# HBV/HIV Co-infection in sub-Saharan Africa

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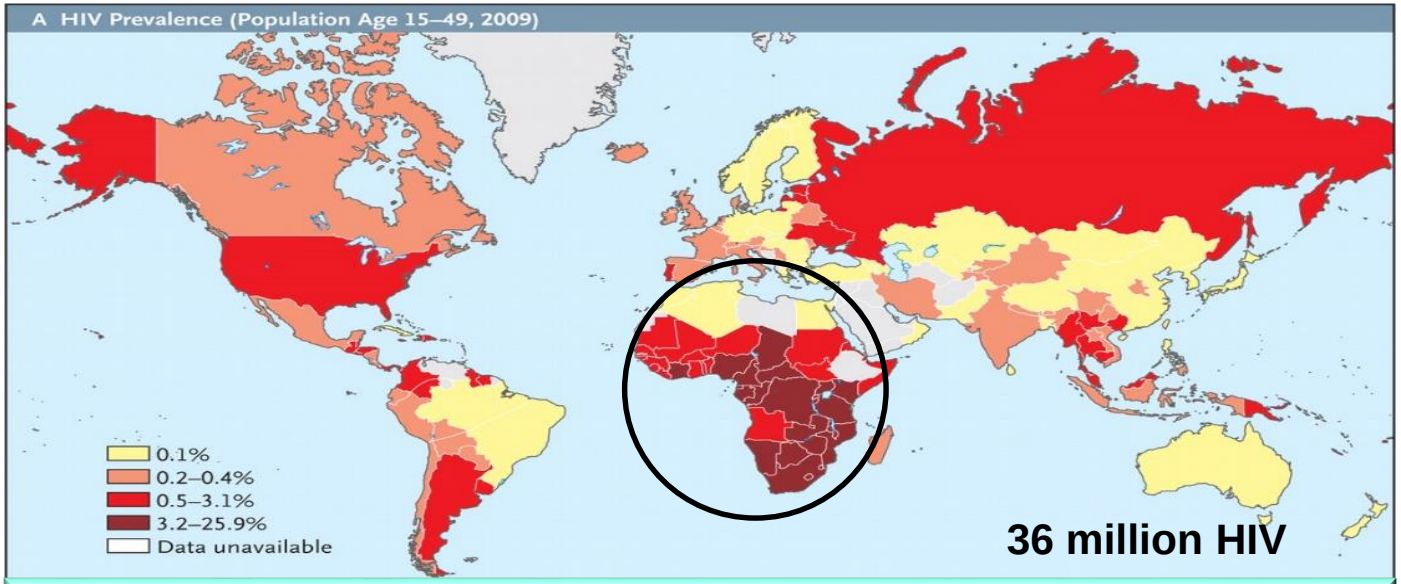
# HIV/HBV Co-infection

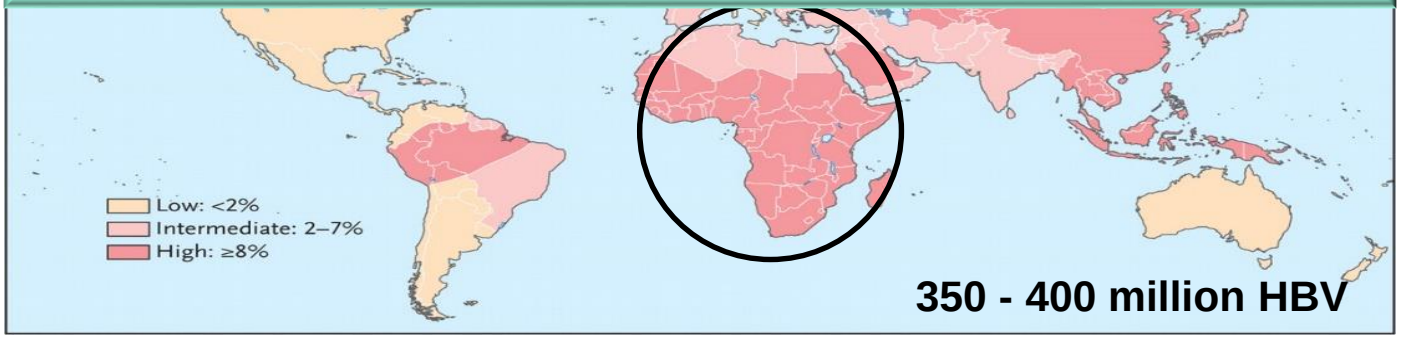
## Outline of Talk

- 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



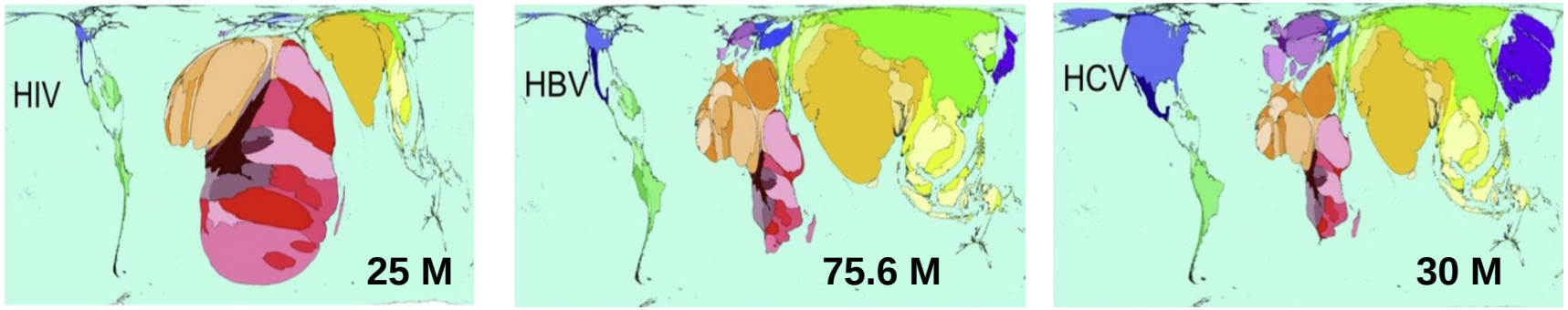

- **Globally, up to 10% of HIV-infected individuals have HBV co-infection**
  - 4-6 million HIV/HBV co-infected individuals
- **HBV endemic countries up to 25% HIV/HBV co-infected**




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**
  - **$9.72 \times 10^7$ IU/ml v. $1.19 \times 10^6$ 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

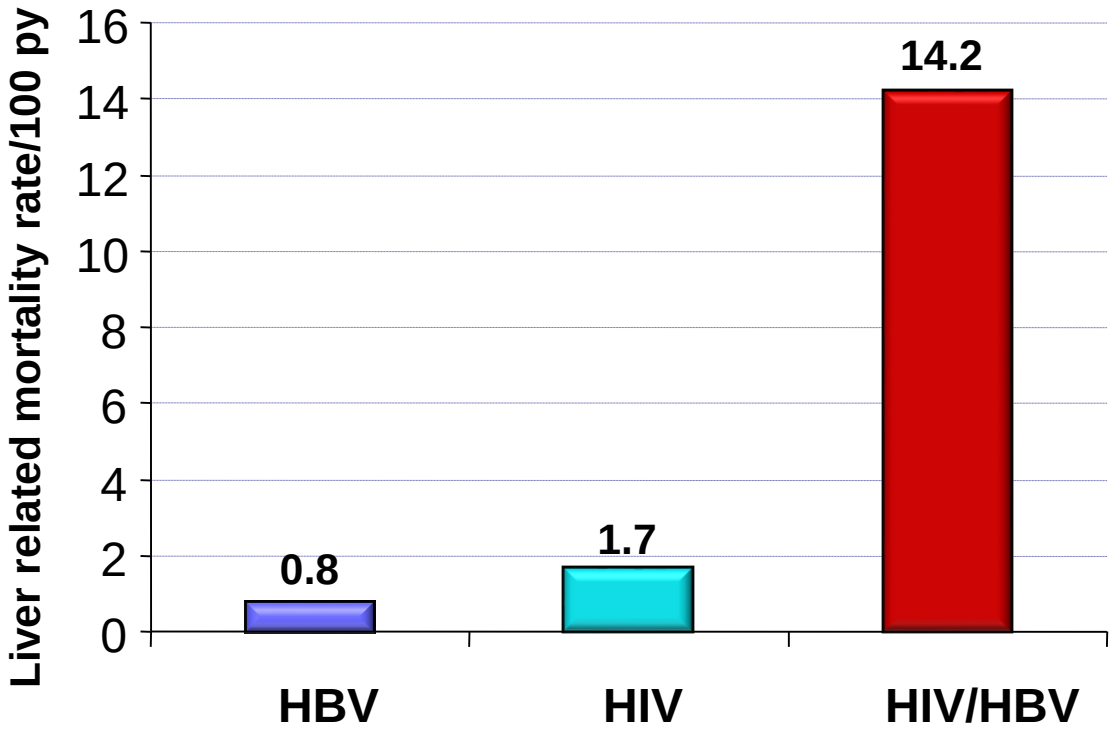
# MACS: Mortality of HIV/HBV co-infection: pre-ART era

