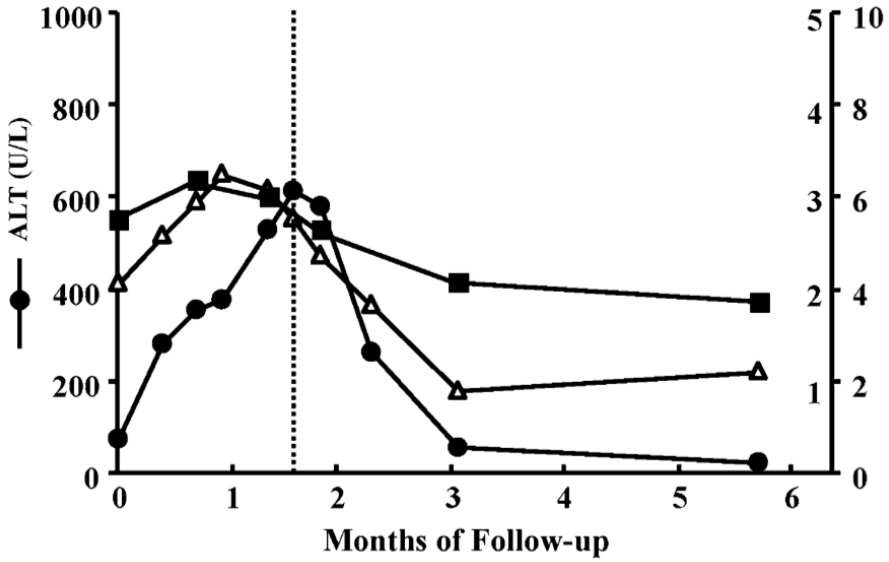
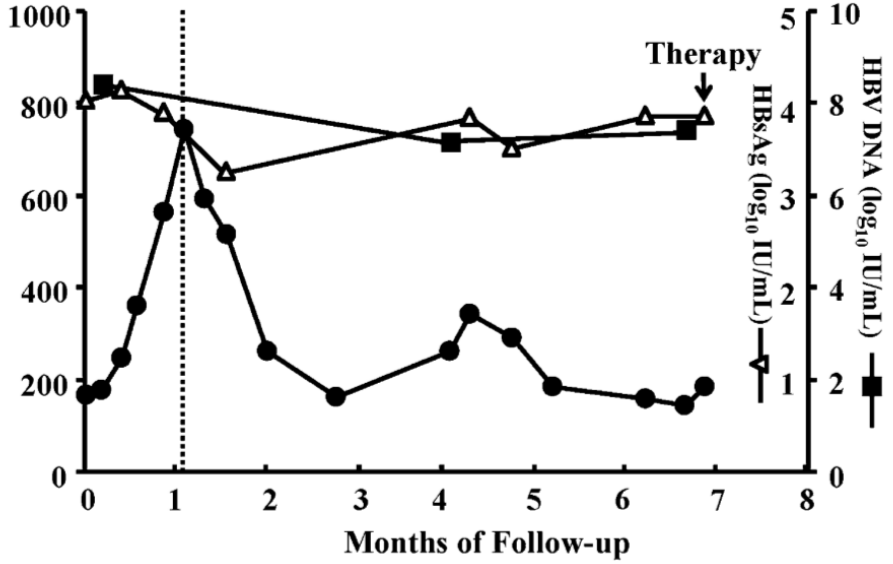


Hepatitis Flares Following Antiviral Cessation in HBV: Good or Bad?



HOST-DOMINATING FLARE



VIRUS-DOMINATING FLARE

Liaw, Hepatology Intl 2019

Events following antiviral cessation in chronic HBV mono-infection

Event	Estimated frequency (12 months post-cessation)
HBV DNA reactivation ("Virological Relapse")	65- 80%
Hepatitis flares ("Clinical Relapse")	35%
HBeAg reversion	9%
Acute liver failure ("Fulminant Hepatitis")	<1%*
HBsAg loss ("Functional Cure")	2 - 4%
Long-term risk of cirrhosis and hepatocellular carcinoma	???

