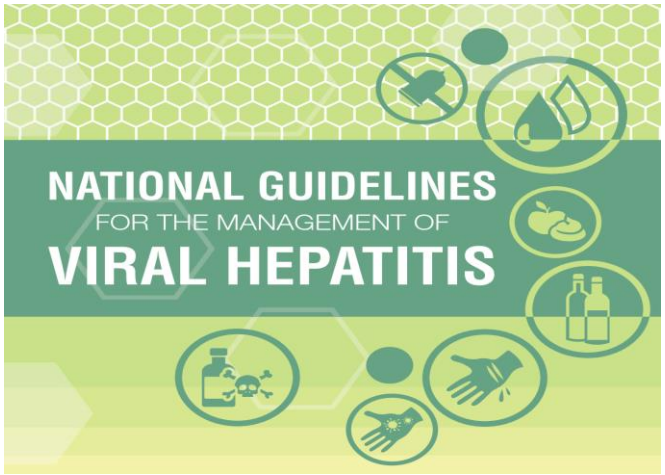
HIV/HBV Co infection Management

National Department of Health

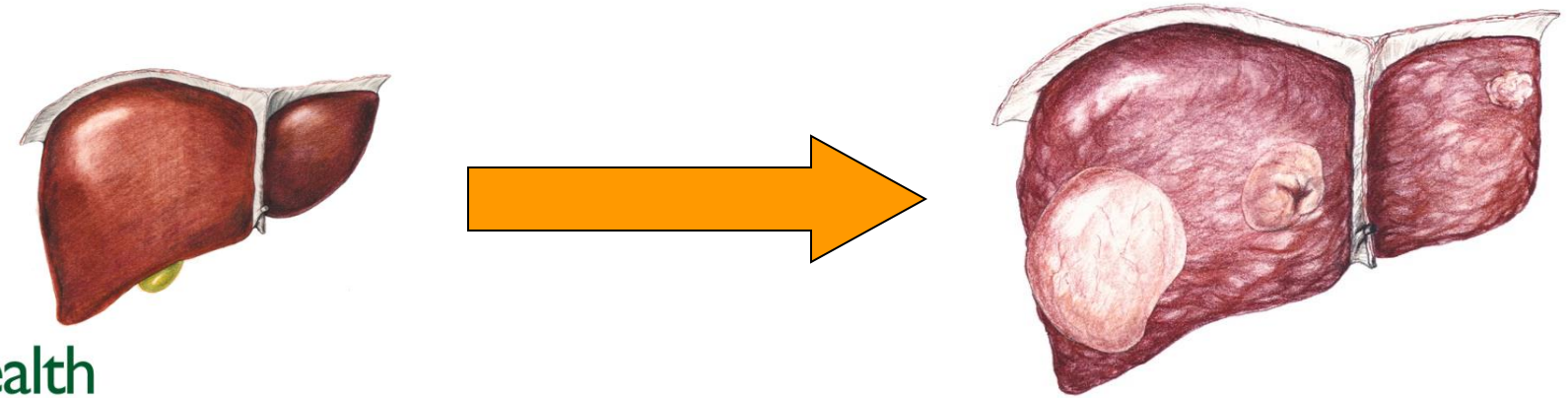
Goal of Session

To capacitate clinicians and programme managers on the management of HIV/HBV Co infection as per the current Viral Hepatitis Clinical Guideline (2019)



What Is Hepatitis?

- Hepatitis means inflammation of the liver
  - Hepat (liver) + itis (inflammation)= Hepatitis
- Viral hepatitis means there is a specific virus that is causing your liver to inflame (swell or become larger than normal)



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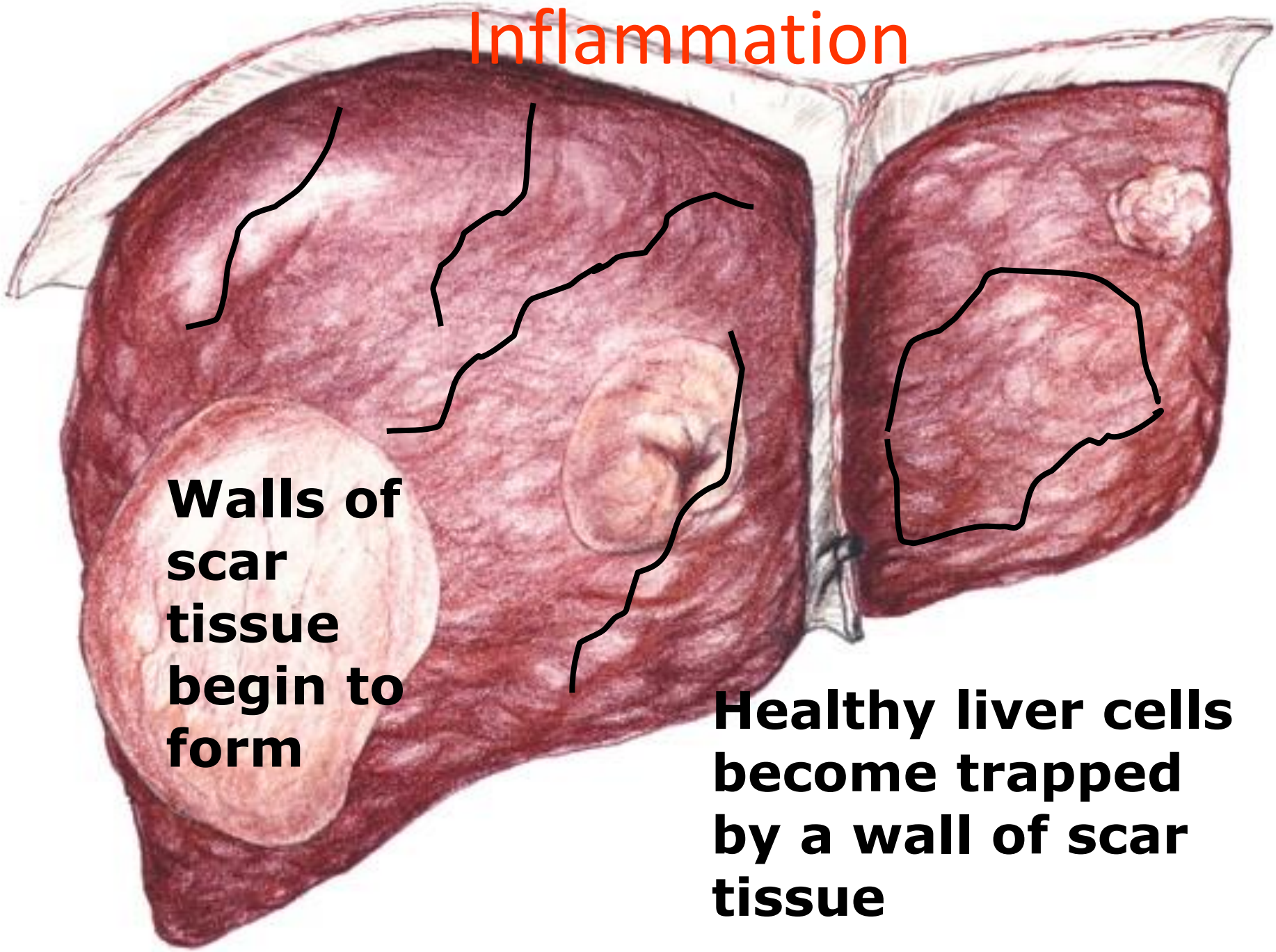
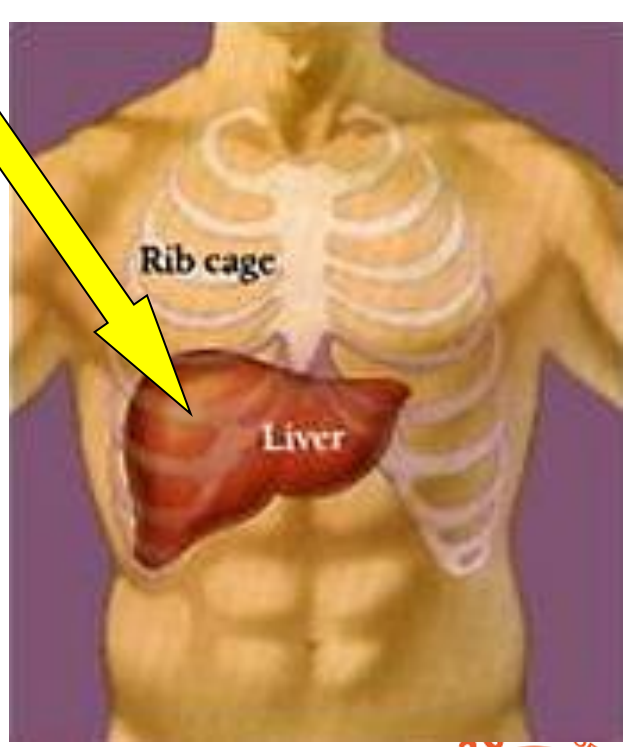
Inflammation