## 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**

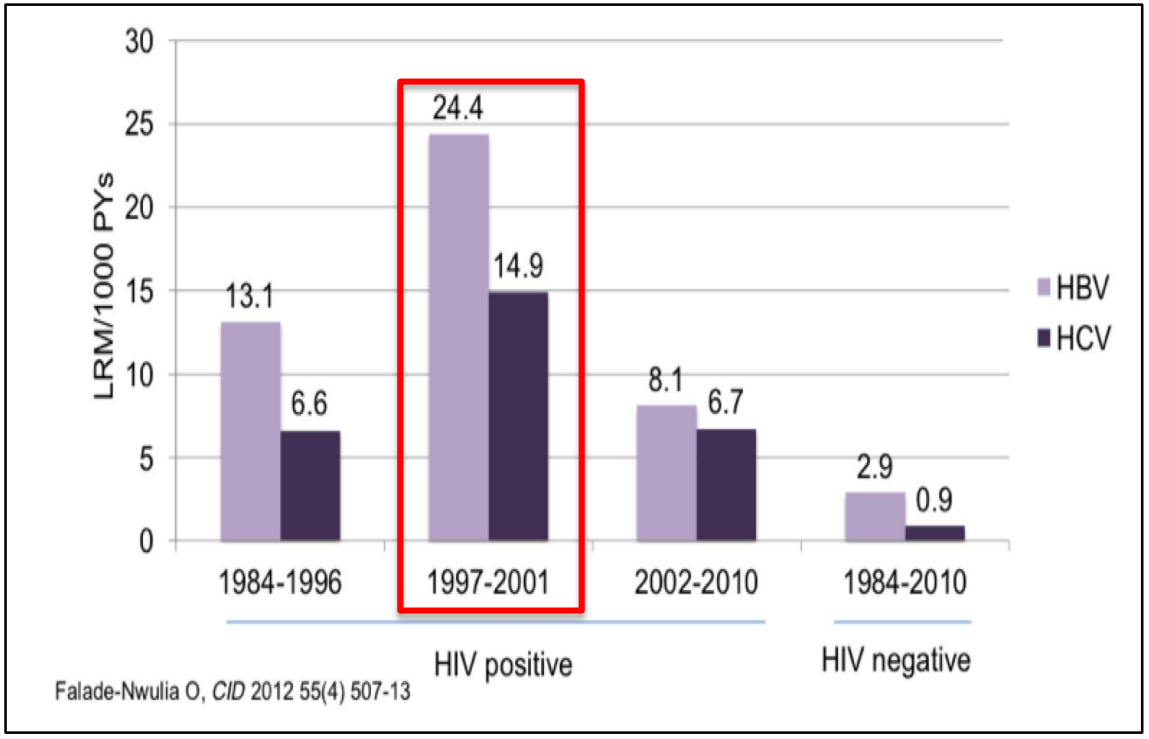



Thio CL, et al. Lancet 2002;360(9349):1921–6

# 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

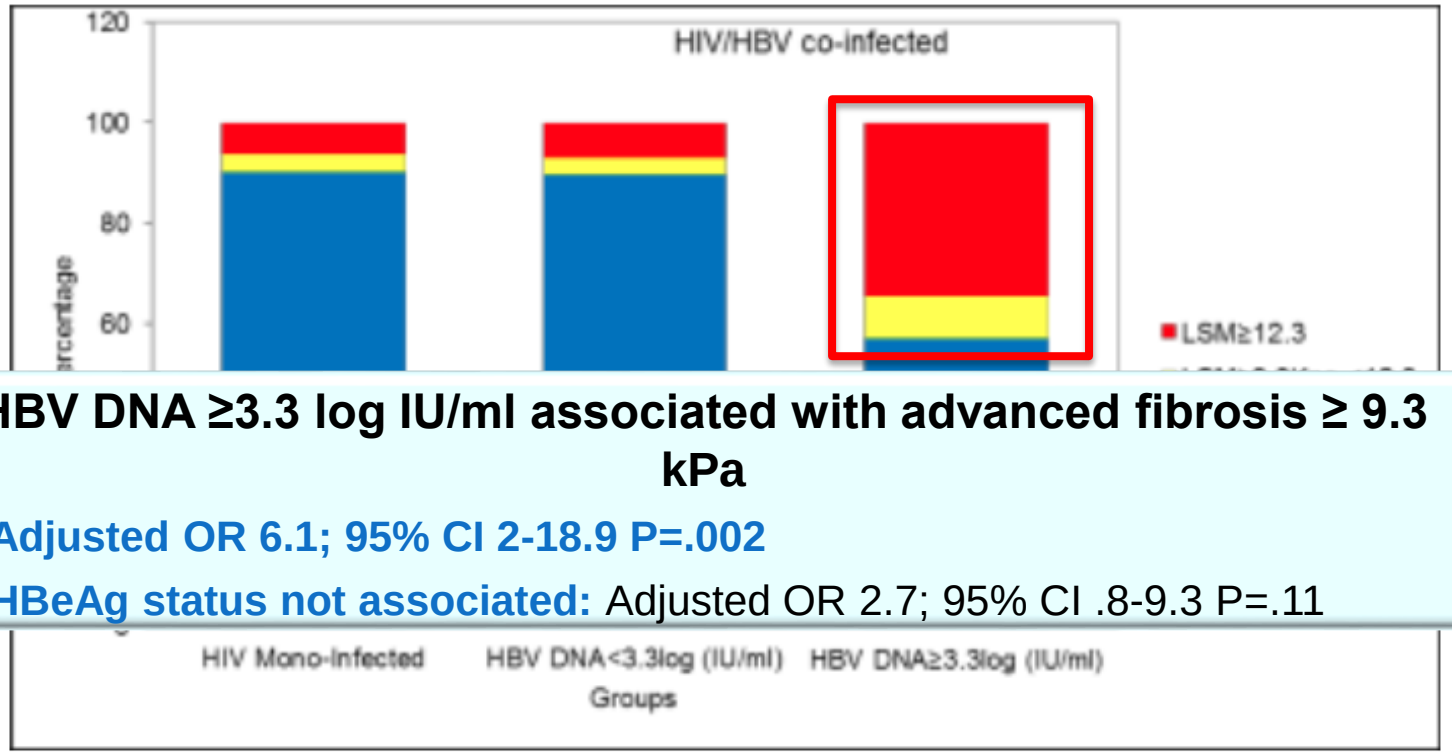
## Liver-related deaths declined over time

- 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



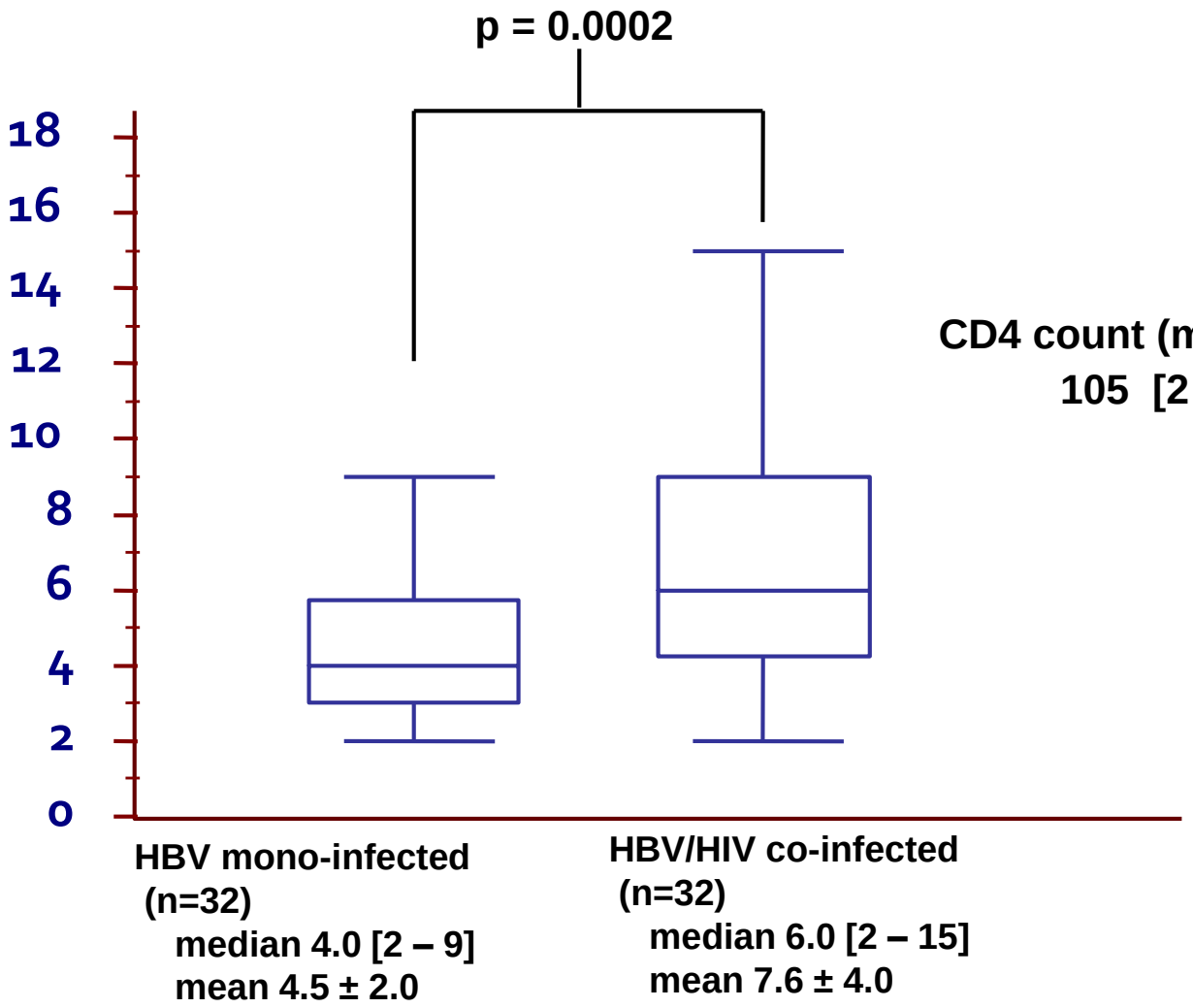

**HBV DNA ≥3.3 log IU/ml associated with advanced fibrosis ≥ 9.3 kPa**

- **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)