* Subject to reporting bias and differing definitions

HBV/Hepatitis Flares after ART simplification Case Series from New York City

	HIV Parameters at Time of Switch	ART Regimen		Reason for Switch	HBV Vaccination	HBV Studies		Outcomes
		Preswitch	Postswitch			Preswitch	Postswitch	
Case 1 65 yo M	CD4 202 VL <20 Mutations: M184V, M41L, L210L, T215T, D67T, M46I, I54V, V82F	ABC 3TC Nevirapine FPV/r	DTG RPV	Patient preference for single-tablet regimen	Completed 2 series 6 y prior: Time 0, 1, 6 mo 1 y prior: Time 0, 3 mo	HBsAg− HBcAb−HBsAb− (Immediately prior)	HBsAg+ HBcAb+ HBsAb− HBeAg+ HBV DNA 1.75 mil	Peak ALT 570 Recovered on tenofovir
Case 2 33 yo M	CD4 304 VL 30,600 Mutations: M184V, K65R, K103N, E138Q	TAF FTC RPV	DTG DRV/r	NRTI resistance	Completed 1 series 3 y prior: Time 0, 8 mo, 11 mo	HBsAg− HBcAb− HBsAb+ (titer=41) (3 y prior)	HBsAg+ HBcAb− HBsAb− HBeAg+ HBV DNA 380 mil	Peak ALT 2640, Tbili 17, INR 3.3 Hepatomegaly Evaluated for transplant; recovered on tenofovir
Case 3 67 yo F	CD4 13 VL 211,000 No significant mutations	TDF FTC ATV/r	DTG DRV/c	Chronic kidney disease	Completed 1 series 8 y prior: Time 0, 1 mo	HBsAg− HBcAb+ HBsAb+ (titer = 86) (4 y prior)	HBsAg+ HBcAb+ HBsAb+ (titer = 79) HBV DNA 141 mil	Peak ALT 155 Lost to follow-up
Case 4 66 yo M	CD4 716 VL <20 Mutations: M184V, M41L, L210L, T215T, K103N	TAF FTC DRV/r DTG	DTG RPV	Patient preference for single-tablet regimen	Not applicable	HBsAg+ HBsAb− HBV DNA <10 (1 y prior)	HBsAg+ HBcAb+ HBsAb− HBV DNA 24.6 mil	Peak ALT 680, Tbili 21, INR 4.7 Hepatomegaly with gastric varices Required transplantation

Vasishta, JAIDS 2023

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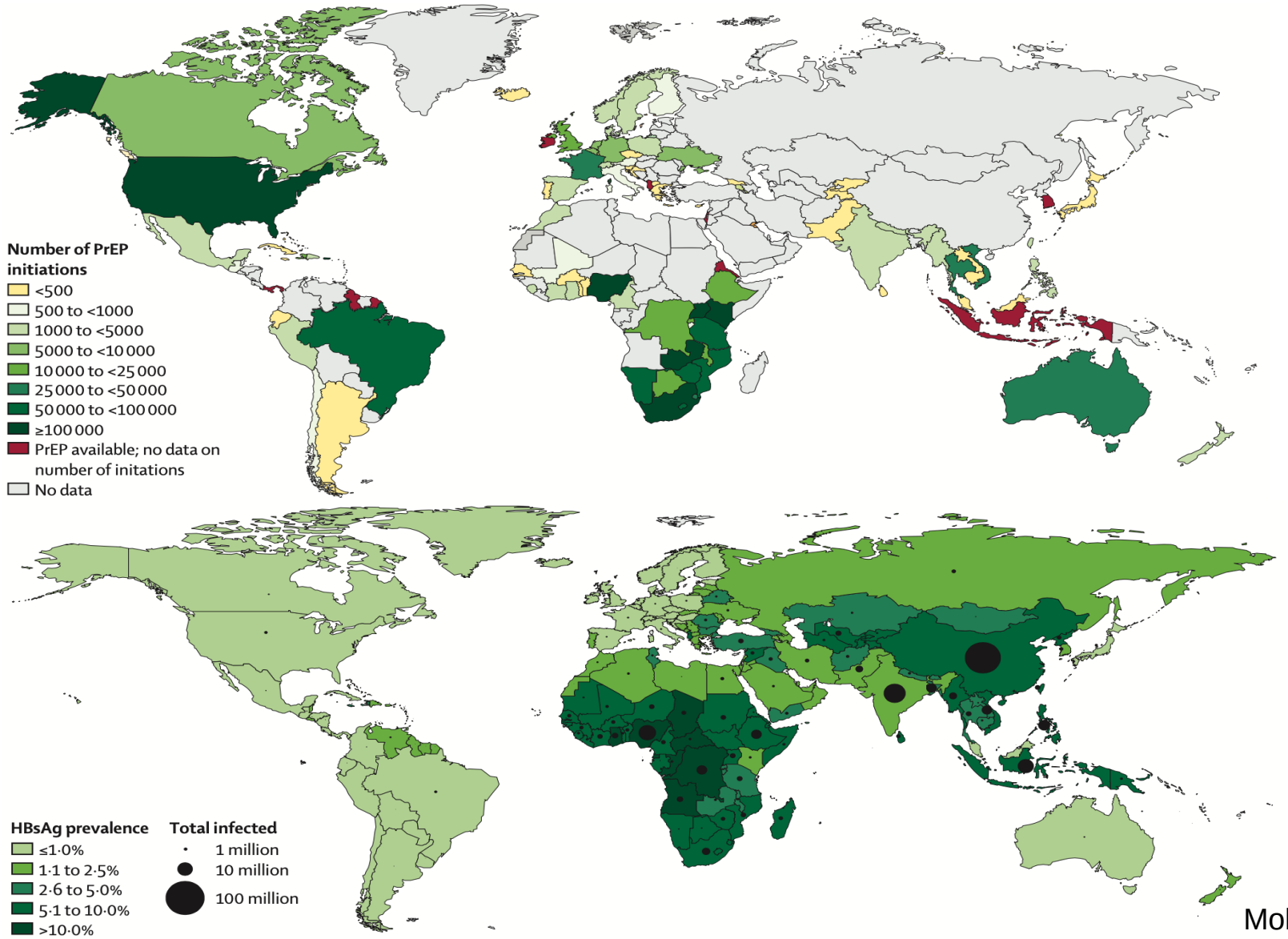
Vasishta, JAIDS 2023

