HBV/HIV Co-infection in sub-Saharan Africa

CWN Spearman

Division of Hepatology
Department of Medicine
Groote Schuur Hospital &
University of Cape Town

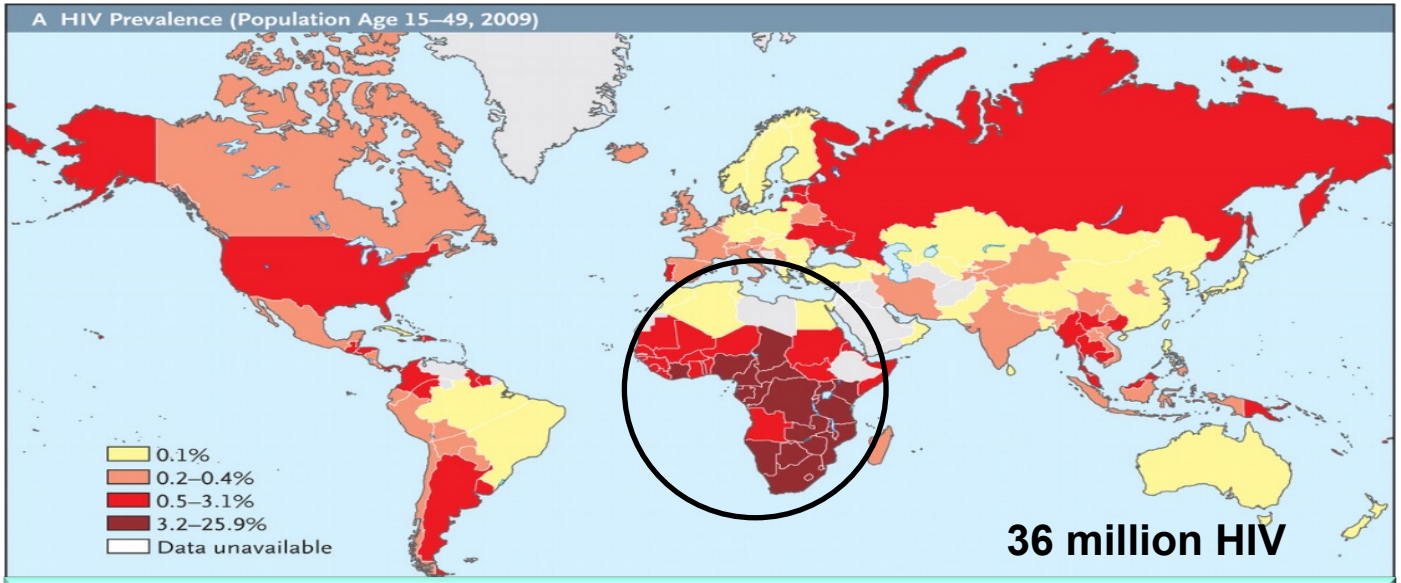
DIVISION OF HEPATOLOGY AND LIVER LABORATORY

HIV/HBV Co-infection

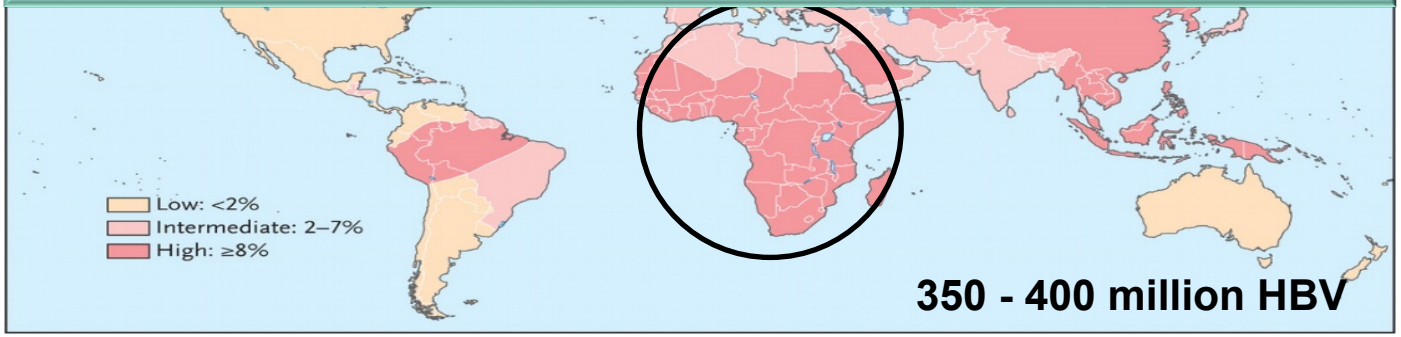
Outline of Talk

- Epidemiology of HIV and HBV
- Impact of HIV/HBV Co-infection
  - HIV on HBV
  - HBV on HIV
- Management of HIV/HBV Co-infection
- Guidelines for initiation of HAART

Global HIV and HBV Prevalence



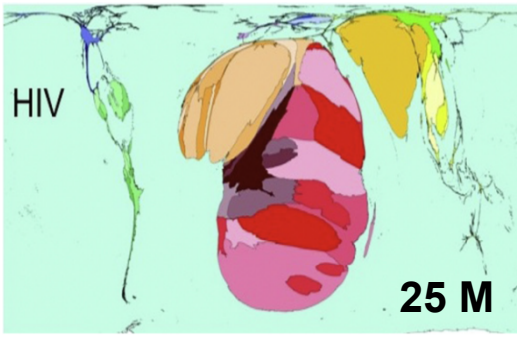
- **Globally, up to 10% of HIV-infected individuals have HBV co-infection**
  - 4-6 million HIV/HBV co-infected individuals
- **HBV endemic countries up to 25% HIV/HBV co-infected**

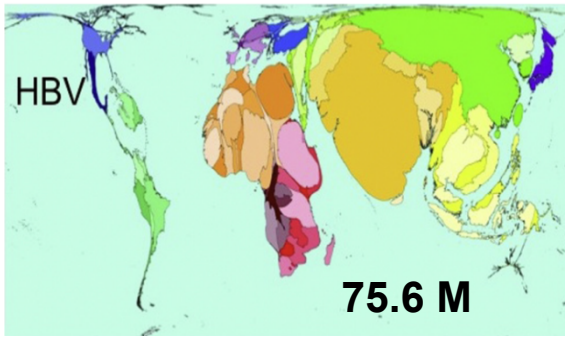


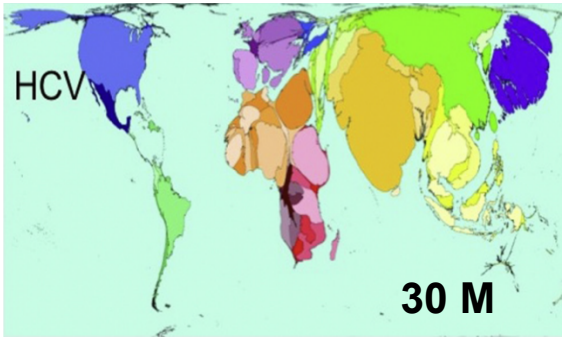
Kourtis et al. N Engl J Med 2012;366:1749

Epidemiology of HIV/HBV: sub-Saharan Africa

- **70% of global 36 million people with HIV live in sSA**
  - **Corresponding to regions of high HBV endemicity: 8.83% seroprevalence**







HIV/HBV/HCV Mortality (annual death rate) (www.worldmapper.org in Nov 2012)

- **HIV/HBV co-infections tend to outnumber HIV/HCV co-infections**
  - Chronic HBV co-infection reported in up to 36% of all HIV-positive subjects
  - Highest rates in West and Southern African cohorts
  - Reflects present low prevalence of IDU in sSA
- **Liver-related mortality 2x higher in HBV/HIV than HCV/HIV co-infection**