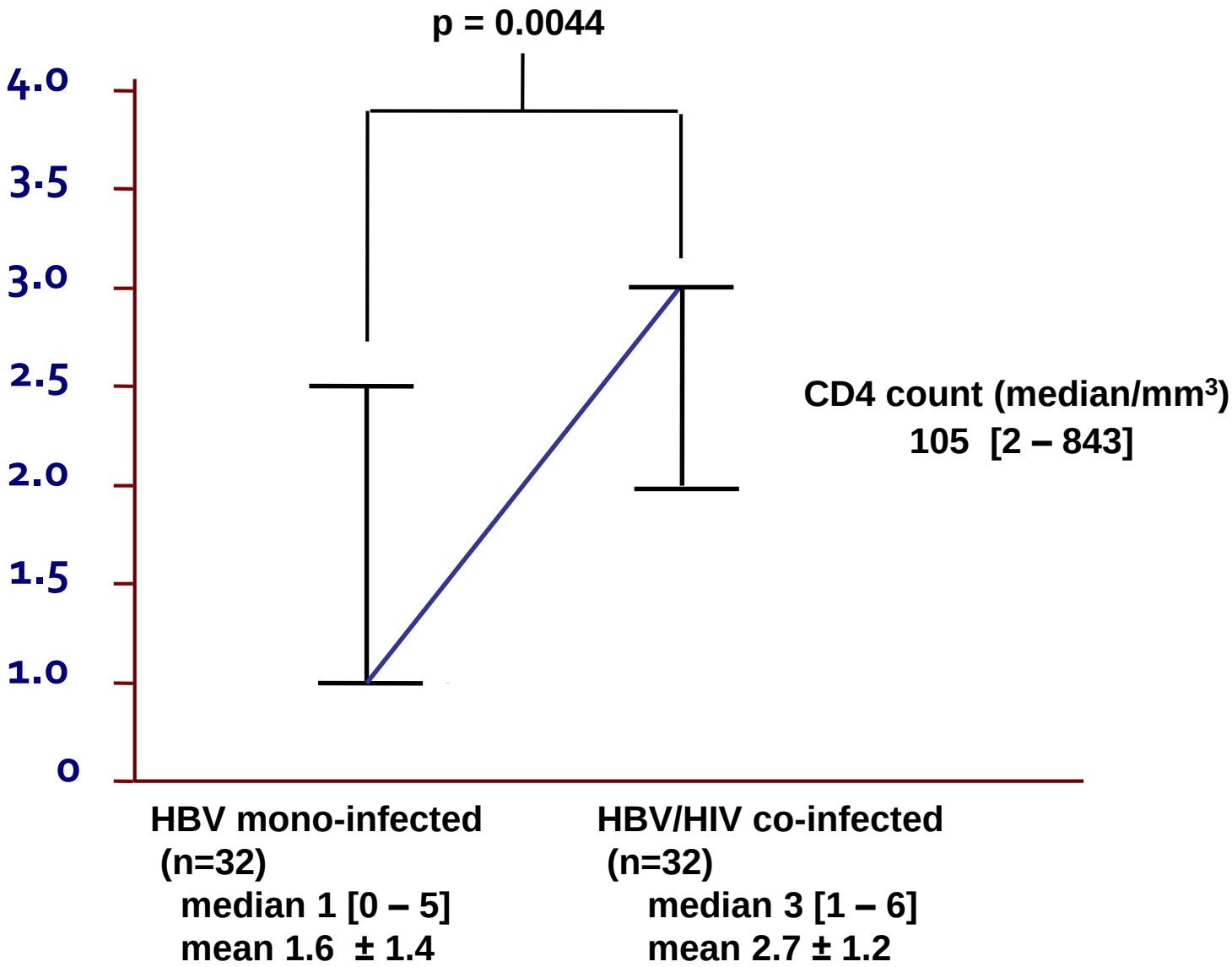
## Necro-inflammatory activity (n=64, ART naive)




*Sonderup et al Hepatology November 2008*

# Impact of HIV/HBV Co-infection

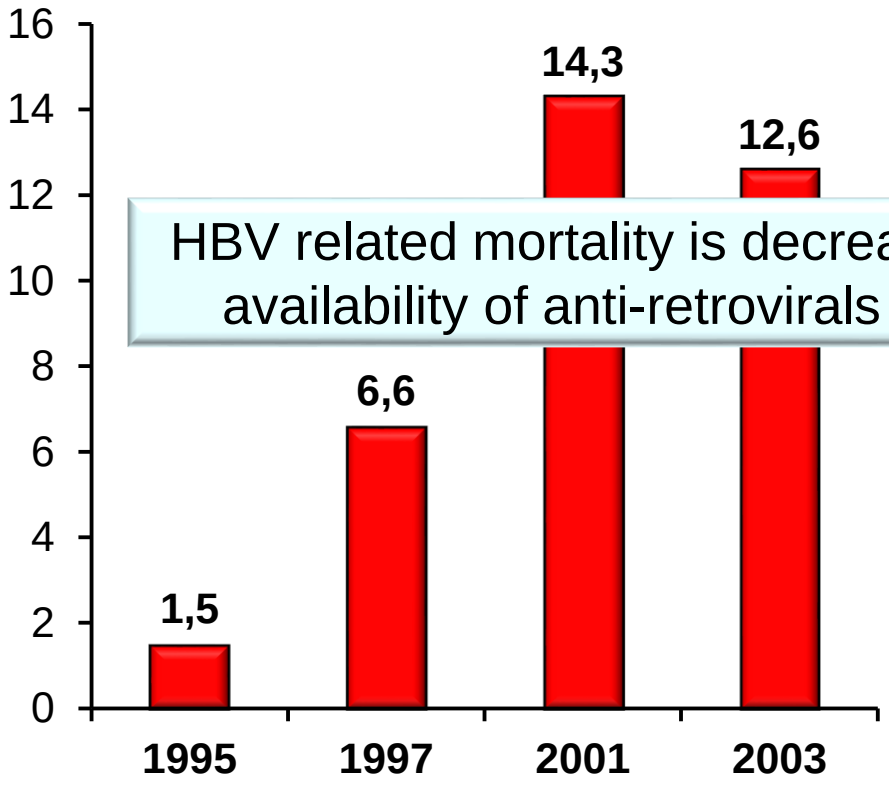
## Fibrosis (n=64, ART naive)