The Liver

- Is located in the upper right quadrant of the abdomen

  - Cleans the blood
  - Regulates hormones
  - Helps with blood clotting
  - Produces bile
  - Produces important proteins
  - Maintains blood sugar levels
  - And much, much, more



- The liver is essential for life !

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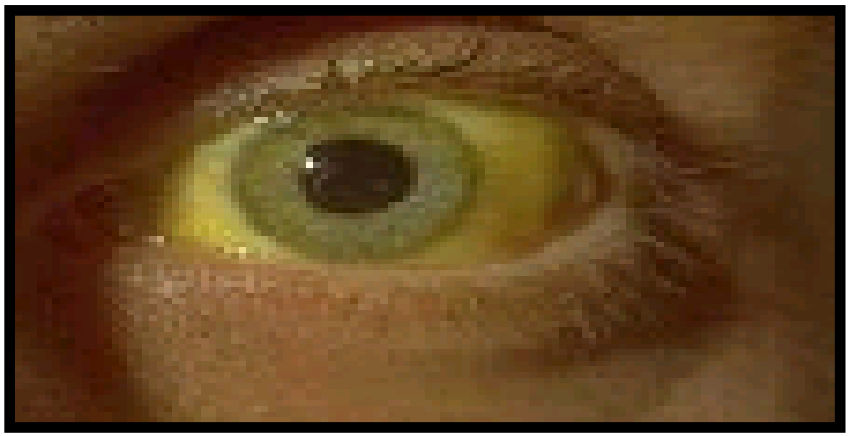
Signs and Symptoms

- Most infected individuals are asymptomatic
- A few may have specific liver related symptoms initially:
  - Pale stool (poo)
  - Jaundice (yellowing of the skin or eyes)



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Viral Hepatitis

5 types:

A: fecal-oral transmission

B: sexual fluids & blood to blood

C: blood to blood

D: travels with B

E: fecal–oral transmission

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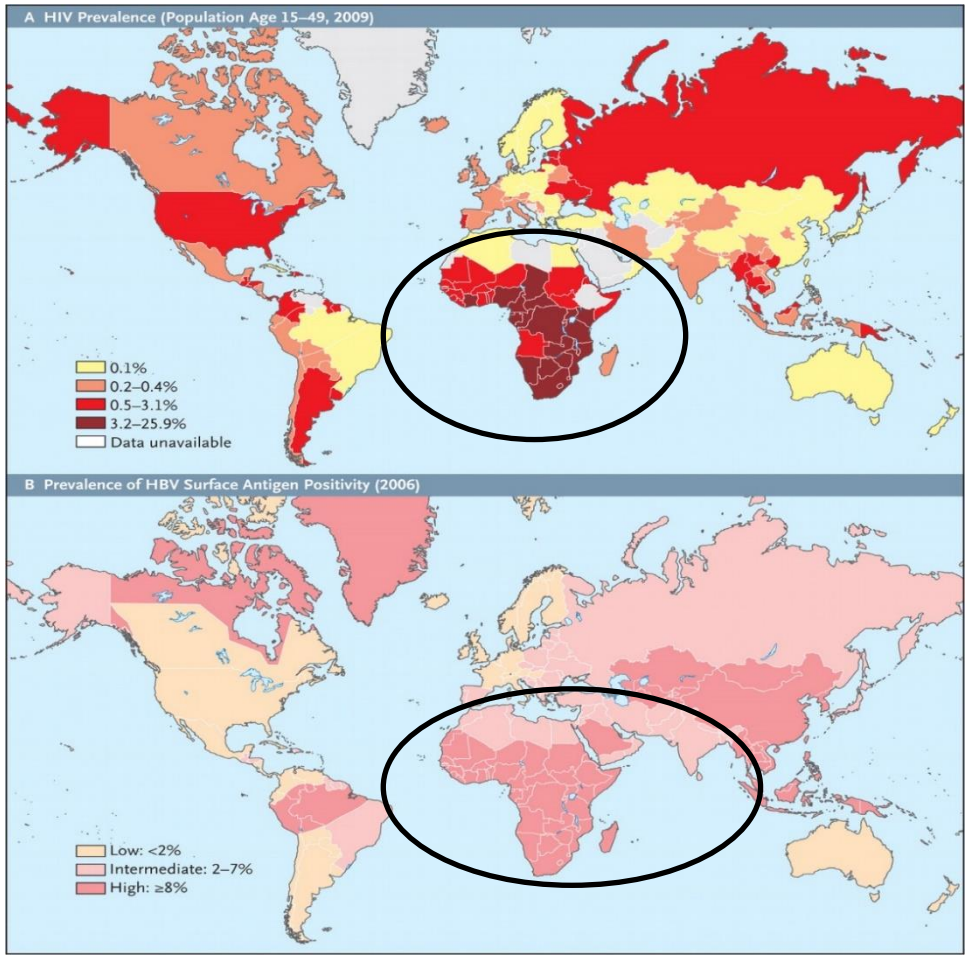
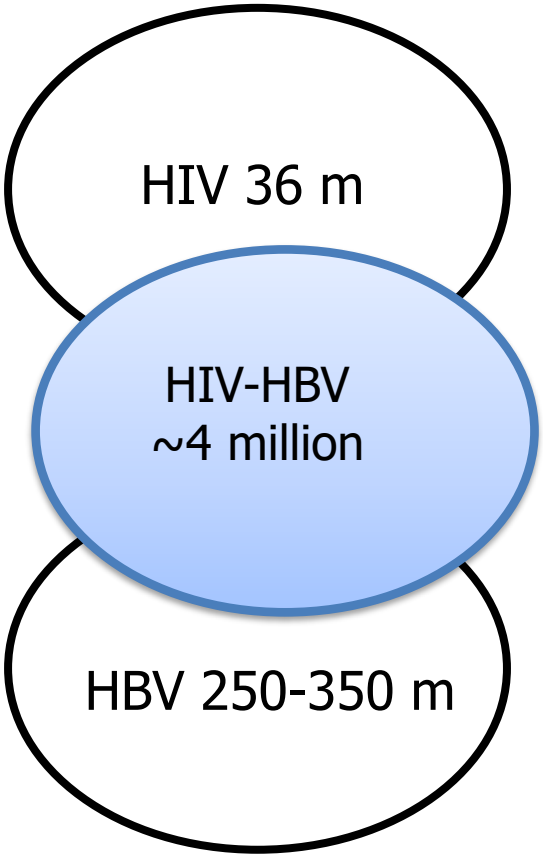
Global HBV and HIV prevalence





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Kourtis AP et al. N Engl J Med 2012;366:1749-1752.

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Epidemiology of HIV/HBV in sub-Saharan Africa
Patterns of co-infection transmission

Independent transmission and acquisition of HBV and HIV

- **HBV** generally acquired in childhood < 5 years of age
- **HIV** infection occurs later in life, primarily via sexual route

Series from West, East and Southern Africa

- Chronic HBV infection over-represented in HIV patients suggesting shared risk factors or co-transmission events
- Maternal HIV infection increases mother-to-child transmission up to 2.5-fold as HIV promotes Hepatitis B replication.
- HIV/HBV co-infected mothers are more likely to be HBeAg positive, have higher HBV DNA levels and are thus potentially more infectious leading to increased perinatal transmission risk

Bull Soc Pathol Exot 2009;102:226; J Clin Virol 2014;61:20

Epidemiology of HIV/HBV: sub-Saharan Africa
Patterns of co-infection transmission

Co-infection in sub-Saharan Africa

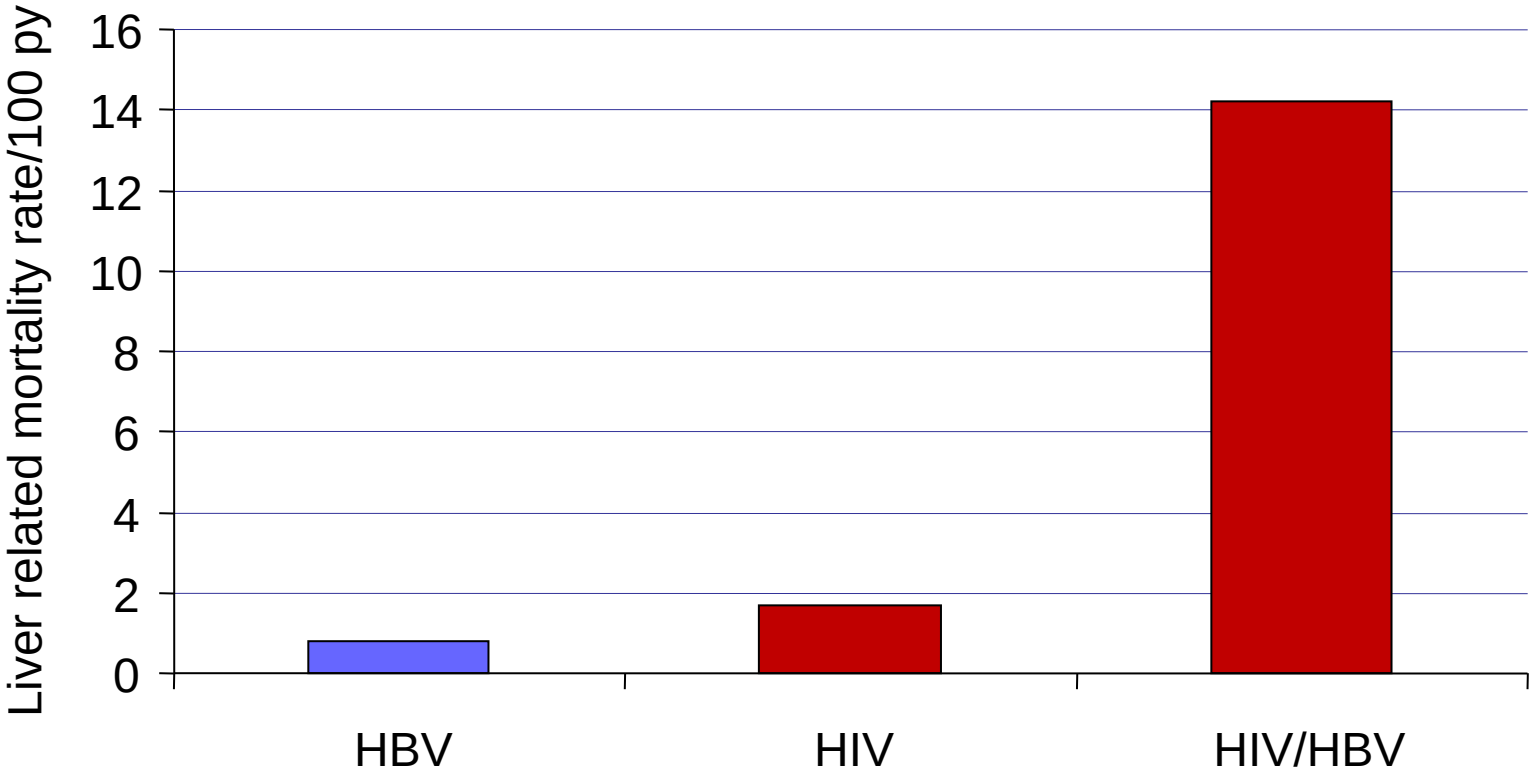
- **Most -** infected or exposed to HBV in childhood prior to HIV acquisition as adults
- **Other transmission mechanisms**