Clinical Infectious Diseases 2012; 55(4):507; J Clin Virol 2014;61:20

Epidemiology of HIV/HBV: sub-Saharan Africa

Independent transmission and acquisition of HBV and HIV

- HBV generally acquired in childhood under age of 5 years
  - Prior to HIV acquisition
- HIV infection occurs later in life, primarily via sexual route

Series from West, East and South Africa

- Chronic HBV infection over-represented in HIV patients suggesting:
  - Shared risk factors
  - Co-transmission events

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

Epidemiology of HIV/HBV: sub-Saharan Africa

Shared transmission routes : HBV and HIV

- **HIV and HBV may share transmission routes in infants and children**
  - Mother-to-child transmission
  - Lack of resources for diagnosis and management of blood-borne viruses in pregnancy and peri-partum period
- Maternal HIV infection increases mother-to-child transmission of HBV (2.5 fold in one West African study) → HIV promoting HBV replication
- **Blood/blood product transfusions**
  - PEPFAR, Global fund & WHO blood safety programmes
    - HBsAg screening increased from 76 to 94%
    - Laboratory processes frequently not accredited, variable
- **Unsafe injection/medical and traditional scarification practices**
- **Sexual co-acquisition**

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

Impact of HIV/HBV Co-infection

HIV co-infection promotes

increased HBV replication and rates of HBV reactivation

- Increased MTCT of HBV
- More aggressive natural history of chronic hepatitis B

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

HIV impacts Maternal HBV Transmission

HIV/HBV co-infection increases risk of perinatal transmission

- **Maternal HIV infection increases HBV MTCT up to 2.5 fold**
  - HIV/HBV co-infected mothers are 2x more likely to be HBeAg positive
    - HBV increases risk of HBeAg seroversion
  - 3x more likely to be HBV DNA positive
  - Higher HBV DNA levels
- **Essential to screen mothers for HIV and HBsAg to prevent MTCT**
  - Antiviral prophylaxis - 2 agents against HBV
  - Hepatitis B Birth dose vaccine and full HBV vaccine coverage
- **HBV vaccination schedules in sSA: Majority**
  - 6, 10 and 14 weeks : Most mothers HBeAg negative, low HBV DNA levels
  - No Hepatitis B Birth dose vaccine
  - Full HBV vaccine coverage only 75%

SA : Impact of HIV : Maternal Transmission

Western Cape, RSA *(9 355 pregnant women from antenatal clinics comparing HIV-positive and negative women)* *Vaccine 2013;31(47):5579*

- **Low HBsAg prevalence region in RSA**
  - HBsAg 3.4% (53/1 543 HIV pos) v. 2.9% (44/1 546 HIV neg)
- **HBeAg: 18.9%** (10/53 HIV pos) v. **17.1%** (7/41 HIV neg)
- **HBV DNA levels were much higher in HIV positive women**
  - **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 in absence of Hepatitis B birth dose vaccine

HBV MTCT increases if HBV DNA >200 000 IU/ml

SA : Impact of HIV : Maternal Transmission

KwaZulu-Natal, RSA *(African Journal of Laboratory Medicine 2016; 5(1):1-5)*

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

10% overall HBV seroprevalence in infants <18 months

- **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
- Difference not statistically significant

Concern

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

HIV impacts on 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 bet 5-15 years
- **HBsAg positive** in **2.1% vs. 0%** in HIV + vs. HIV negative children
- **anti-HBs response to immunization: 15.8% (HIV+) vs 61.1% (HIV-)**

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%)

HIV-infected children remain at risk of HBV infection

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.

Impact of HIV/HBV Co-infection

HIV co-infection promotes a more aggressive natural history of hepatitis B infection

- ALF in acute HBV
- Increased rates of occult HBV
- *Chronicity of newly acquired HBV infections: 3-6x*
- *Progression to fibrosis and cirrhosis: 5x faster*
- *HCC: occurs at a younger age and is more aggressive*
- Increased risk of ART hepatotoxicity
- HAART- related immune reconstitution hepatitis

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

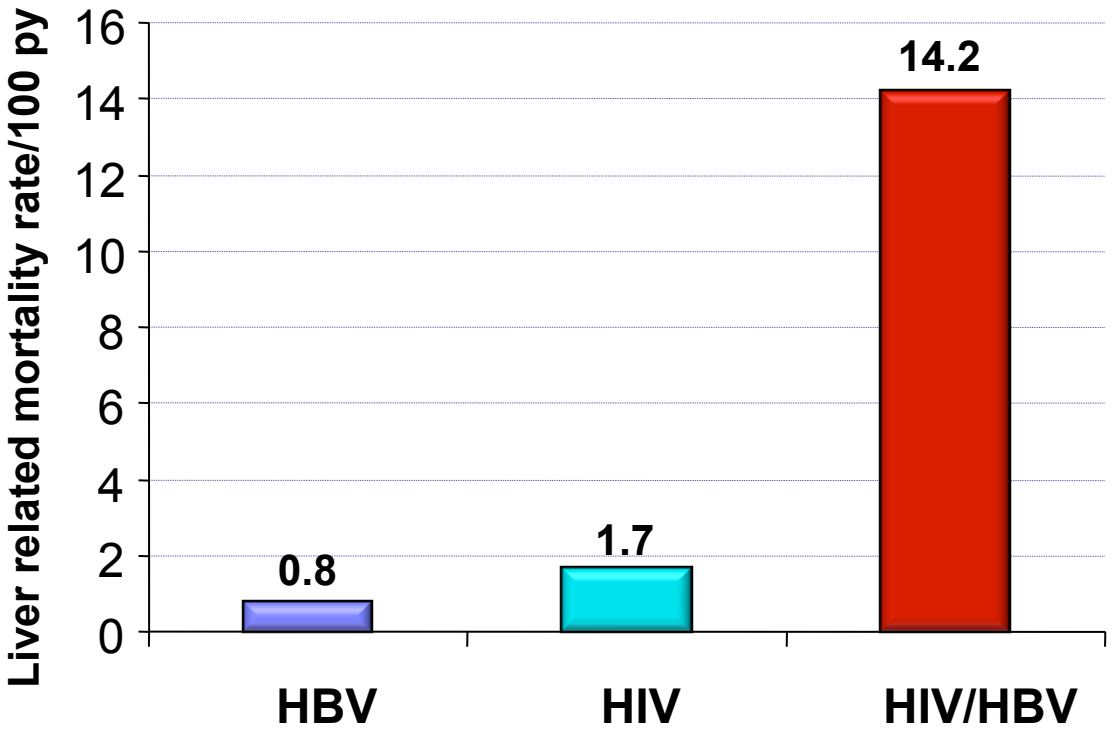
MACS: Mortality of HIV/HBV co-infection: pre-ART era

5293 MSM

- HBV: 326 (6%)
- **HIV/HBV: 213 (65%)**
- HIV: 2346/4967 (47%)