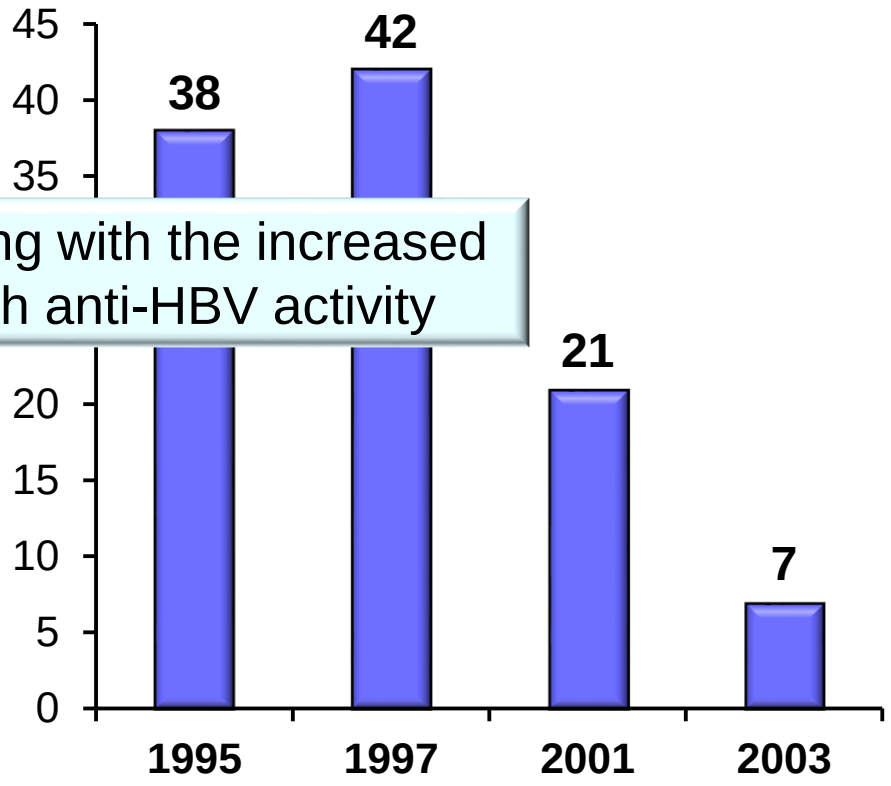

*Sonderup et al Hepatology November 2008*

# 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

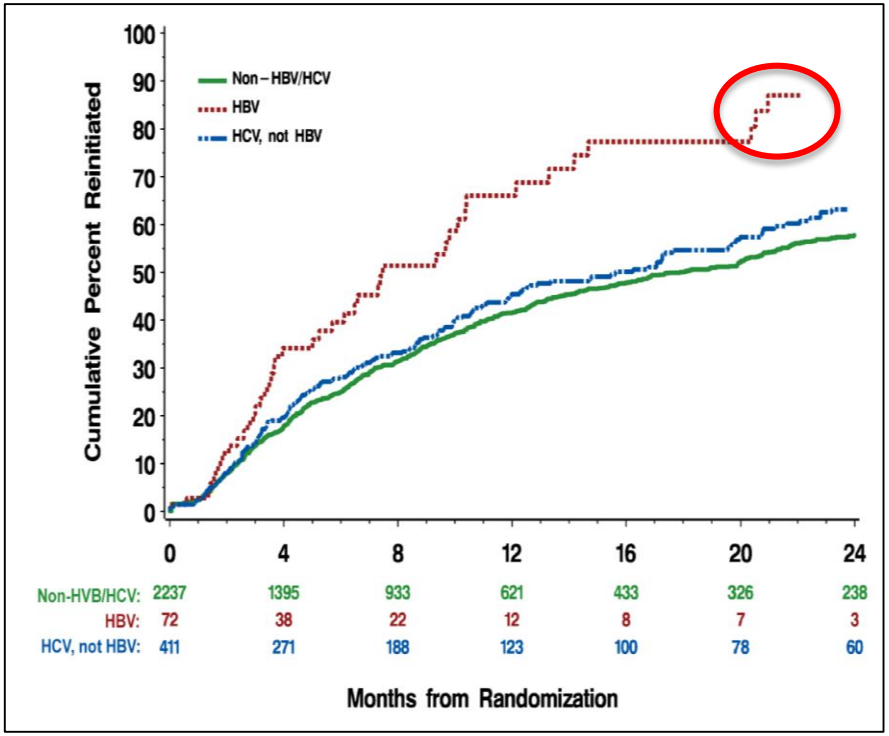
Rosenthal E, et al. J Viral Hepat 2007;14:183–8

# 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 |

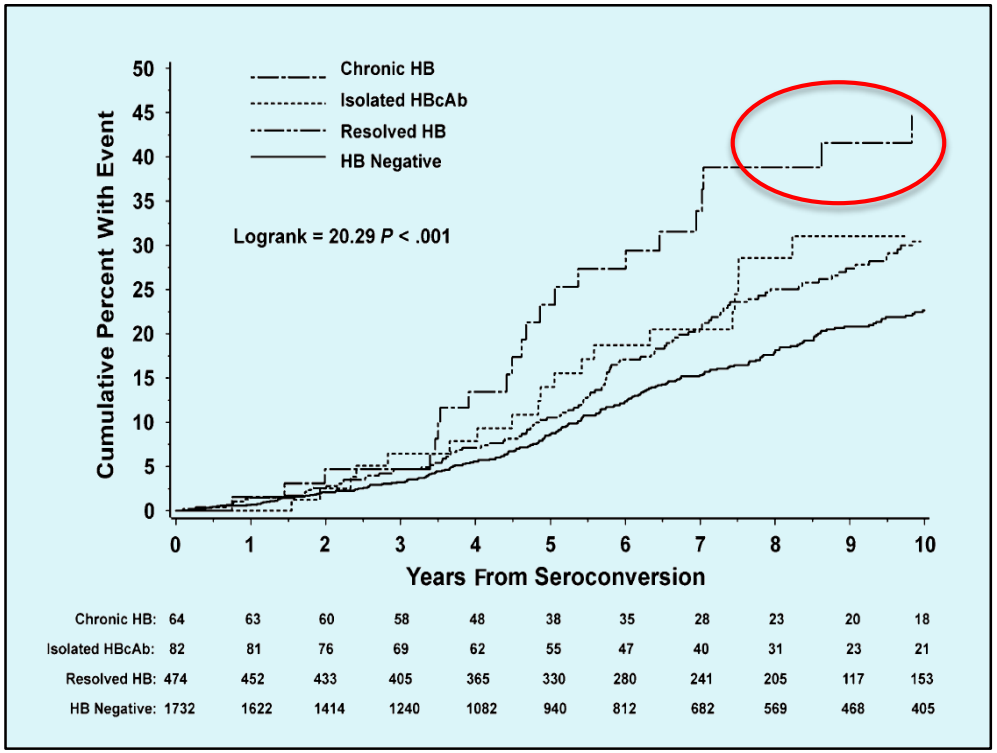
# Impact of HBV on HIV

## 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**

- 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

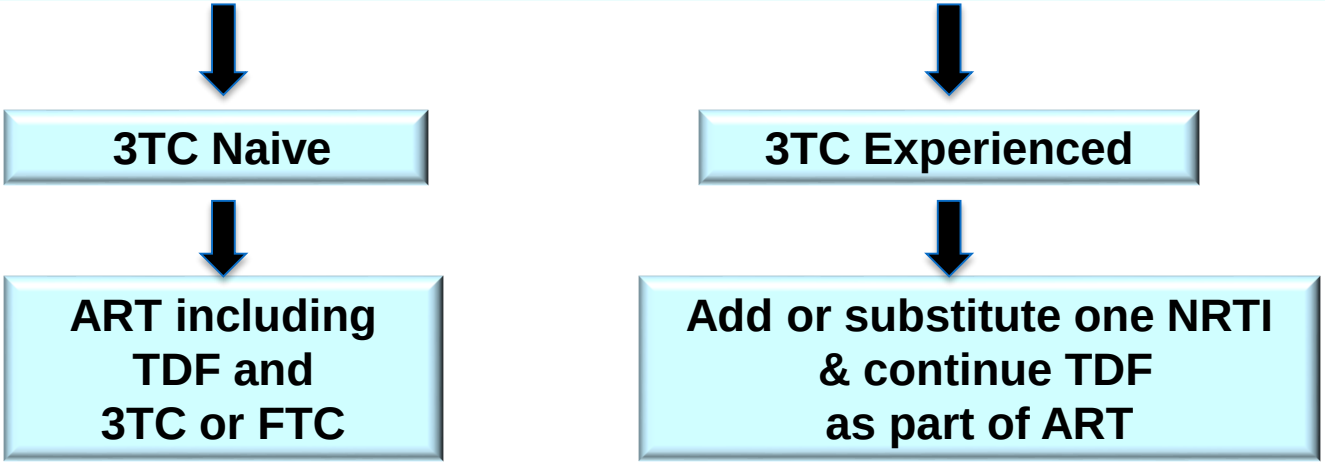
Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2016

# 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




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)**

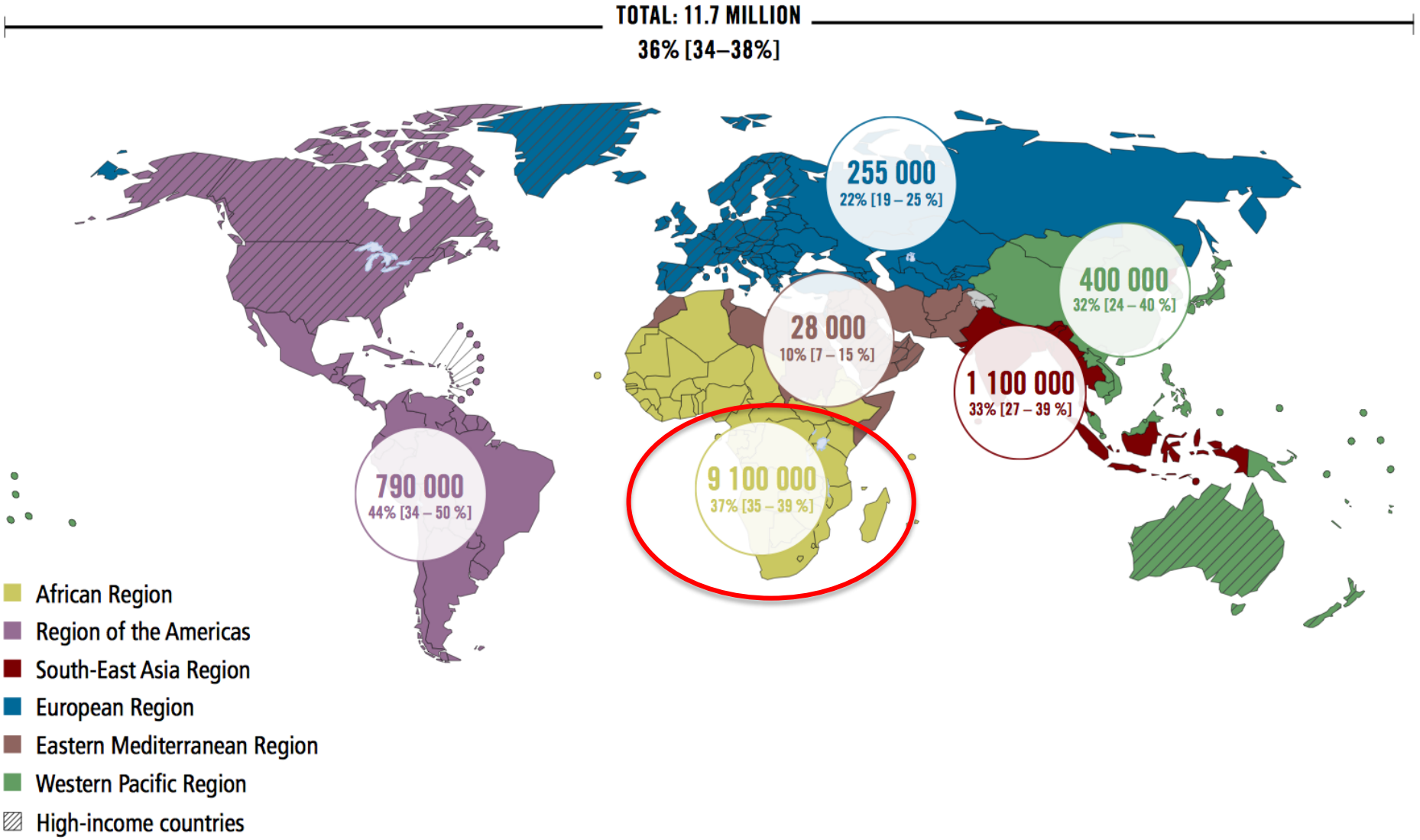
**HBeAg-positive patients after 5 years of treatment: High rates of:**