  Perinatal transmission of HIV and HBV
  Reactivation/sero-reversion of HBV in immunocompromised patients
  De novo adult acquisition of both HBV and HIV

Co-infection in high income countries / developed world

- ▶ HIV and HBV share a similar mode of transmission
- ▶ more typically shared transmission route e.g. PWID,

Mortality of HIV/HBV co-infection pre-ART era



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Thio CL, et al. Lancet 2002;360:1921–6

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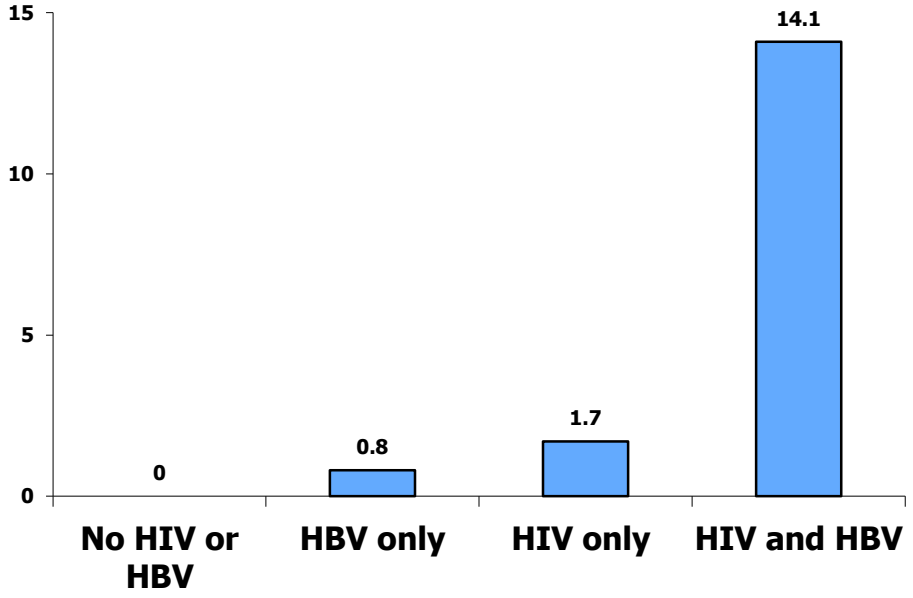
HIV Co-infection Increases the Risk of ESLD due to HBV

- MACS, 4,967 men
  - HIV, 47%
  - HBV, 6% (n=326)
  - HIV/HBV, 4.3% (n=213)
- HIV/HBV: 17-fold higher risk of liver death compared to HBV alone

Liver Mortality by HIV and HBV Status



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Thio C *et al. Lancet* 2002;360:9349.

Liver disease remains 2nd leading cause of death in later ART era in HIV-infected people in D:A:D study

- 33,308 participants from 1999-2008
  - 15.3% with HCV (Ab or RNA+)
  - 11.5% HBV (prior/active)
- 2482 deaths
  - 29.9% AIDS-related
  - **13.7% liver-related**
  - 11.6% CVD-related
- **Liver-related deaths declined over time**
  - **2.67/1000 PYs (99-00) to 1.45/1000 PYs (07-08)**
- Rates highest in CD4<100 cells/mm3

D:A:D study, *AIDS* Jun 2010 24 (10)