HIV/HBV

- **17-fold higher risk of liver death compared to HBV alone**

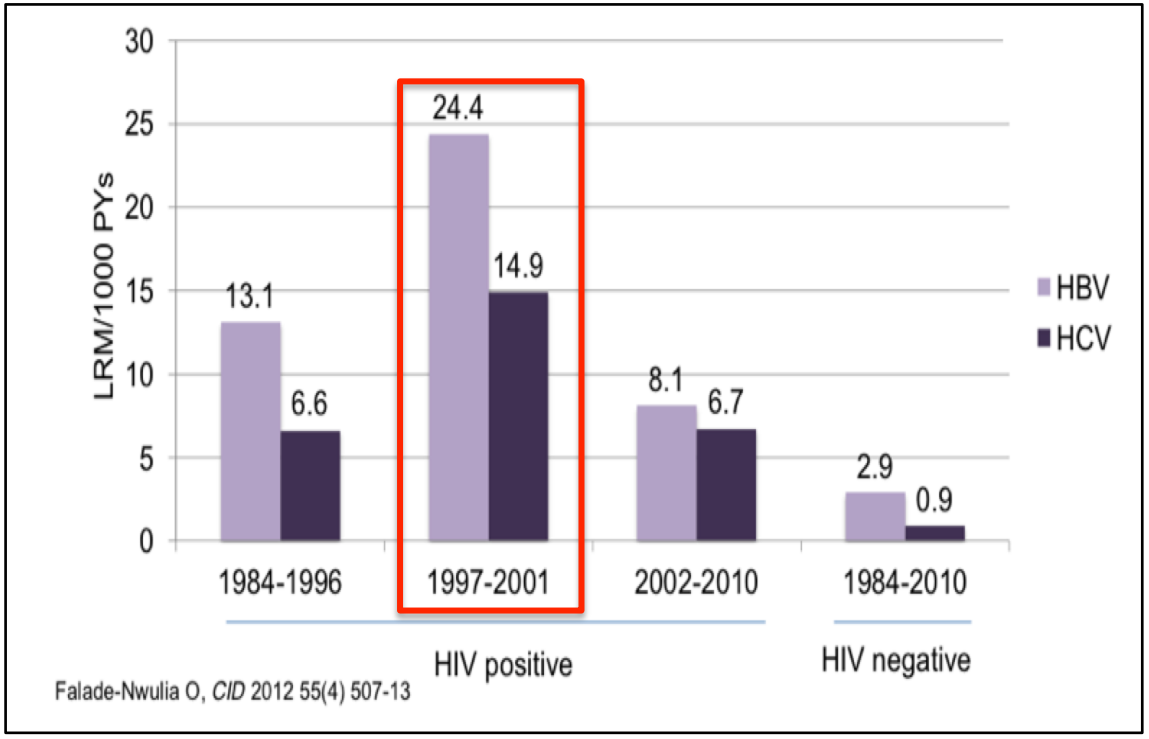


Thio CL, et al. Lancet 2002;360(9349):1921–6

MACS: Liver-related Mortality is higher from chronic HBV than from HCV

337 men with CH-B and 343 men with CH-C at study entry into MACS

- All-cause MR similar
- **Liver-related MR** significantly higher in **CH-B (9.6 per 1000 PYs**; 95% CI, 6.9-13.2) compared to **CH-C (5.0 per 1000 PYs**; 95% CI, 3.0–8.4)
  - **Incidence rate ratio: 2.2; *P* = .03**



CD4 count <200 cells/mm^3

- **16.2 fold increase in risk of liver-related death** compared to CD4 count >350 cells/mm^3

Liver disease remains 2nd leading cause of death in later HAART era in HIV-infected people

D:A:D study : 33,308 participants from 1999-2008

- 15.3% with HCV (Ab or RNA+)
- 11.5% HBV (prior/active HBV infection)

2482 deaths

- **29.9% (743) AIDS-related: 4.12/1000 PY**
- **13.7% (341) Liver-related: 1.89/1000 PY**
- 11.6% (289) CVD-related: 1.6/1000 PY
- 11.5 % (286) Non-AIDS malignancy: 1.59/1000 PY

Overall mortality declined over time

- 16.9/1000 PY (1999-2000) to 9.6/1000 PY (2007-2008)
- **Diabetes Mellitus: Risk factor for all specific causes of death**
- **CD4 counts <100 cells /ml associated with higher risk of death from all specific causes of death**

AIDS 2010;24: 1537

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

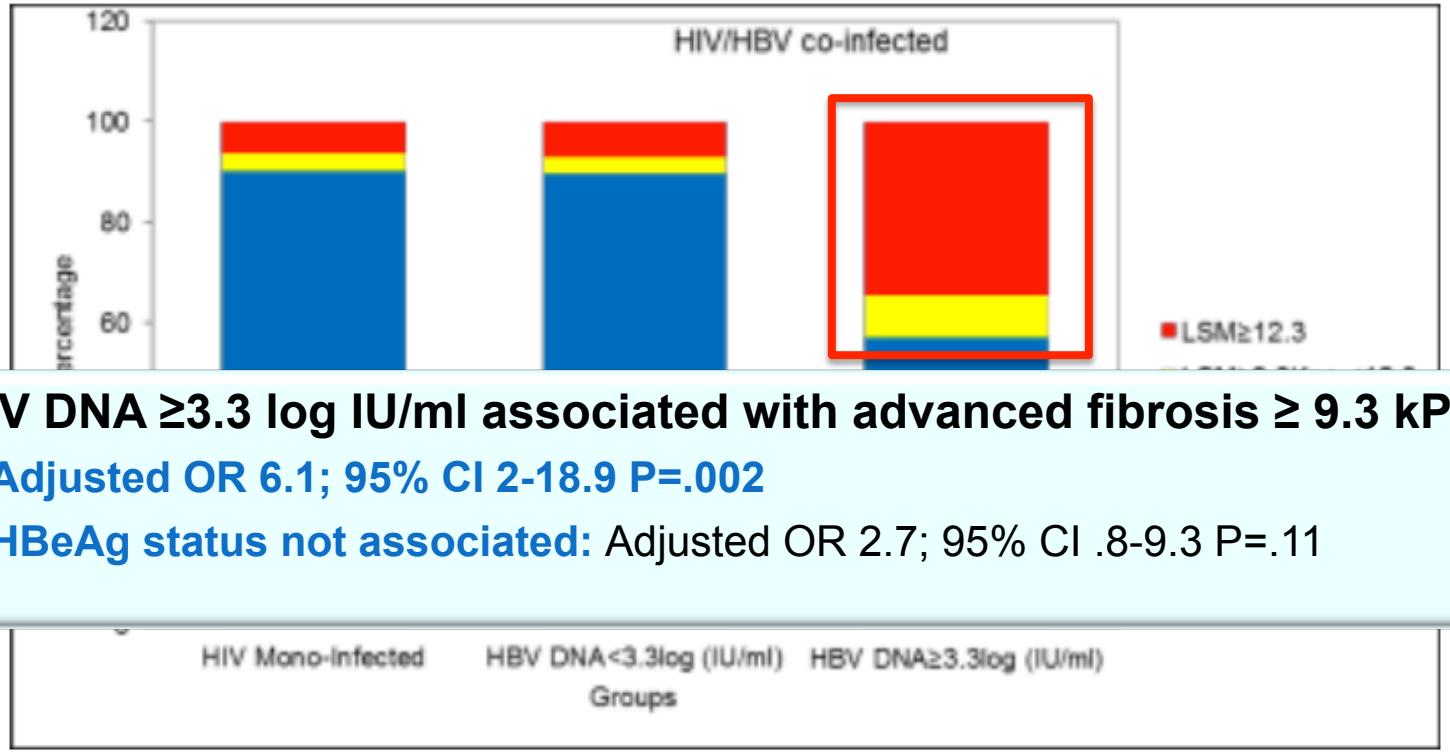
Liver-related deaths declined over time

- 2.67/1000 PY (1999-2000) to 1.45/1000 PY (2007-2008)
  - **8.30/1000 PY for those with latest CD4 count <50 cells/ml**
  - **0.58/1000 PY if CD4 count >500 cells/ml**

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
Hypertension	2.34	1.83-2.99
Diabetes Mellitus	2.37	1.68-3.35
HBV	**2.37**	**1.74-3.22**
HCV	1.67	1.21-2.31
CD4 count per 50 cell/uL increase	0.82	0.79-0.85
HIV RNA >5 log copies/ml	1.68	1.01-2.80

Liver fibrosis advanced in HIV-HBV co-infection with higher HBV DNA in Nigeria

- Cross sectional study of 232 HIV+ and 93 HIV-HBV patients in Nigeria
- Transient elastography prior to HAART