- 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

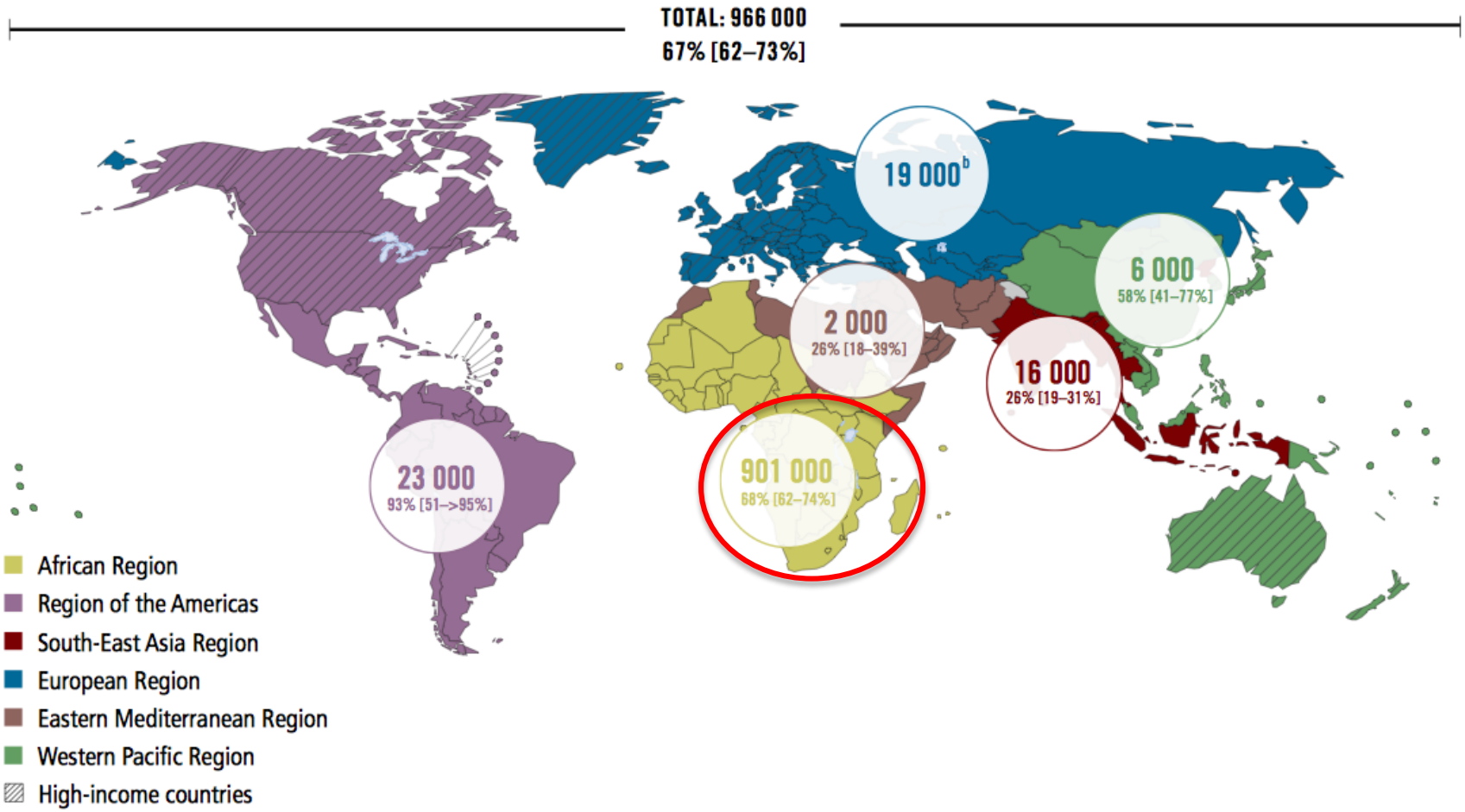
# Number of people receiving ART and percentage of all people living with HIV receiving ART in low- and middle-income countries overall and by WHO region, 2013[a]




[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.

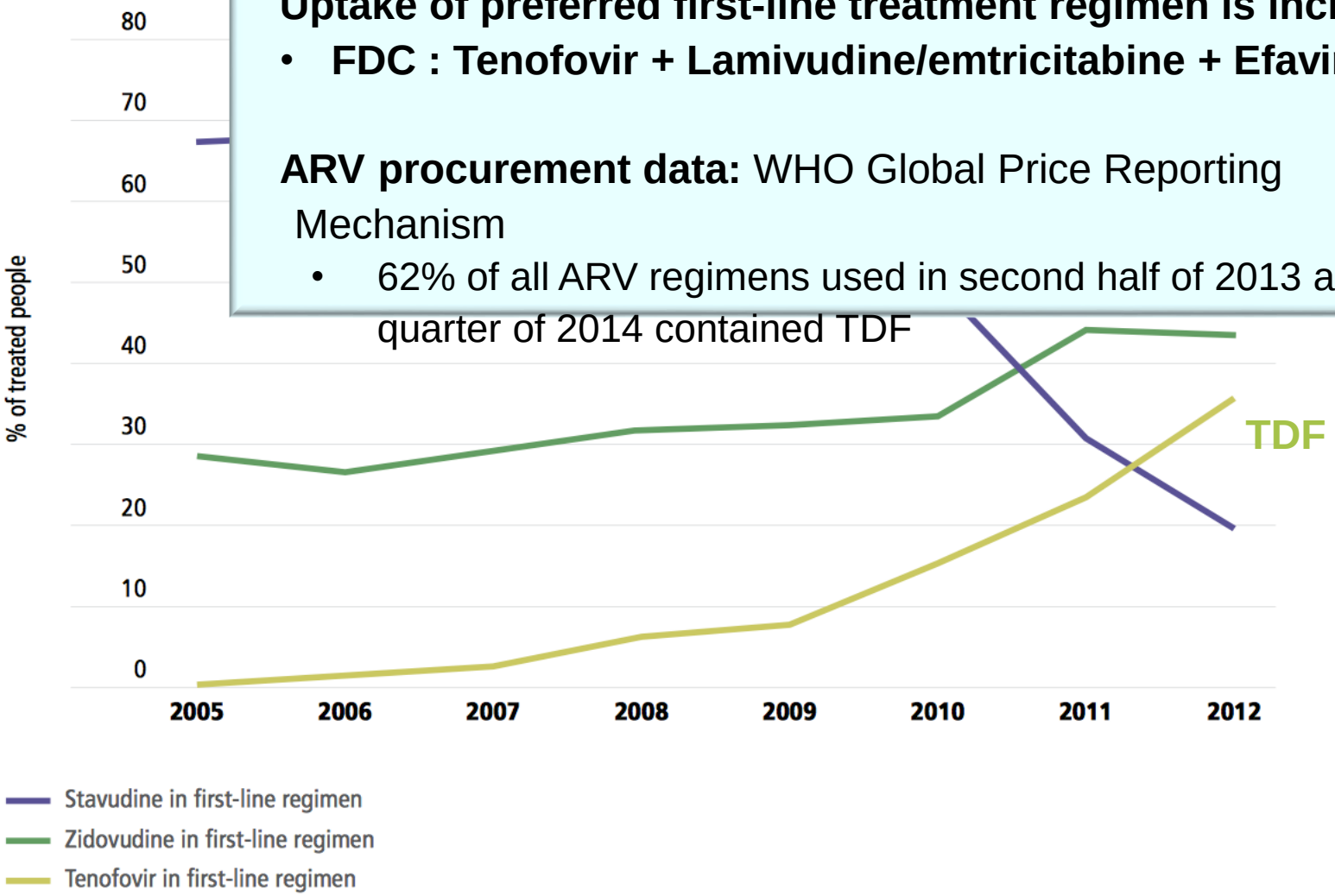
**Fig. 5.11.** Evolution of d4T, AZT and TDF in first-line antiretroviral therapy among adults and adolescents, 2005 to end-2012