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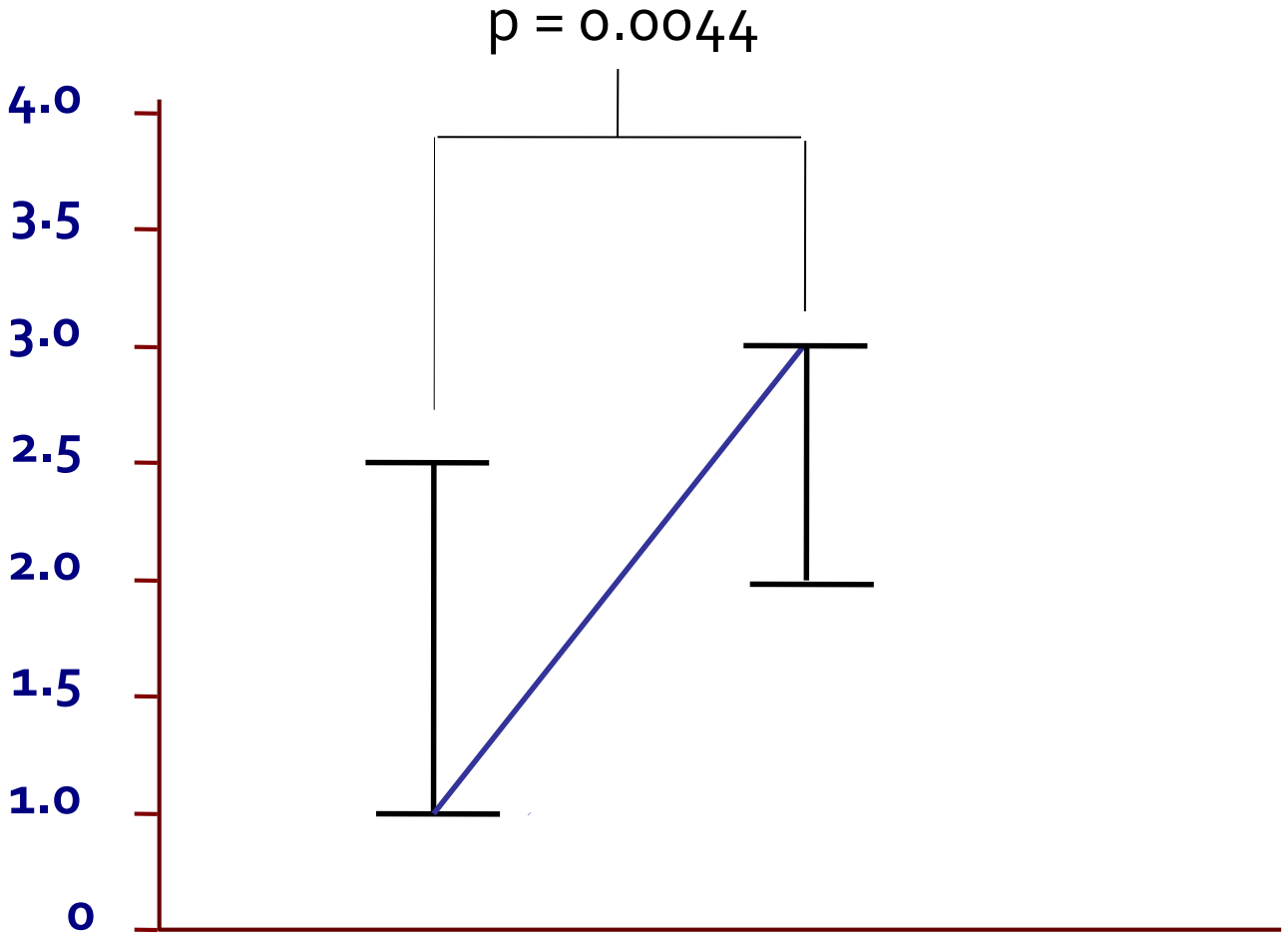
Factors associated with liver-related death in D:A:D study

Factor	Adjusted RR	95% CI
Age, per 5 years older	1.16	1.09-1.24
IDU (MSM reference)	5.02	3.56-7.08
HTN	2.34	1.83-2.99
Diabetes	2.37	1.68-3.35
HCV	1.67	1.21-2.31
HBV	**2.37**	**1.74-3.22**
CD4 count per 50 cell/uL increase	0.82	0.79-0.85
HIV RNA >5 log cp/ml	1.68	1.01-2.80

D:A:D study, *AIDS* Jun 2010 24(10)

Fibrosis (n=64, ART naive)



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HBV mono-infected (n=32)
median 1 [0 – 5]
mean 1.6 ± 1.4

HBV/HIV co-infected (n=32)
median 3 [1 – 6]
mean 2.7 ± 1.2

CD4 (median/mm^3)
105 [2 – 843]

Sonderup et al Hepatology November 2008

HIV/HBV co-infection influences the natural history of hepatitis B

- HIV + pateints 3–6x more likely to develop chronic HBV than HIV-negative patients after acute HBV infection
- Hepatitis B in HIV charachterized by signifcantly elevated HBV replication - despite elevated HBV replication – ALT/AST often mildly elevated or normal
- Elevated risk of HBV reactivation
- Elevated risk of Acute Liver Failure with acute HBV in HIV + patients
- Increased rates of occult HBV
- Progression to fibrosis and cirrhosis enhanced
- HCC risk elevated
- Increased risk of ART hepatotoxicity
- ART- related immune reconstitution hepatitis

Lacombe K, Rockstroh J. Gut 2012;61 (Suppl 1):i47–58; AIDS 2005;19(6):593; J Acquir Immune Defic Syndr 2000;24(3):211; J Inf Dis 2013;208(9):1454; South Afr Med J 2012; 102:157; World J Hepatol 2010; 2: 65-73; AIDS 2011; 25: 1727; Antivir Ther 2011;16:405; South Afr Gastroenterol Rev 2004; 2(3): 14; South Afr J Epidemiol Infect 2008: 23(1): 14; Lancet 2002; 360 (9349):1921; Vaccine 2013;31:5579

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Impact of HIV/HBV Co-infection: Additional factors

- CD4 count <200 cells/mm^3 is associated with 16.2-fold increase in risk of liver-related death compared to CD4 count >350 cells/mm^3

- Earlier studies found no consistent evidence for a significant effect of HBV on HIV disease progression

- Some longitudinal cohort studies –> suggests HBV co-infection also leads to increased progression to AIDS-related outcomes and all-cause mortality

DAD study Arch Intern Med 2006;166(5):1632, J Hepatol 2005;42(6):799; Lancet 2011;377(9772):1198; Lancet 2002;360(9349):1921; Ann Int Med 1992;117(10):837; Scand J Infect Dis 1997;29(2):111; J Inf Dis 2012;205(2):185; Clin Infect Dis 2009;48(12):1763; AIDS 2011; 25: 1727; Ann of Int Med 2015;16: 405; South Afr J Epidemiol Infect 2008: 23(1): 14; Hepatol 2010;52(3):1143; Clin Infect Dis 2009; 49:1268

Impact of HBV on HIV

ART re-initiation and HBV Rebound among HIV/HBV-co-infected Patients following ART Interruption in the Strategies for the Management of ART (SMART) Study

- SMART study randomized HIV patients with a CD4 count above 350 cells/µL to a drug conservation (interrupt ART until CD4 <250 cells/µL) versus viral suppression (continued use of ART) group
- 120 HBV co-infected
- Frequent HBV DNA rebound following ART interruption with accelerated immune deficiency.