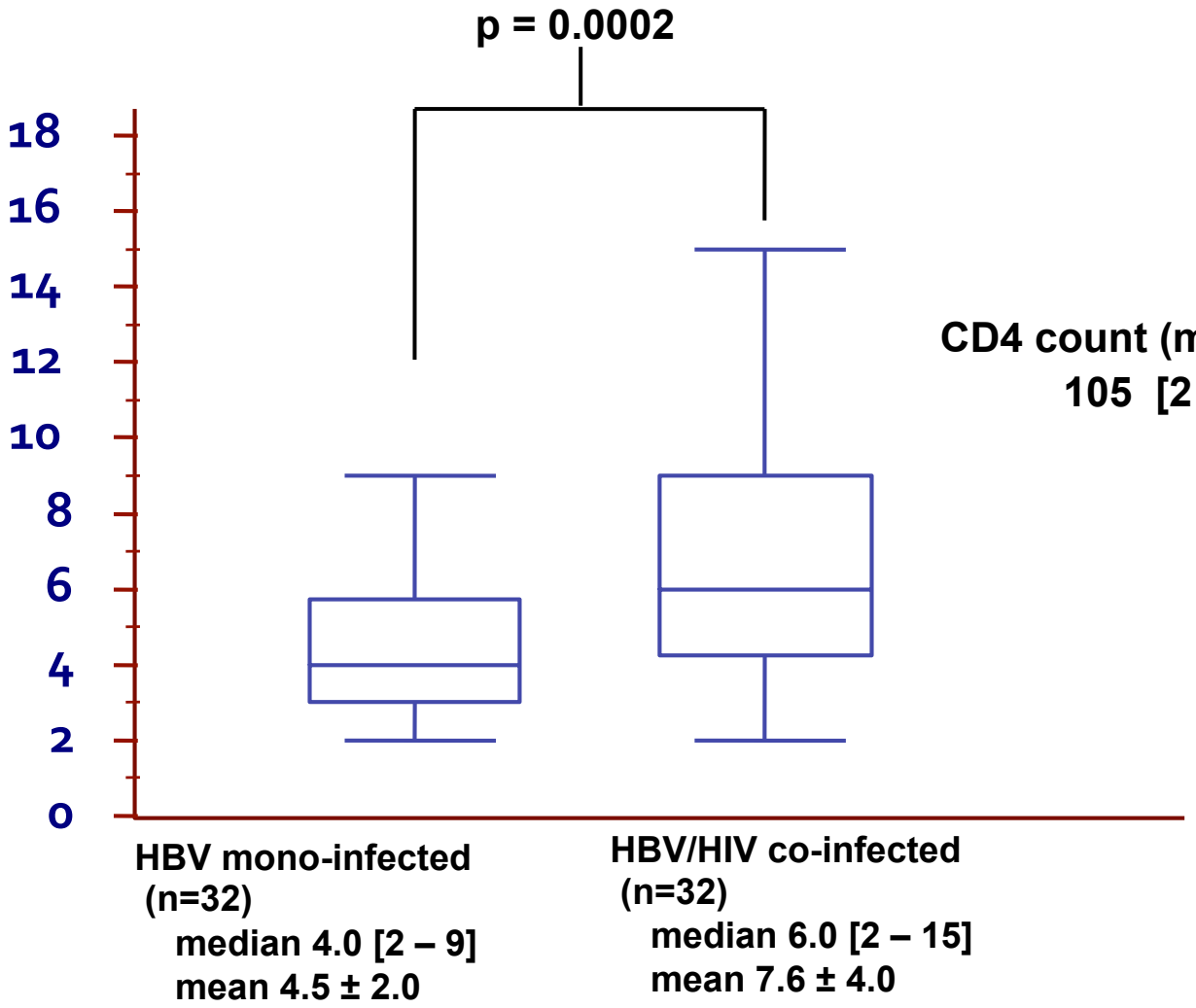
HBV DNA ≥3.3 log IU/ml associated with advanced fibrosis ≥ 9.3 kPa

- **Adjusted OR 6.1; 95% CI 2-18.9 P=.002**
- **HBeAg status not associated:** Adjusted OR 2.7; 95% CI .8-9.3 P=.11

Hawkins et al, *CID* 2013 57(12): e189-92

Impact of HIV/HBV Co-infection
Modified Histological Activity Index (Ishak)

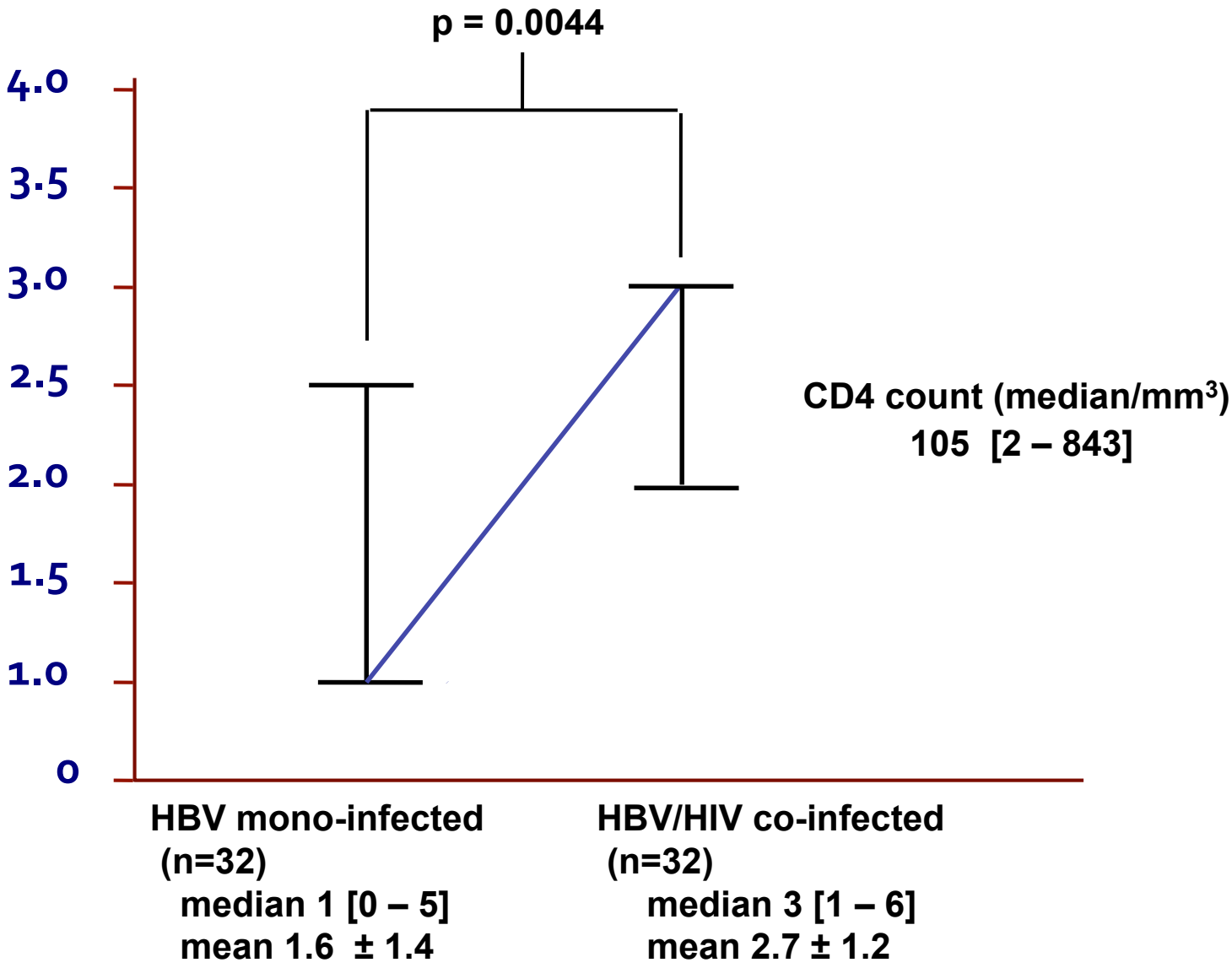
Necro-inflammatory activity (n=64, ART naive)