**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

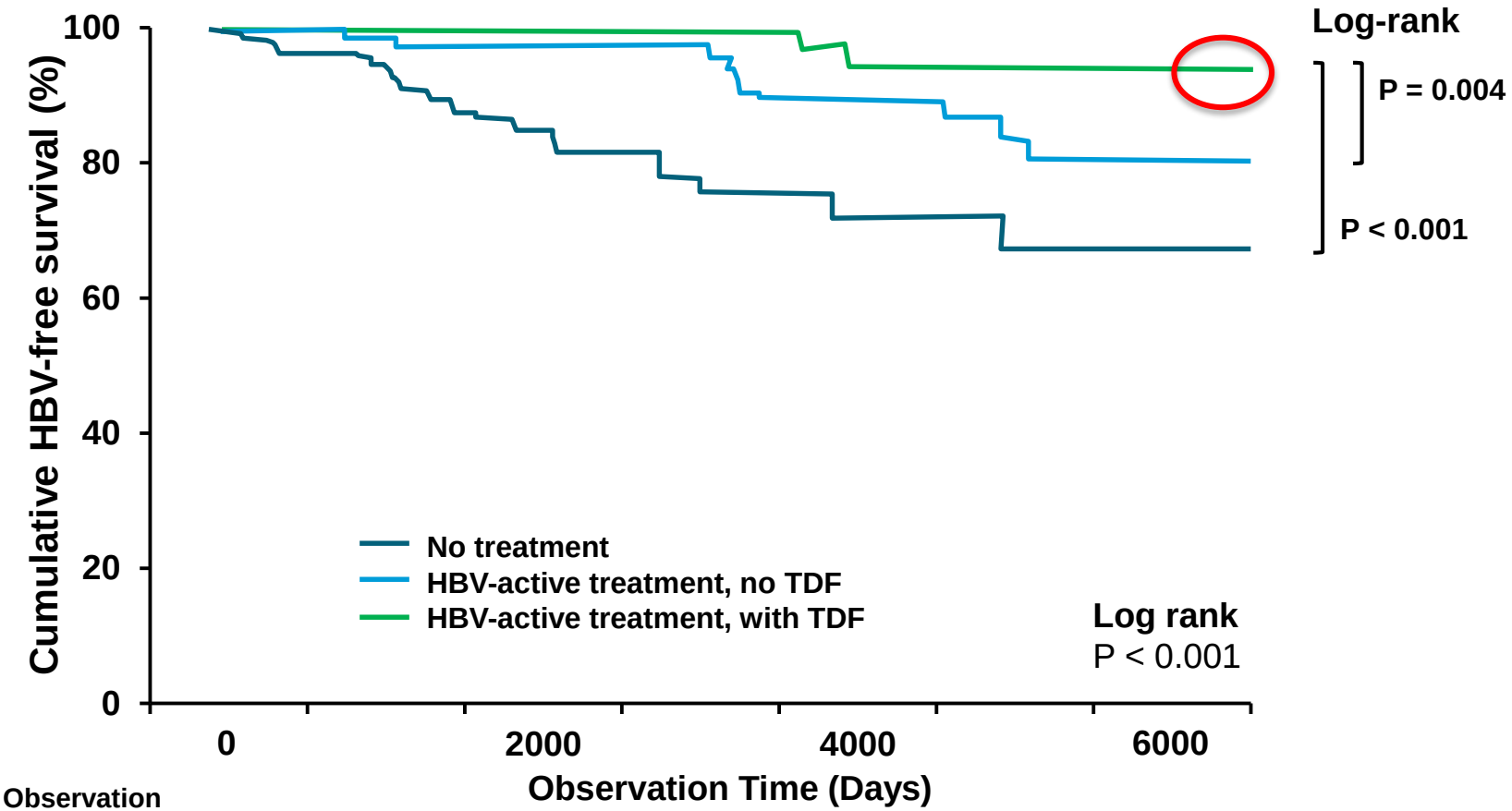
## New HBV Cases (N=35)

- 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**

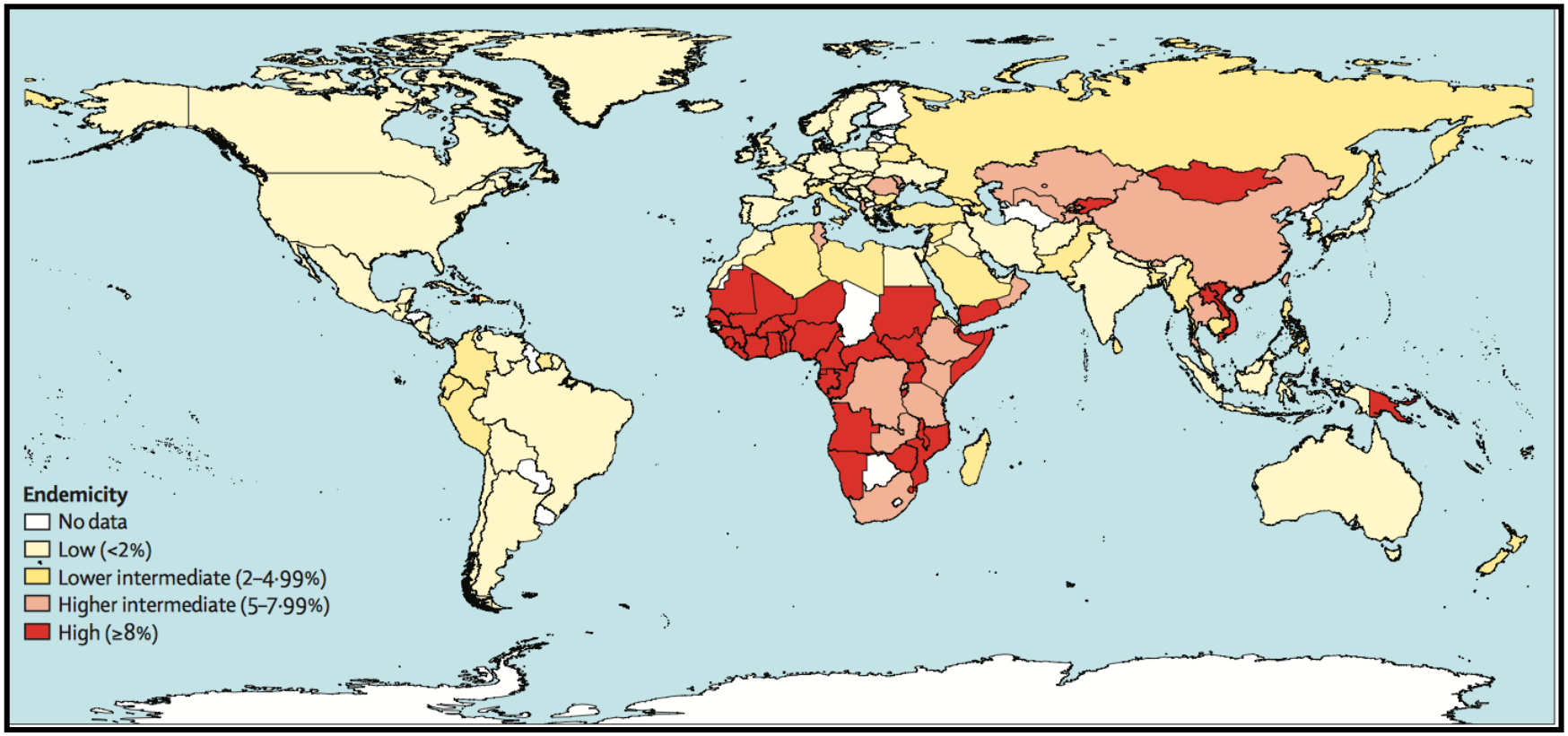
**HBV IS VACCINE PREVENTABLE**

# HIV/HBV Co-infection
# Treatment Options : Children

## Additional management challenges

- Choice of HAART regimen in children not requiring Rx for HBV
- Tenofovir cannot be used in children <12 years
- Logistically challenging to use a lamivudine-free regimen
- Use a standard HAART regimen (that may include the use of lamivudine)
    - with subsequent modification to tenofovir-based regimen at 12 years

# Hepatitis B Epidemiology




**Global HBsAg endemicity (1957–2013)**

**HBV endemicity is established in early childhood with HBsAg seroprevalence studies showing no difference between children aged 5-9 years and adults**