Figure 3. Kaplan-Meier plot of time to antiretroviral therapy re-initiation in the DC arm by hepatitis status

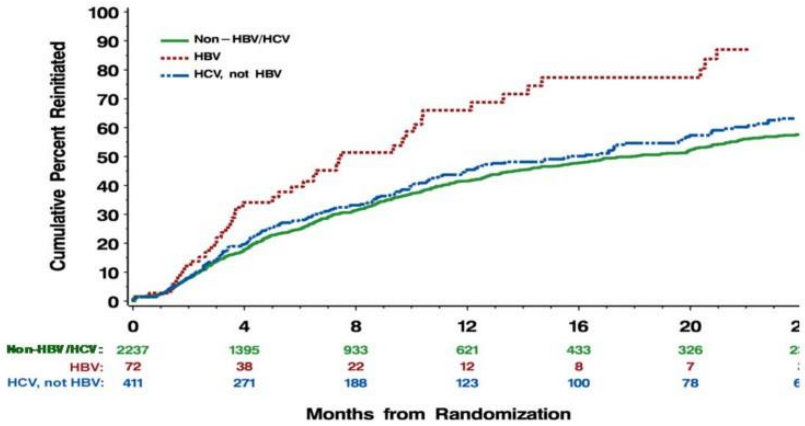

Table 3. Predictors of antiretroviral therapy re-initiation in the SMART drug conservation arm. Multivariate model.

	Univariate Hazard ratio	*P*	*Multivariate Hazard ratio*	*P*
HBV	1.95 (1.45-2.63)	<0.0001	1.71 (1.27 - 2.31)	0.0005
HCV	1.01 (0.87-1.18)	0.87	1.04 (0.88 - 1.22)	0.66
Prior AIDS	2.17 (1.91-2.45)	<0.0001	1.41 (1.24 - 1.61)	<0.0001
Nadir CD4 count (/100 cells lower)	1.67 (1.60-1.75)	<0.0001	1.50 (1.42 - 1.58)	<0.0001
Baseline CD4 count (/100 cells lower)	1.20 (1.16-1.23)	<0.0001	1.14 (1.11 - 1.18)	<0.0001
Baseline HIV RNA ≤400 copies/ml	1.18 (1.04-1.34)	0.011	1.19 (1.04 - 1.37)	0.012
Highest HIV RNA (Log_{10})	1.34 (1.25-1.44)	<0.0001	1.19 (1.11 - 1.28)	<0.0001
Female	0.97 (0.84-1.11)	0.61	1.01 (0.88 - 1.16)	0.89
Age (/10 years)	1.15 (1.08-1.22)	<0.0001	1.13 (1.06 - 1.20)	0.0003

Dore JG et al AIDS 2010; 24: 857-65

Management of HIV/HBV Co-infection

HBV screening and Vaccination

- All newly diagnosed HIV infected individuals should be screened for HBV
  - HBsAg and anti-HBs
- Non-immune (HBsAg and anti-HBs negative) - Vaccinate
- Lower response to vaccination notably with low CD4 counts
- *Meta-analysis* - 4 double dose (40ug) vaccine schedule gives higher protective anti-HBs

Hepatitis A Vaccination

- Should be considered in all HIV positive patients esp. MSM

Screen for Hepatitis C

the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013; Int J STD AIDS 2013;24(2);117

Universal HBV Vaccination

Taiwan *(JAMA 1687;257:2597; JAMA 1988;260:2231; JAMA 1996;276:906; Ann Int Med2001;135:796)*

- Universal vaccination (1984), together with
  - Catch-up vaccination programme
  - Improved maternal screening

  HBsAg seroprevalence in children <15 years decreased from 9.8% in 1984 to 0.7% in 1999

- **HCC prevalence in children aged 6 - 9 years decreased from 5.2 cases/million population (1984) to 1.3/million in first vaccination cohort**

Chinese government in partnership with GAVI *(Vaccine 2013;31(Suppl 9):J29-J35)*

- Free birth dose vaccine
- Upscaling of full vaccine schedule improved maternal screening
- Utilising village lay healthcare workers
- **HBsAg seroprevalence now <1% in children**

Hepatitis B : Vaccination

- **South Africa introduced universal HBV vaccination in April 1995**
  - Added to existing 6-, 10- and 14-week EPI schedule, now 18-month booster
  - Hexavalent vaccine
- **Pre - HIV era epidemiological studies**
  - sSA: Mothers predominantly HBeAg negative
  - Lower risk of perinatal transmission: lower HBV replication
- No birth dose and no catch-up programmes
- **Overall HBsAg seroprevalence declining from 12.8% to 3% in some studies**

HIV impacts Maternal HBV Transmission

HIV/HBV co-infection increases risk of perinatal transmission

- Maternal HIV infection increases mother-to-child transmission up to 2.5-fold

  - HIV/HBV co-infected mothers are more likely to be HBeAg positive
  - HBV increases risk of HBeAg seroversion
  - HIV promotes Hepatitis B replication
  - Higher HBV DNA levels

HIV impacts Maternal HBV Transmission

Reduced seroprotection in <2 yr old HIV positive vs. HIV negative children

Vaccine 2009;27(1):146-151

- 78.1% (57/73) v. 85.7% (197/230) anti-HBsAb-positive (titre ≥10 mIU/ml)
- 2.7% (2/73) v. 0.4% (1/230) HBsAg positive
- Equivalent anti-HB core Ab positivity of 3% and 2.7%

HIV reduces transfer of maternal anti-HBs

(JAMA 2011;305(6):576)

- 21% HIV exposed v. 54% unexposed babies had protective anti-HBs
- 79% babies born to HIV-positive mothers have no protective anti-HBs until after the first hepatitis B vaccination at 6 weeks

HIV impacts Maternal HBV Transmission

Western Cape, South Africa *(9355 pregnant women from antenatal clinics comparing HIV-positive and negative women)*

Vaccine 2013;31(47):5579

- HBsAg 3.4% (53/1 543) v. 2.9% (44/1 546)
- HBeAg 18.9% (10/53) v. 17.1% (7/41)
- HBV DNA levels were much higher in HIV positive vs. negative women viz. **9.72×10^7 IU/ml v. 1.19×10^6 IU/ml**
- **One in six HBV-infected pregnant women, irrespective of HIV status is HBeAg seropositive**
- Neonates remain unprotected for first 6 weeks of life without birth dose vaccine

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HIV impacts Maternal HBV Transmission

Kwazulu-Natal *(S Afr Med J 2014;104(4):307)*

- Retrospective analysis: 570 pregnant women who participated in an HIV sero-incidence study between March & December 2009
- Antenatal HIV prevalence 41.6% (215/570)
- Antenatal HBsAg prevalence 5.3% (30/570)
  - 7.4% in HIV pos v 4.8% HIV negative
  - 6 were HBeAg positive (20.0%), all HIV positive
- **Median HBV DNA load: 3.3 $\log_{10}$ (HIV pos) v 1.5 $\log_{10}$ (HIV negative)**