Sonderup et al Hepatology November 2008

Impact of HIV/HBV Co-infection

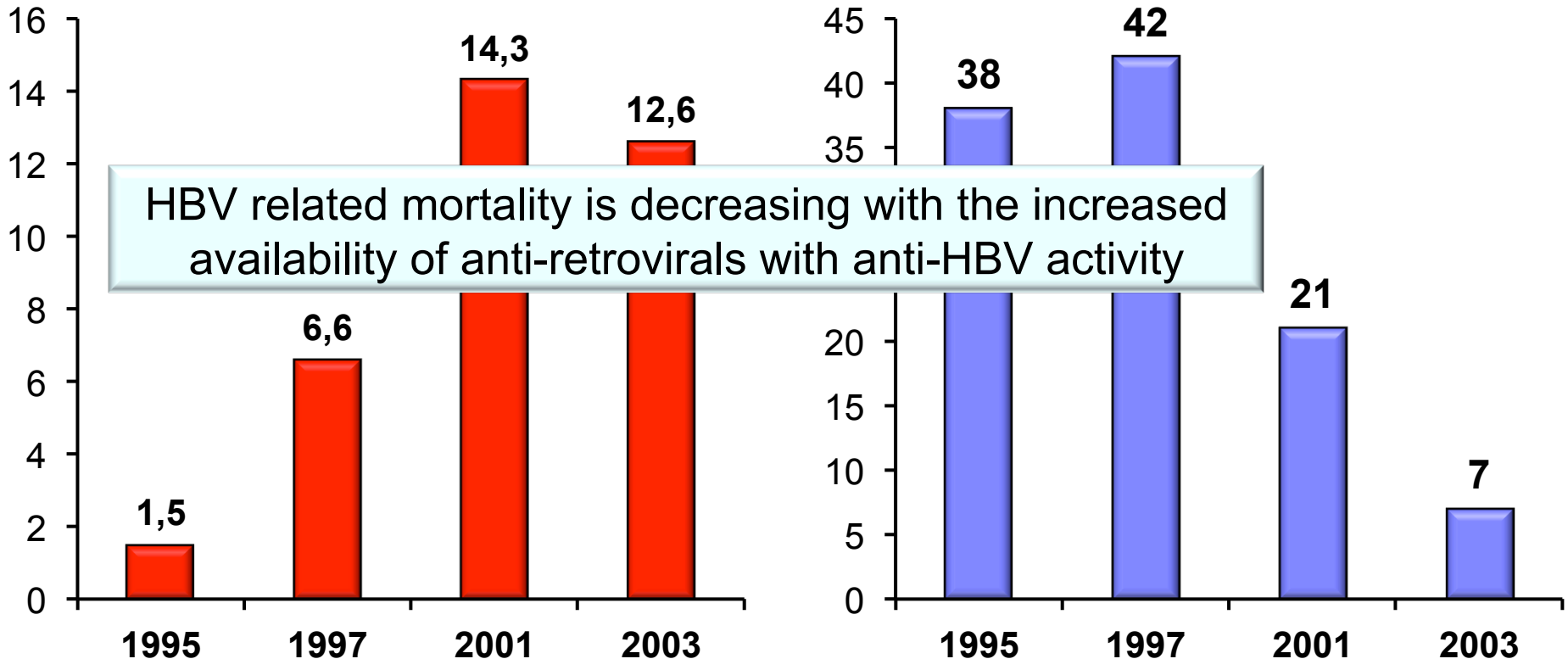
Fibrosis (n=64, ART naive)



Sonderup et al Hepatology November 2008

Liver disease associated mortality in HIV 1995–2003 GERMIVIC

- **ESLD associated death: % total mortality**
- **ESLD associated death: % HBsAg +**



HBV related mortality is decreasing with the increased availability of anti-retrovirals with anti-HBV activity

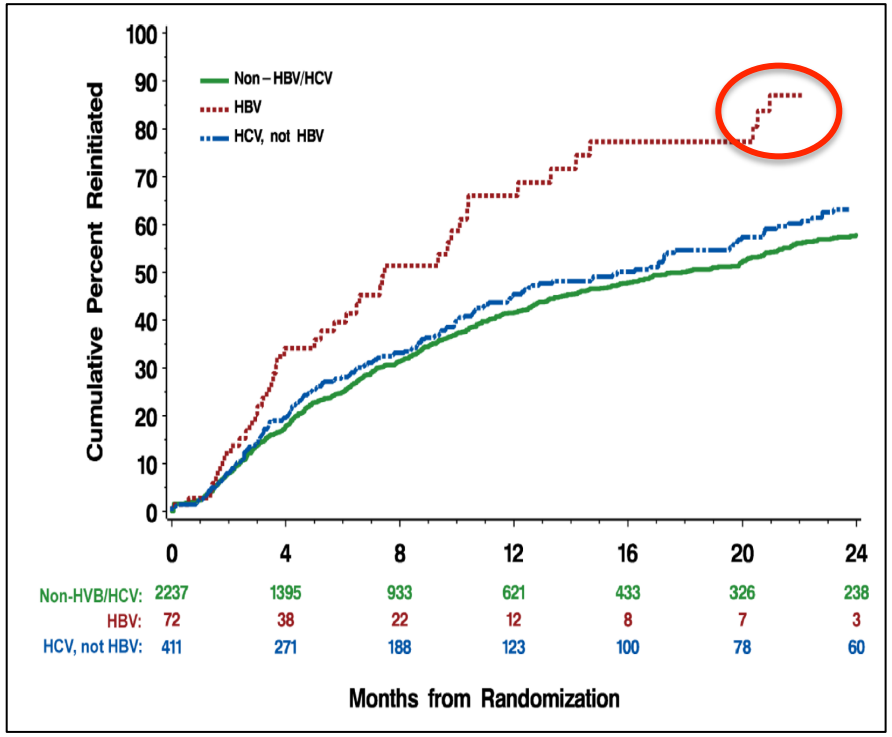
Rosenthal E, et al. J Viral Hepat 2007;14:183–8

Impact of HBV on HIV : SMART Study

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

- HIV pos individuals with CD4 count >350 cells/μL randomised to drug conservation (interrupt ART until CD4 <250 cells/μL) vs viral suppression (continued use of ART)
- 120 HIV/HBV co-infected individuals

Frequent HBV DNA rebound following ART interruption with accelerated immune def



Dore et al, AIDS 2010;24:857

Multivariate Model: Predictors of ART re-initiation

	Univariate		Multivariate	
	Hazard ratio	P-value	Hazard ratio	P-value
Non-HBV/HCV	1.00		1.00	
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