Lancet 2015; 386: 1546-55

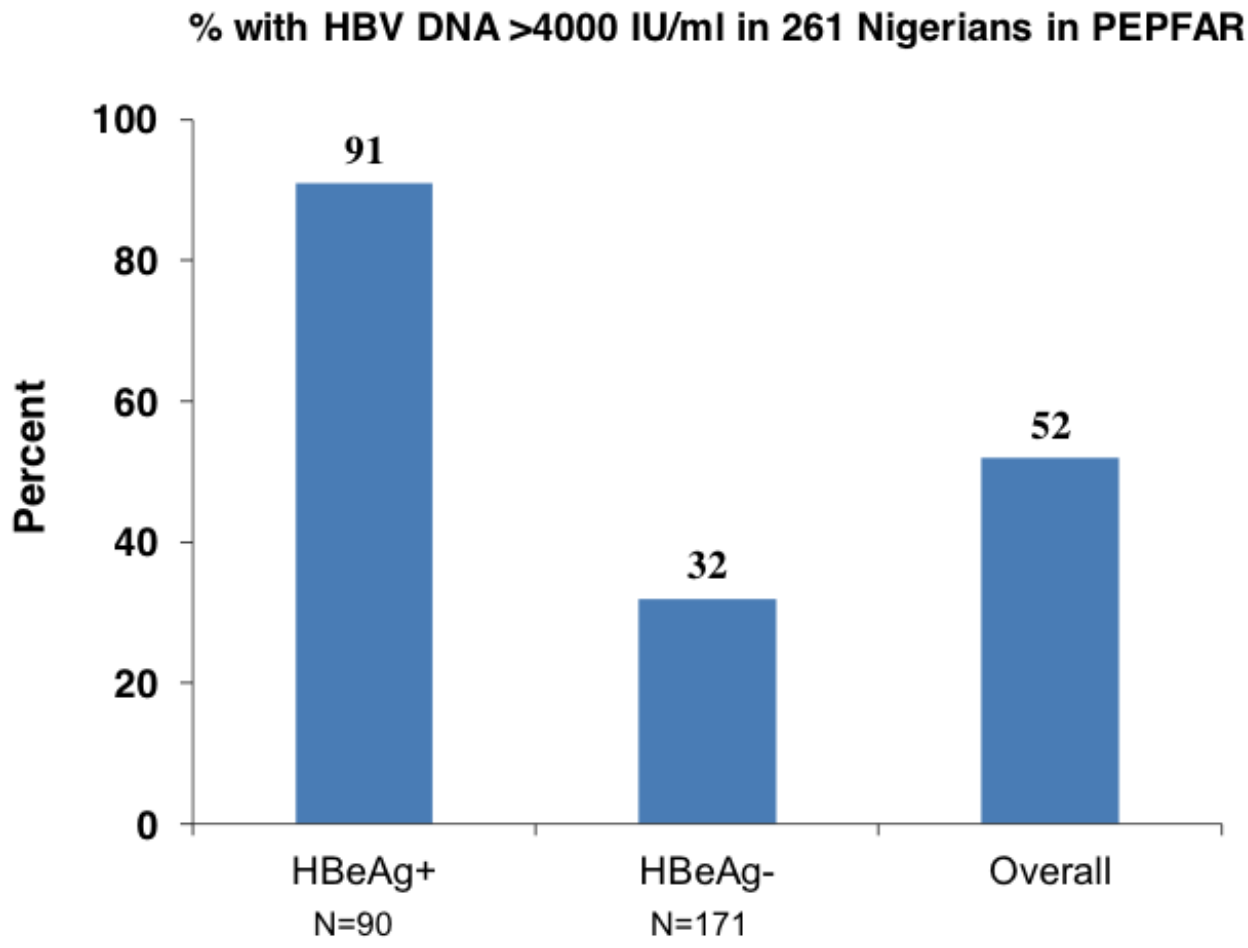
# Epidemiology of HIV/HBV: sub-Saharan Africa

## Efficacy of the HBV vaccination preventing HBV acquisition in sSA

- Most sSA countries: HBV vaccine schedule 6, 10 and 14 weeks
  - epidemiological studies African mothers predominantly HBeAg-negative
  - low risk of transmitting HBV vertically
  - increasing horizontal acquisition (6 mnths and 5 yrs)
  - policy initiated pre-HIV epidemic
- Efficacy of HB vaccine in the South African EPI over past 20 years
  - decreased HBV infection prevalence from 10% to 1% in one to five year olds
- Local study: **One in six HBV-infected pregnant women, irrespective of HIV status is HBeAg seropositive**
  - median HBV load 9.72 $x10^7$ IU/ml HIV- infected vs 1.19 $x10^6$ IU/ml HIV-neg
- Neonates remain unprotected for first 6 weeks of life
- Local study: prevalence of HBV infection was 4/1000 HIV exposed infants
  - all mothers were HBeAg positive and not on HAART

**WHO has recommended universal HBV Vaccine Birth Dose**

# HBV DNA >4000 IU/ml in HIV-HBV co-infected Nigerian subjects prior to HIV therapy




Idoko et al *CID* 200949(8): 1268

# Initiation of HAART in HBV/HIV co-infection

## Goal of therapy

- Virological suppression of both HBV and HIV replication
- Chronic Hepatitis B: Amelioration of transaminitis and histological injury and prevention of liver-related complications

## 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
  - First line therapy for adults, adolescents and children >5 yrs

Hepatology 2000;31:1030-1031; Lancet 2001;358:718-723; J Hepatol 2012;31:167-185 (EASL) ; Hepatol 2009;50:661 (AASLD); AIDS 2013;27(14):2219

# Initiation of HAART in HBV/HIV co-infection

**2013 WHO ARV guidelines recommend initiation of HAART in**

- All HIV-infected adults with a CD4 cell count <500 cells/$mm^3$
  - regardless of stage of liver disease
- Individuals with severe chronic liver disease regardless of CD4 count
  - at greatest risk of progression and mortality from liver disease
  - HAART initiation may improve overall survival in cirrhotics
- All pregnant or breastfeeding women regardless of CD4 count
  - **local concerns of life-threatening EFV DILI presenting post-partum in women initiated on HAART at HIGH CD4 counts**
- All children less than 5 years of age regardless of CD4 count

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.

**For management of cirrhotic persons**, see page 49-52. Persons with liver cirrhosis and low CD4 count require careful surveillance in the first months after starting ART in order not to overlook immune reconstitution syndrome and subsequent liver decompensation due to flares of liver enzymes.

**ii All persons with HBV/HIV co-infection should receive ART including TDF + 3TC or FTC unless history of TDF intolerance.** In HBV/HIV co-infected persons with chronic kidney disease, see recommendations for Dose Adjustment of ARVs for Impaired Renal Function and page 45.
If TDF
is strictly contra-indicated, entecavir + adefovir may be tried. However, efficacy and renal toxicity need to be closely monitored, because of the proven renal toxicity of adefovir. In persons with no prior 3TC exposure, entecavir may be used alone. NRTI substitution should only be perfor- med if feasible and appropriate from the perspective of maintaining HIV suppression. Caution is warranted to switch from a TDF-based regimen to drugs with a lower genetic barrier, e.g. FTC or 3TC, in particular in 3TC-pretreated cirrhotic persons as viral breakthrough due to archived YMDD mutations is likely to happen. This has also been described in individuals with previous 3TC HBV-resistance who have been switched from TDF to entecavir. The addition of entecavir to TDF in persons with low persistent HBV-replication has not statistically proved to be efficient and should therefore be avoided. Results of trials are awaited.

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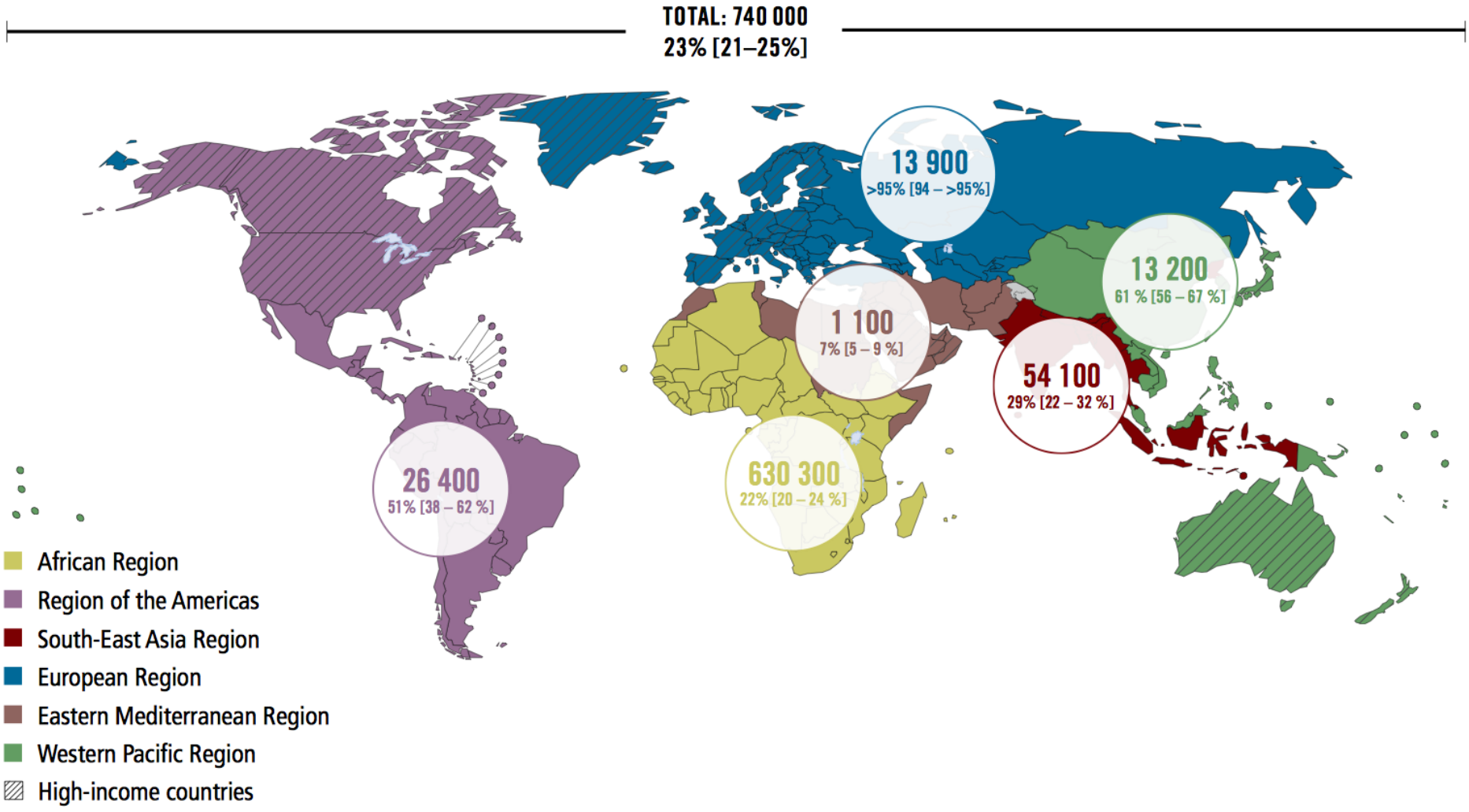
# Number of children receiving ART and percentage of all children living with HIV receiving ART in low- and middle-income countries overall and by WHO region, 2013[a]