HIV impacts Maternal HBV Transmission

Kwazulu-Natal, South Africa (*African Journal of Laboratory Medicine 2016; 5(1):1-5)*

- Retrospective cross-sectional study: July 2011 to December 2011
- Samples from discarded residual dried blood spot samples following routine infant diagnosis of HIV

10% overall HBV sero-prevalence

- HIV-positive infants: 21/161 infants HBV positive :13.0%; 95% CI 6.8-19.9
- HIV-negative infants: 12/161 HBV positive: 7.5%; 95% CI 2.5-13.7

Concern

- High prevalence of HBV infection in children despite HBV vaccination
- Independent of HIV

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HIV impacts HBV vaccination

Kwazulu-Natal, South Africa

- September to December 2014
- Screened for HBsAg, anti-HBs, anti HBc
- 183 HIV infected vs. 108 HIV uninfected children between 5-15 years
- HBsAg positive in 2.1% vs. 0% in HIV + vs. HIV negative children

TABLE I. Serologic Markers of Past and/or Ongoing Infection in the HIV-Infected and Uninfected Cohorts

	HIV-infected			HIV-uninfected		
	5–10 years	11–15 years	Total	5–10 years	11–15 years	Total
Ongoing infection	0/103 (0%)	1/80 (1.3%)	1/183 (0.5%)	0/74 (0%)	0/34 (0%)	0/108 (0%)
Past infection	2/103 (1.9%)	1/80 (1.3%)	3/183 (1.6%)	0/74 (0%)	0/34 (0%)	0/108 (0%)

TABLE II. Comparison of the Immunity Against HBV in the HIV-Infected and Uninfected Cohorts According to the Age Subgroup of the Patients

	HIV-infected			HIV-uninfected		
	5–10 years	11–15 years	Total	5–10 years	11–15 years	Total
Presence of anti-HBs	21/103 (20.4%)	8/80 (10%)	29/183 (15.8%)	49/74 (66.2%)	17/34 (50%)	66/108 (61.1%)

Beghin et al. *J Med Virology* 2016, epub.

What is needed?

- Screening of pregnant women for HBsAg
- PMTCT
- Birth dose vaccination
- Post-vaccination testing for HBsAg and anti-HBs at 9-18 months of age
  - anti-HBs ≥10 mIU/ml are protected and need no further management
  - anti-HBs <10 mIU/ml : 2nd course of vaccination - at risk of household exposure

Treatment options for HIV/HBV

Drug	HBV	HIV
3TC / FTC	++	++
Tenofovir	+++	+++
Adefovir	++	?
Entecavir	+++	+
Telbivudine	+++	-/+
IFN / Peg-IFN	+++	+

HIV/HBV Co-infection : Treatment

- **All guidelines recommend TDF-containing ART as preferred regimen**
- **TDF and 3TC or TDF and FTC plus DTG**

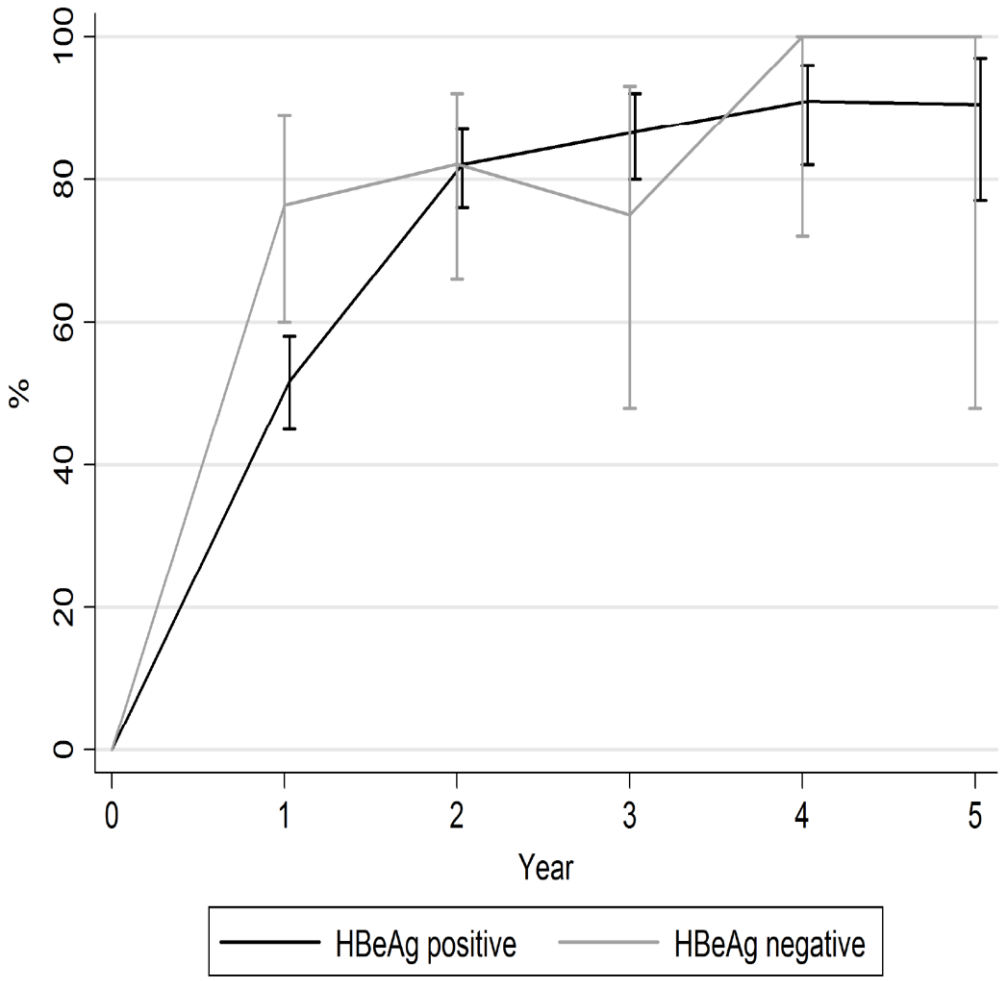
Renal impairment

- Adjust TDF dose according to eGFR

TDF contraindicated (e.g. HIV nephropathy)

- Consider **Entecavir** as part of ART regimen
  - ad on ETV, not used alone as has weak HIV antiviral activity
  - caution with 3TC resistance
- **If ARVs need to be changed because of HIV drug resistance/toxicity**
  - Tenofovir/3TC or Tenofovir/FTC should be continued together with new ARV drugs

13 years of Tenofovir (TDF)



Meta-analysis 23 studies 550 HIV-HBV patients on TDF

Increasing suppression over follow-up in majority

Little evidence of resistance

Price et al, PLOs One 2013

Incidence of cirrhosis in HIV-HBV on TDF-based HAART is low

- 508 Spanish HIV-hepatitis non-cirrhotic patients
- Two TEs 2.6 ± 1.0 yrs apart
- 54 (10.6%) developed cirrhosis
- 1/24 (4.2%) with HBV

Multivariable analysis for risk of developing cirrhosis adjusted for baseline factors including TE

	OR	*P*
HIV-HCV with SVR	1	
HIV-HCV	3.73	0.04
HIV-HBV	0.69	0.81

Protective effect of HBV-active ART against primary HBV-infection?