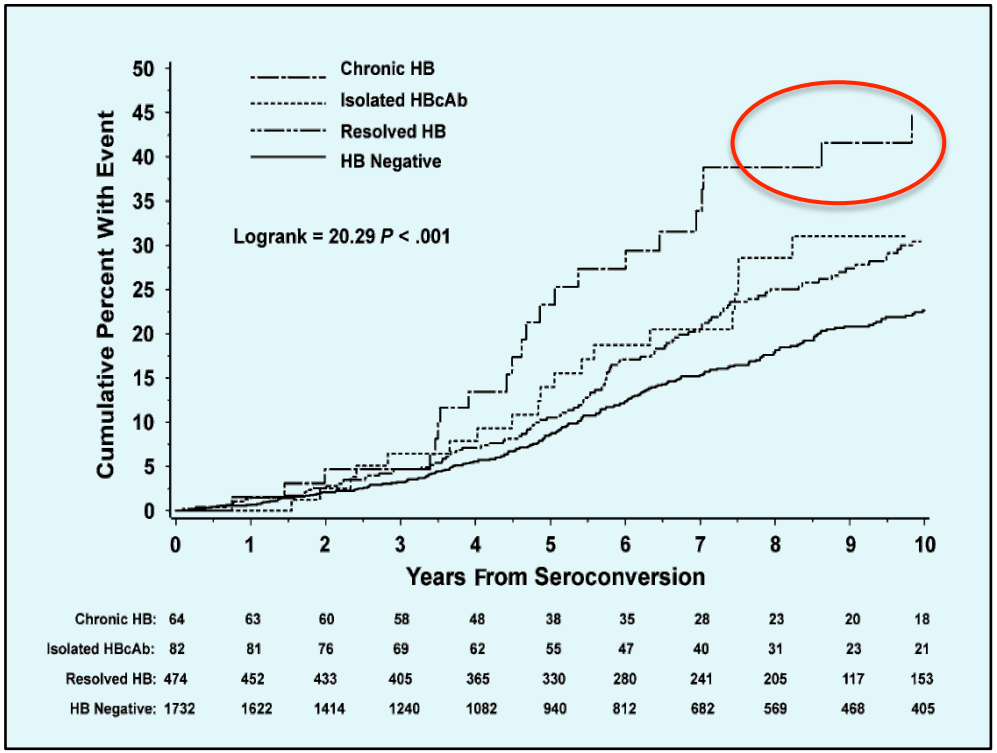
Impact of HBV on HIV

2352 HIV seroconverters

- Resolved HB: 474 (20%); Isolated total HBcAb: 82 (3%) and Chronic HB: 64 (3%)

Unadjusted rates (95% confidence intervals [CIs]) of clinical AIDS/death

- HB-negative : 2.43 (2.15–2.71)
- Resolved HB: 3.27 (2.71–3.84)
- Isolated HBcAb: 3.75 (2.25–5.25)
- **Chronic HB: 5.41 (3.41–7.42)**



Multivariable risk of clinical AIDS/death significantly higher in chronic HB group compared to HB-negative group

- **HR 1.80; 95% CI, 1.20–2.69)**

HRs were increased but non-significant

- **Resolved HB** (HR 1.17; 95% CI 94-1.46)
- **Isolated HBcAb** (HR 1.14; 95% CI .75–1.75).

Chun et al, JID 2010;205: 185

Management of HIV/HBV Co-infection

HBV screening and Vaccination

- All newly diagnosed HIV infected individuals screened for HBV
  - HBsAg and anti-HBs
- Non-immune (HBsAg and anti-HBs negative) - Vaccinate
- Lower response to vaccination especially with low CD4 counts
- ***Meta-analysis*** *(Int J STD AIDS 2013;24(2);117):* **4 double dose (40ug) vaccine schedule gives higher protective anti-HBs:** 0, 1, 2 & 6 months

Hepatitis A Vaccination

- Should be considered in all HIV positive patients esp MSM

Screen for Hepatitis C

- Triple HIV/HBV/HCV : DAA interaction with ART

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013

Management of HIV/HBV Co-infection

Aetiology of abnormal liver profile : often multifactorial

- Drug-induced liver injuries
  - HAART, TB drugs, Cotrimoxazole, Fluconazole, Traditional meds, Herbal/Alternative supplements

More aggressive natural history of HBV and possibility of co-morbidities

Lower threshold for performing liver biopsy to assess

Differential diagnosis and the stage and grade of histologic injury

Fibroscan & APRI: Assessment of progressive fibrosis

- Reactivation after withdrawal of therapy
- Super-infection with HCV, HAV, HDV and HEV
- Co-morbidities - Non-alcoholic fatty liver disease, alcoholic liver disease

Initiation of HAART in HBV/HIV co-infection

Goals of therapy

- Virological suppression of both HBV and HIV replication
- Reduce both AIDS and Liver-related morbidity and mortality

Choice of ARV regimen in HBV/HIV co-infected patients

- HAART regimen containing 2 agents that are also active against HBV
  - Reduces the risk of resistance

WHO recommendation

- Tenofovir + lamivudine/emtricitabine + efavirenz as FDC

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2016

WHO 2016 HIV Treatment Initiation Guidelines

Treat all people with HIV regardless of CD4 cell count

It is essential to initiate treatment in the following clinical situations

- All HBV/HIV co-infected adults with a CD4 cell count <500 cells/mm^3 regardless of the stage of liver disease
- Individuals with severe chronic liver disease regardless of CD4 count
  - At greatest risk of disease progression and mortality from liver disease
  - HAART initiation may improve overall survival in cirrhotics
- All pregnant or breastfeeding women regardless of CD4 count
- All children less than 5 years of age regardless of CD4 count

3TC Naive → **ART including TDF and 3TC or FTC**

3TC Experienced → **Add or substitute one NRTI & continue TDF as part of ART**

WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. 2016

HIV/HBV Co-infection : Treatment Options

- **Treatment of HIV without the use of tenofovir in the regimen**
  - May lead to flares of hepatitis B due to ART-associated IRIS
- **Treatment discontinuation, especially lamivudine, associated with**
  - HBV reactivation, ALT flares and hepatic decompensation
- **If ARVs need to be changed because of HIV drug resistance/toxicity**
  - Tenofovir and Lamivudine or Tenofovir/Emtricitabine should be continued together with the new ARV drugs
  - ***? Tenofovir Alafenamide (TAF) in renal toxicity***

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013

HIV/HBV Co-infection : Treatment Monitoring

Monitoring on FDC

- Recommended annual renal function assessment
- Consider annual assessment of bone function
- **Consider risk of EFV DILI presenting post-partum in women with high CD4 count**
  - Immunoallergic hepatocellular injury ➔ submassive necrosis and deaths

HIV/HBV Co-infection : Treatment

Fixed drug combination (Tenofovir, Lamivudine/Emtricitabine and EFV)

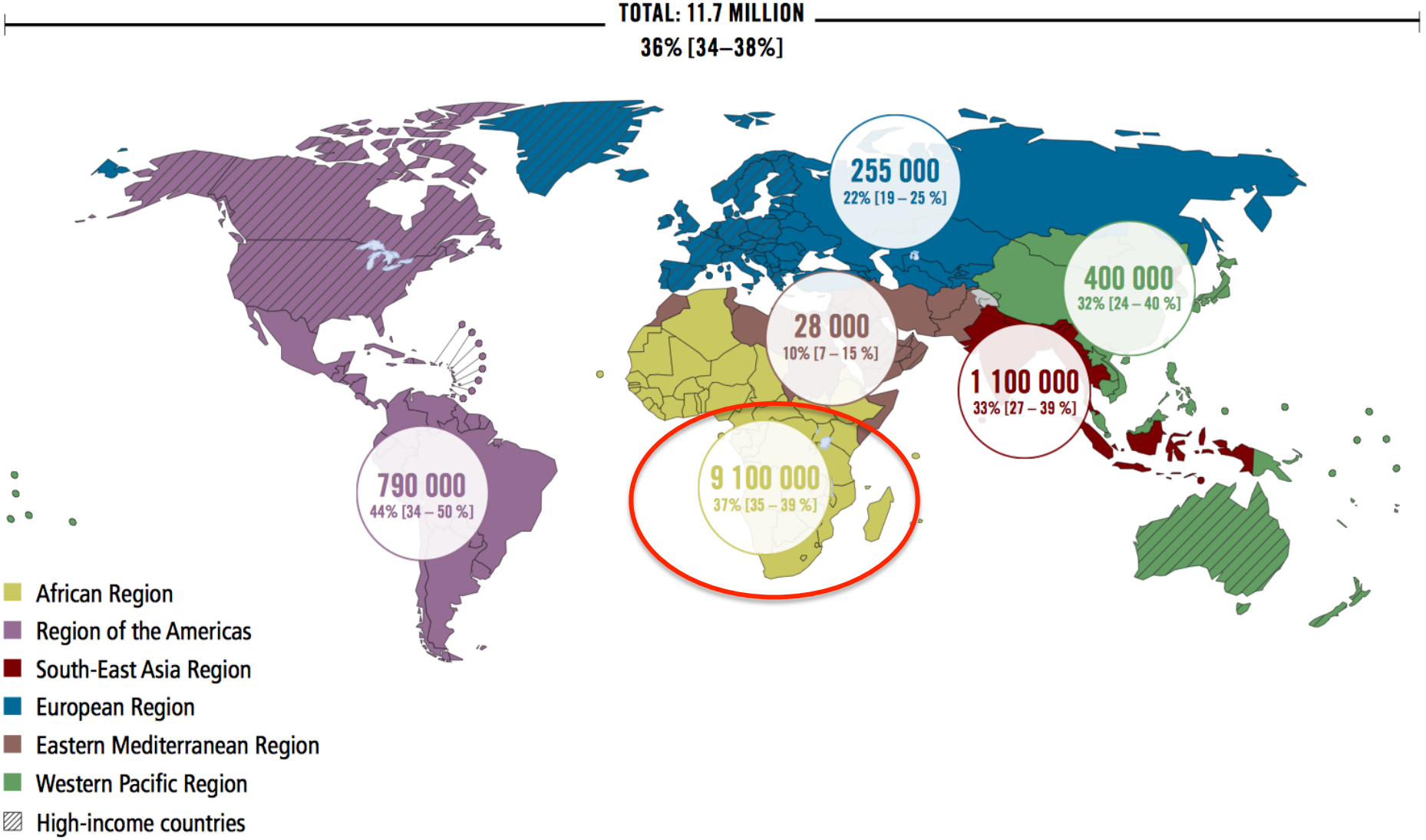
HBeAg-positive patients after 5 years of treatment: High rates of:

- HBV DNA suppression (90%)
- HBeAg loss (46%)
- HBsAg loss (12%)
- No evidence of resistance
- Reduced progression to cirrhosis
- Risk of HCC persists, but is low - ongoing surveillance required

No significant difference in response rates compared with HBV mono-infection

Gastro 2010;139(6):1934; AIDS 2013;27(14):2219

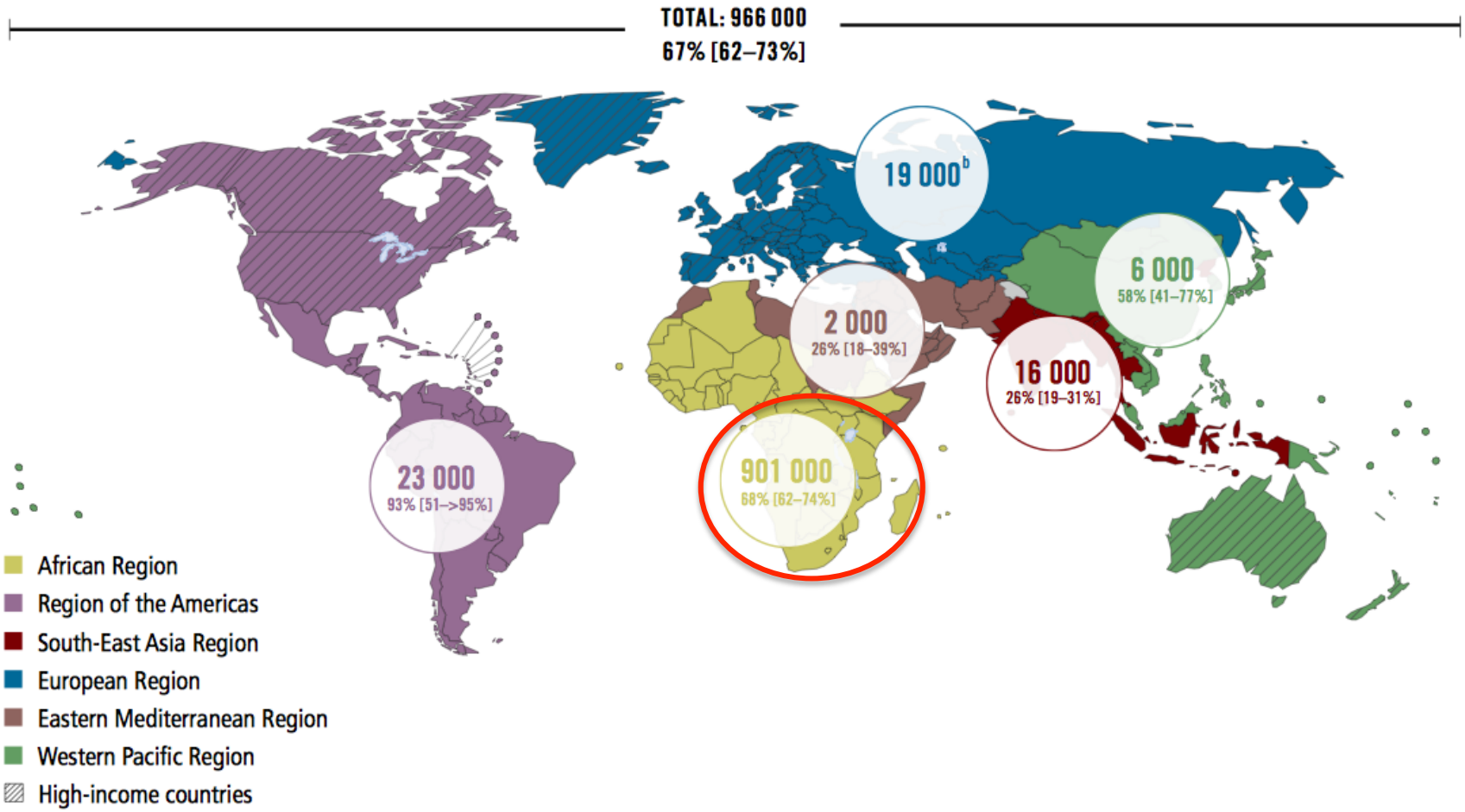
Number of people receiving ART and percentage of all people living with HIV receiving ART in low- and middle-income countries overall and by WHO region, 2013[a]



[a]Country income classification by the World Bank at the time of the 2011 Political Declaration on HIV and AIDS.

Source: Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS) and 2013 UNAIDS/WHO estimates.

Fig. 3.3. Number and percentage of pregnant women living with HIV who received ARV drugs in low- and middle-income countries globally and by WHO region, 2013[a]



[a] Country income classification by the World Bank at the time of the 2011 Political Declaration on HIV and AIDS.
[b] Coverage estimates for the WHO European region are not available due to inconsistencies between programme coverage and estimated PMTCT need.

Sources: Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS) and 2013 UNAIDS/WHO estimates.