[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.

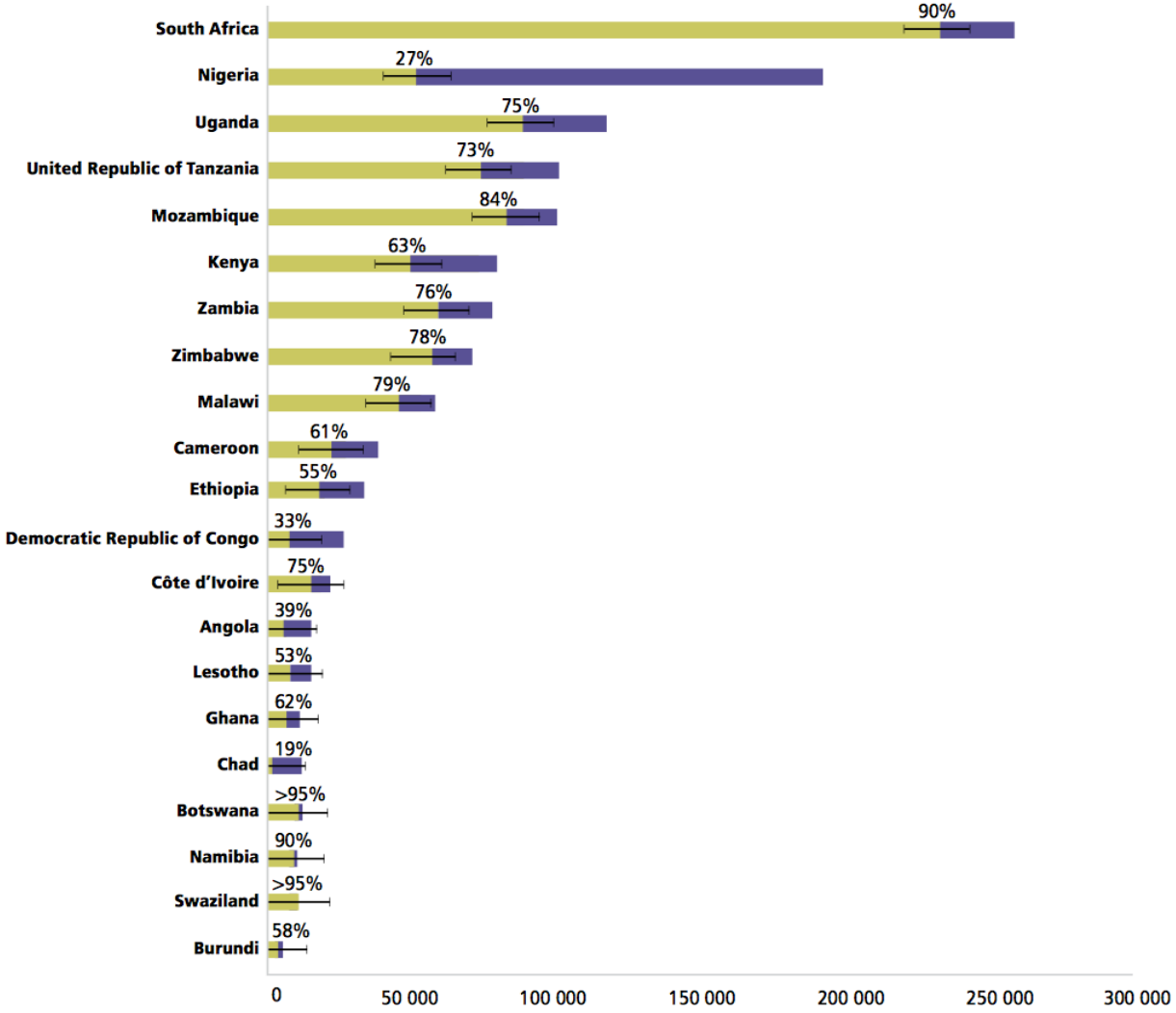
# Initiation of HAART in HBV/HIV co-infection

## Goals of therapy

- Virological suppression of both HBV and HIV replication
- *Chronic Hepatitis B:* Amelioration of transaminitis and histological injury and prevention of liver-related complications
- **HIV/HBV co-infected individuals benefit from early ART**
  - Liver fibrosis progression is reduced with immune reconstitution and suppression of HIV viral load
- **ART initiation with a TDF-based regimen is recommended in all persons with HBV co-infection irrespective of CD4 count**
- HAART initiation may improve overall survival in cirrhotics
- Liver cirrhosis and low CD4 count: careful surveillance in the first months after starting ART
  - Immune reconstitution syndrome and subsequent liver decompensation due to flares of liver enzymes

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.

**Fig. 3.4.** Number and percentage of pregnant women living with HIV receiving ARV medicines for PMTCT of HIV in the 21 Global Plan priority countries in the WHO African Region, 2013




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

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- All children less than 5 years of age regardless of CD4 count

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.

- 508 HIV-infected patients : 2 TEs ± 1.0 yrs apart
  - 54 (10.6%) developed liver cirrhosis, mean follow-up 2.6 ±1.0 yrs (overall incidence was 41.13 cases per 1,000 PY)
- Risk of developing cirrhosis was significantly higher in 297 HCV-RNA-positive patients (either untreated or non-responders to hepatitis C therapy) compared with 55 patients who had cleared HCV with therapy (odds ratio 3.73, 95% confidence interval 1.06-13.17; P=0.04).
- Risk of developing cirrhosis was low and similar in 24 HIV-HBV-coinfected patients under long-term suppressive HBV therapy (mainly tenofovir disoproxil fumarate), 132 HIV-infected patients without chronic liver disease and those who had cleared HCV with therapy.

# HIV impacts on HBV Vaccination

**Reduced seroprotection in <2 yr old HIV positive v. 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 also reduces transfer of maternal anti-HBs** *(JAMA 2011;305(6):576)*

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

# Incidence of cirrhosis in HIV/HBV co-infection on TDF - based HAART

**508 HIV-infected patients : 2 TEs ± 1.0 years apart**

- 54 (10.6%) developed liver cirrhosis, mean follow-up 2.6 ±1.0 yrs (overall incidence was 41.13 cases per 1,000 PY)
- Only 1/24 (4.2%) HBV/HIV co-infected individuals developed cirrhosis

| | OR | P value |
|---|---|---|
| **HIV/HCV with SVR** | 1 | |
| **HIV/HCV** | 3.73 (95% CI 1.06-13.17) | 0.04 |
| **HIV/HBV** | 0.69 | 0.81 |

- **Development of liver cirrhosis in HIV-infected individuals in the HAART era is mainly associated with active HCV co-infection**

**Tuma et al, Antivir Ther 2010;15:881**

# Lack of access to routine testing and monitoring

## World Hepatitis Alliance/WHO global survey 2009:

- ***Testing for HBV and/or HCV***
- >50% people live in countries with no free testing
- Only 4% low-income countries have ready access to testing

| | Testing accessible to >50% | Testing anonymous | Free to all | Free to some |
|---|---|---|---|---|
| **Africa** | 20% | 40% | 10% | 27% |
| **SE Asia** | 29% | 29% | 29% | 14% |
| **Europe** | 86% | 55% | 27% | 55% |

**Easterbrook et al Sem Liv Dis 2012**

# SA : Impact of HIV : Maternal Transmission

**KwaZulu-Natal, RSA** *(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 vs 4.8% HIV negative
  - 6 were HBeAg positive (20.0%), all HIV positive
- **3.1% (16/509) were HBV/HIV co-infected**
- **Median HBV DNA load: 3.3 $\log_{10}$ (HIV pos) v 1.5 $\log_{10}$ (HIV negative)**

# 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*

- 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 women**
  - **$9.72 \times 10^7$ IU/ml v. $1.19 \times 10^6$ 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**