- **Does HBV-active ART protect against new HBV infection (HBV-PrEP)?**

- All HBV-susceptible patients at entry, anti-HBc and anti-HBs negative (<10 IU/L)
- 2nd sample available in time for follow-up HBV serology
- n=2,924 - MSM n=2,280
- HBV susceptible & 2 samples available n=349

New HBV Cases (N=35)

- 1 case: woman (HBsAg negative)
- 1 case: heterosexual man (HBsAg negative)
- 33 cases MSM

Hepatitis (ALT 2x)	7 (20.0%)
HBsAg +	6 (17.1%)
HBeAg +	6 (17.1%)

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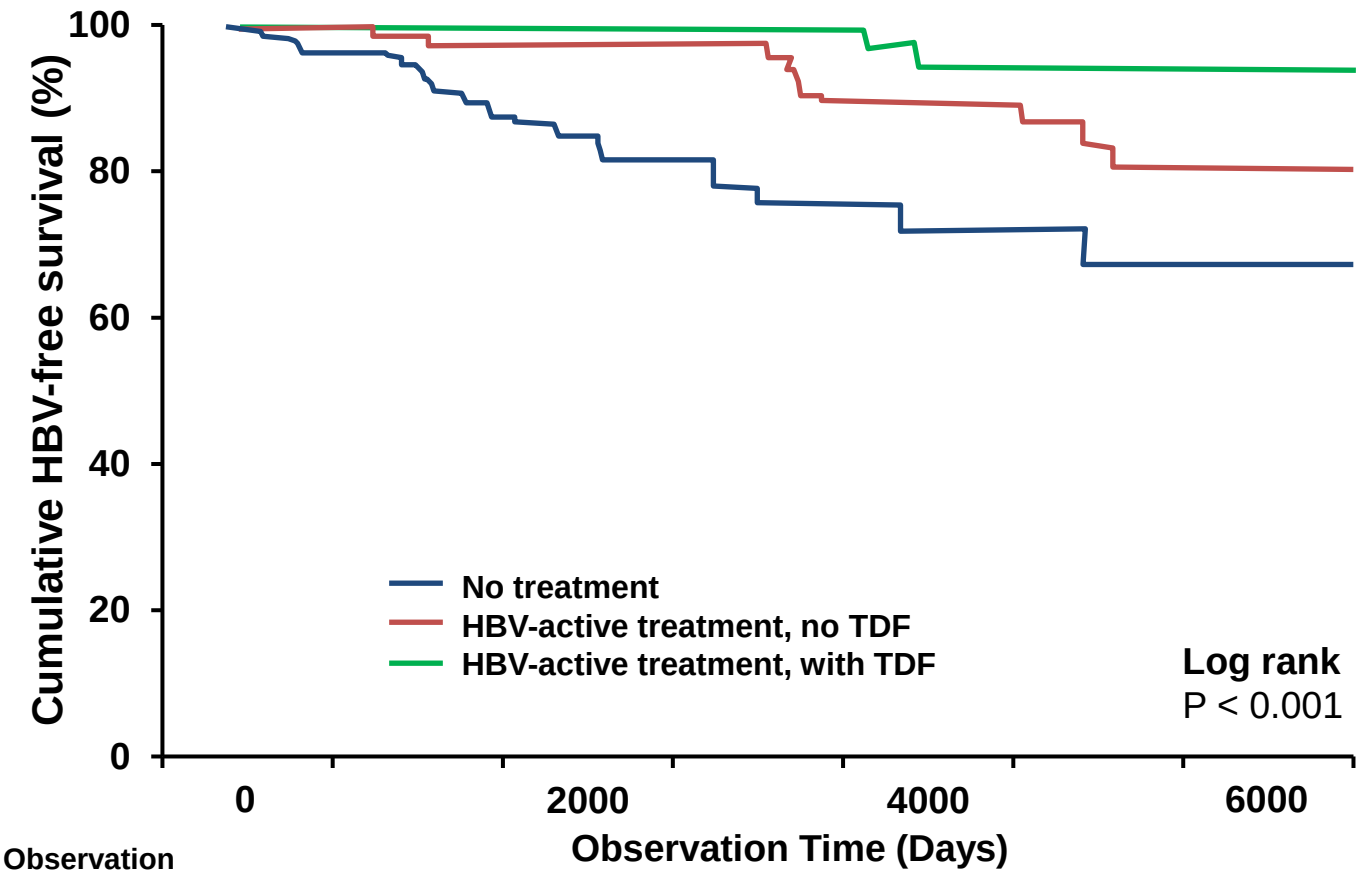
Brinkman K, et al. 20th CROI; 2013

Kaplan Meier: HBV-free survival (MSM)



Numbers in Observation

No Treatment	107	50	19	8
Treatment, No TDF	86	67	36	16
Treatment, with TDF	189	49	38	12

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Brinkman K, et al. 20th CROI; Atlanta, GA; 2013

HIV-HBV co-infection

- Remains a global challenge
- *Prevention is key* – screening, vaccination, PMTCT
- Universal birth dose vaccination a major IMPERATIVE
- Effective therapy (TDF/FTC or 3TC) as part of ART is highly efficacious
- Challenge remains access (cf. HBV mono-infection) and diagnostics(especially RDTs)

Acknowledgements

NDoH appreciates the support towards this training session by:

- World Health Organisation – SA Office
- Prof Mark Sonderup, Prof Wendy Spearman
- UNSW, Kirby Institute
- National Viral Hepatitis TWG
- NDoH TB/HIV and Viral Hepatitis Unit

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