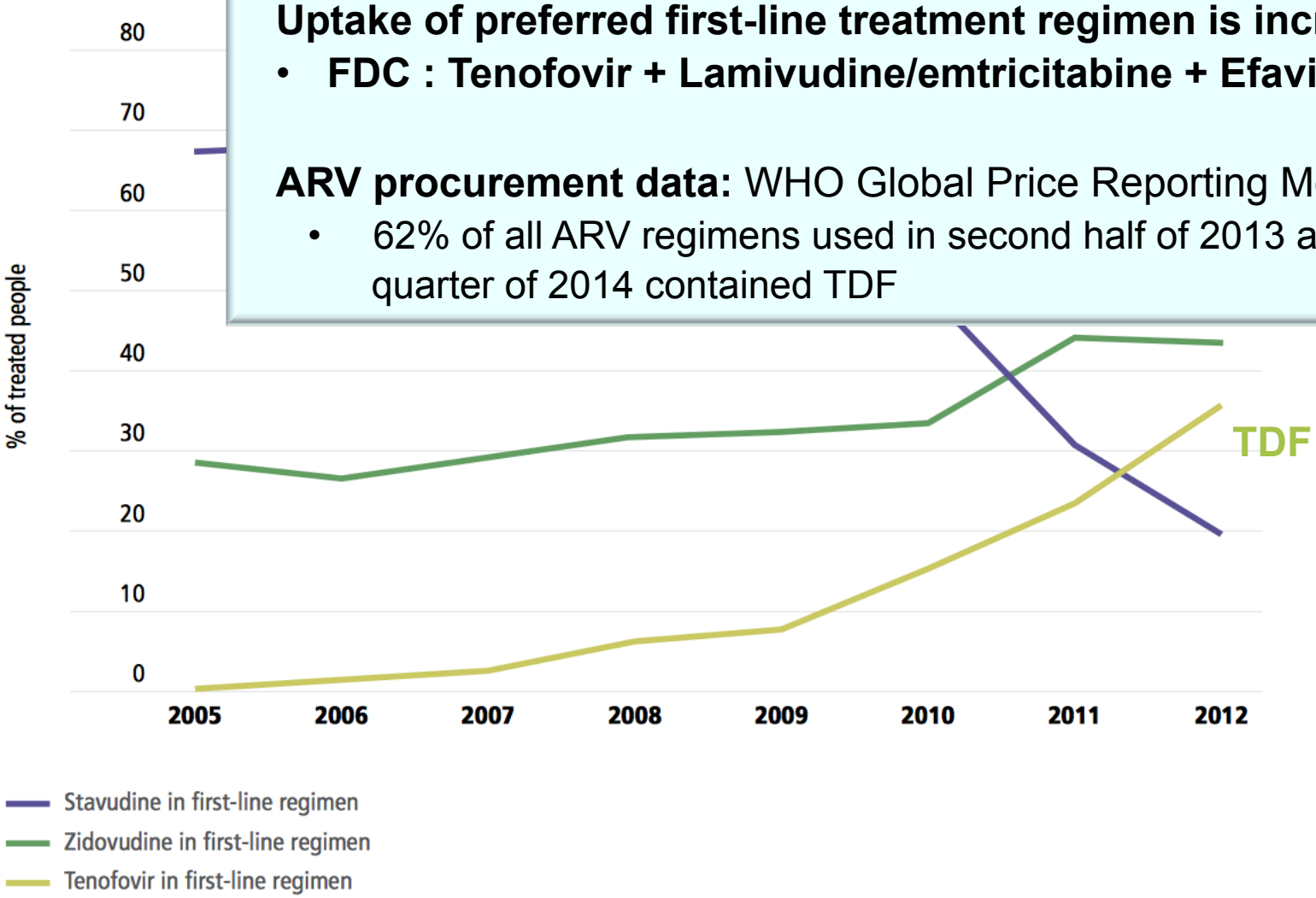
Fig. 5.11. Evolution of d4T, AZT and TDF in first-line antiretroviral therapy among adults and adolescents, 2005 to end-2012

Uptake of preferred first-line treatment regimen is increasing:

- **FDC : Tenofovir + Lamivudine/emtricitabine + Efavirenz**

ARV procurement data: WHO Global Price Reporting Mechanism

- 62% of all ARV regimens used in second half of 2013 and first quarter of 2014 contained TDF



Source: results of WHO ARV surveys from 2005 to 2013.

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 neg (<10 IU/L)
- 2nd sample available in time for follow-up HBV serology
- **n= 2,924 and MSM: n=2,280**
- HBV susceptible & 2 samples available n=349

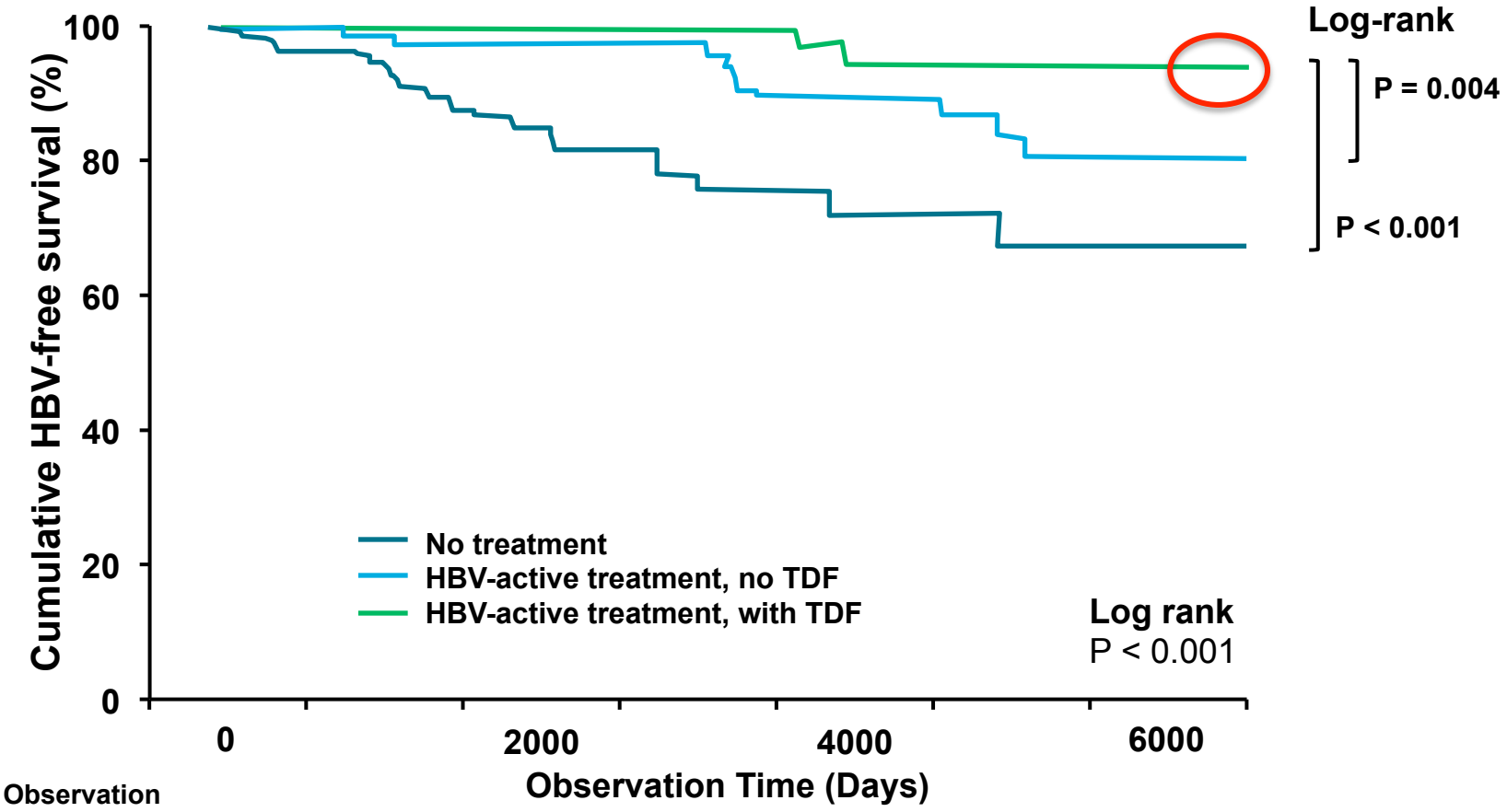
New HBV Cases (N=35)

- 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%)

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

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

Conclusions : HIV/HBV Co-infection

- **sSA is the epicentre of HIV and HBV is endemic**
  - Increased risk of HIV/HBV co-infection
- HIV promotes HBV MTCT and promotes a more aggressive natural history of chronic hepatitis B
- **WHO recommended FDC (Tenofovir, Lamivudine/Emtricitabine & EFV)**
  - Simplifies management of HIV/HBV co-infection regardless of immunological, virological or histological considerations
  - **Improves All-cause and Liver-related mortality in HBV/HIV co-infection**
- Second line ART for HIV resistance
  - Continue Tenofovir, Lamivudine/Emtricitabine to prevent HBV reactivation, ALT flares and potential hepatic decompensation
- **HAART improves overall survival even in cirrhotics**

HBV IS VACCINE PREVENTABLE