Similar Concerns with Tenofovir-based PrEP in people with chronic HBV

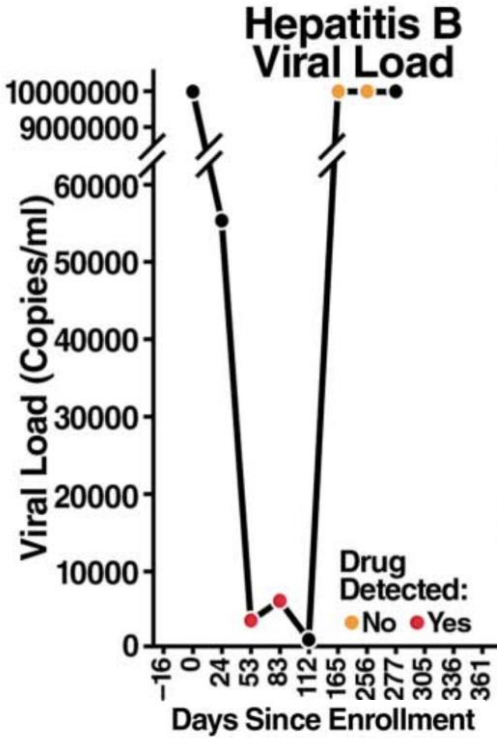


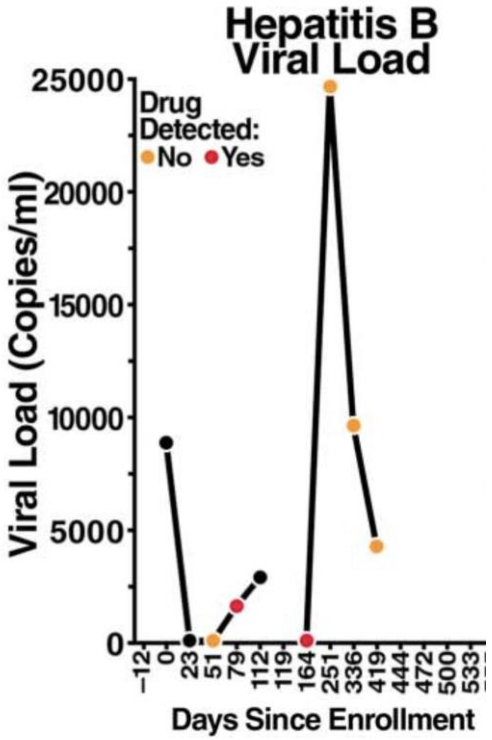
Mohareb AM, Lancet HIV 2022

Most PrEP trials excluded people with HBV…except iPrEx

iPrEx randomized 2499 people to TDF/FTC v placebo

6 participants in the TDF/FTC arm had HBsAg+ (< 0.5%)





Solomon, JAIDS 2016

Principles for managing PrEP in people with chronic HBV

PrEP is an opportunity to screen for HBV (and STIs), but people should not wait for an HBV test result to start PrEP.

Tenofovir-based PrEP is an opportunity to expand access to effective antiviral therapy for people with HBV.

Cessation of tenofovir-based PrEP can risk virologic relapse and hepatitis flares in people with HBV: laboratory monitoring following PrEP cessation is necessary.

Mohareb AM, Lancet HIV 2022

Summary

1. Viral Hepatitis B and C are common coinfections that impact people living with HIV.

2. There are multiple mechanisms of steatosis among people living with HIV.

3. Screening for HCC is important in people with HIV, especially those living with HBV.

4. There are complexities of ART simplification (and PrEP) among people living with HBV.

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