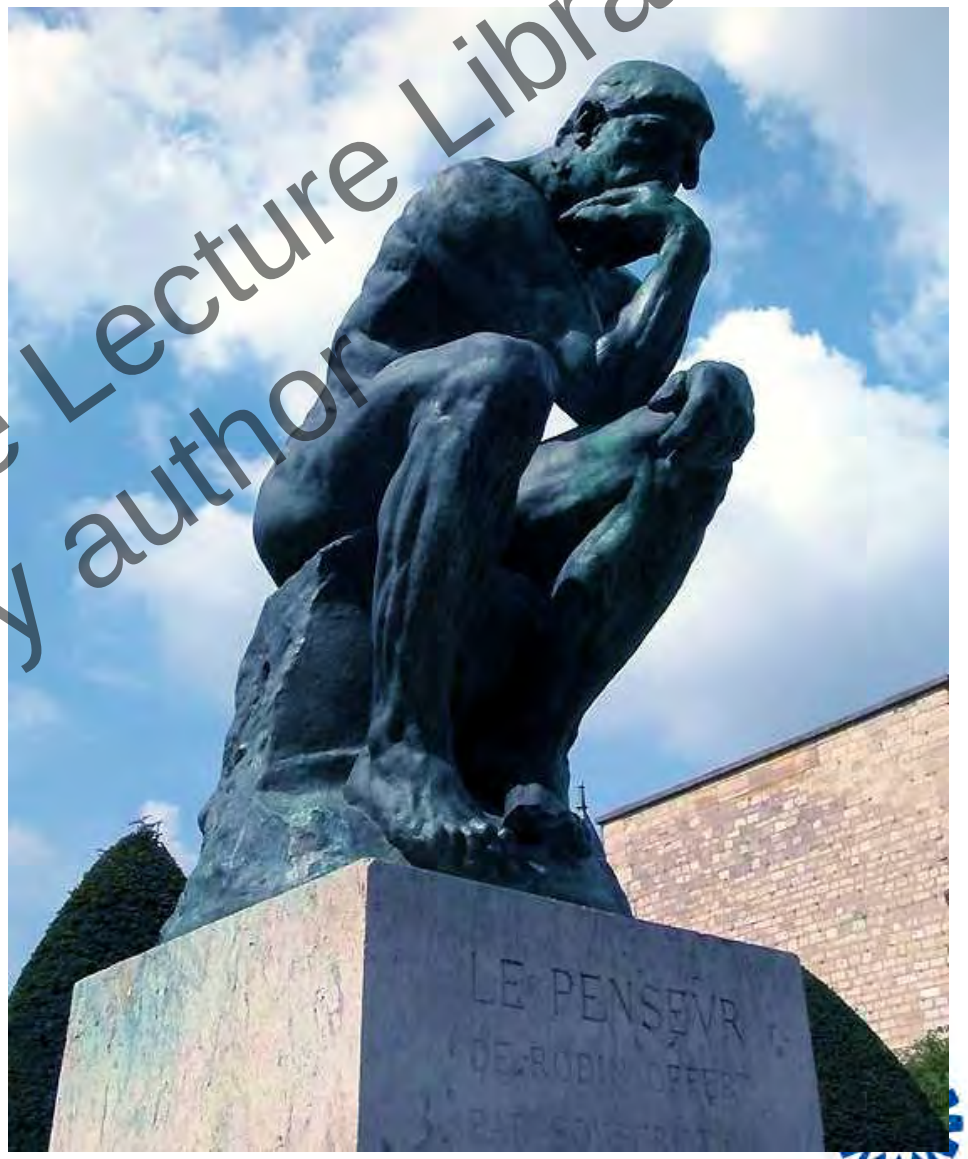
UMC Utrecht

Treatment of HBV in HIV-infected patients: opportunities and challenges

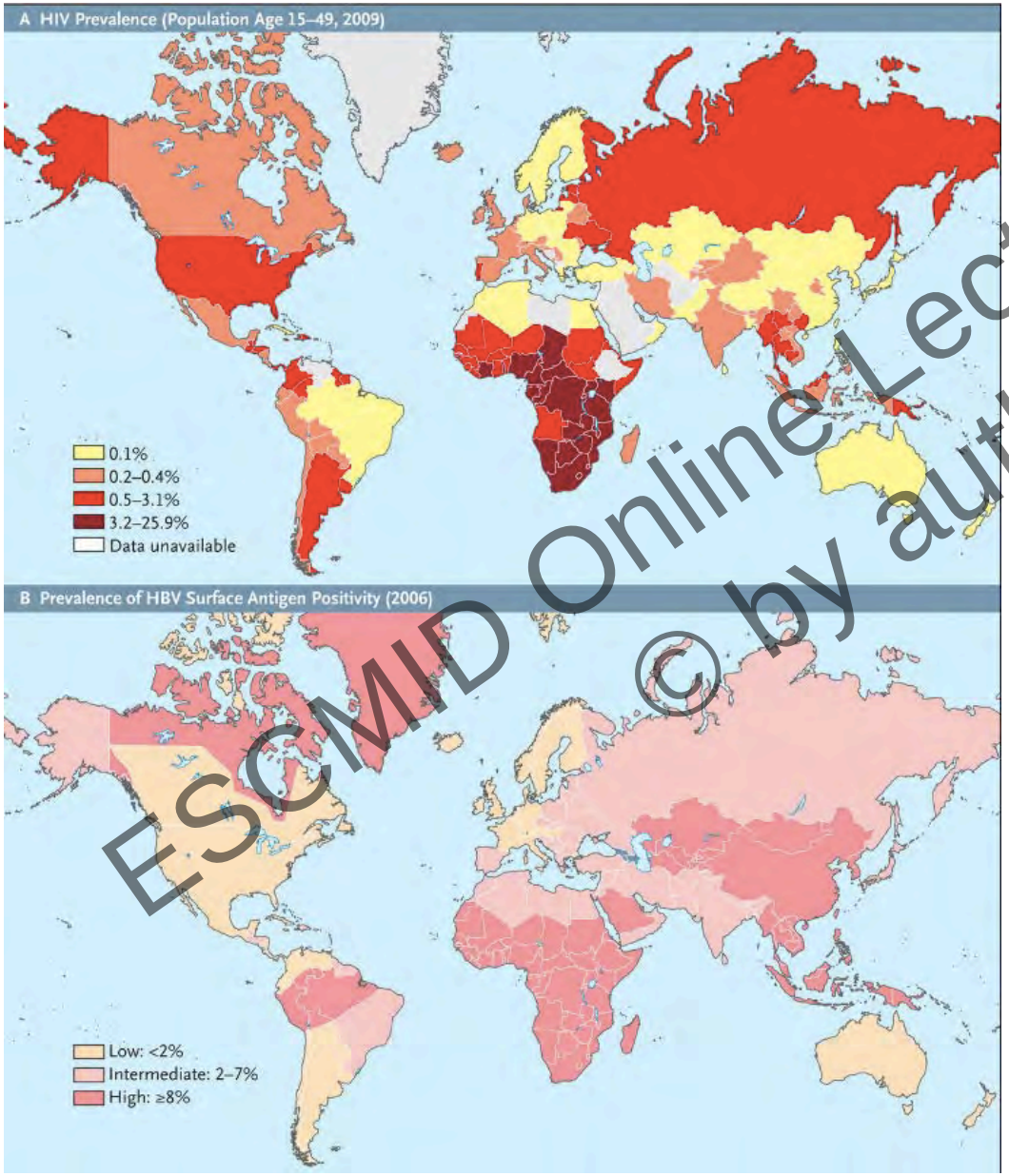
Joop Arends

Infectious Diseases physician
University Medical Center Utrecht (UMCU)
President of the European Study Group of Viral Hepatitis (ESGVH)

Hepatitis Boring



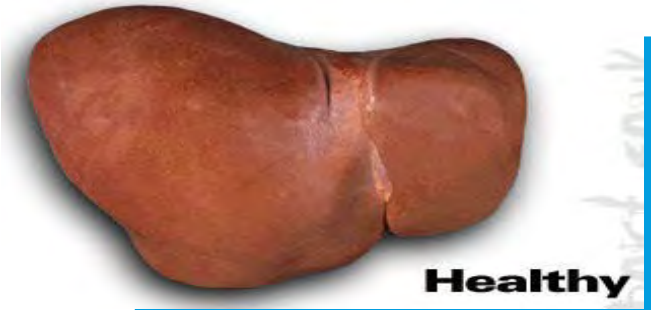
Let's take a closer look at the problem



- around 10%-25% of HIV+ patients is HBV coinfected

Kourtis et al. N Engl J Med 2012

Why do we care about HBV treatment?



Healthy

Cirrhosis

HBV natural history accelerated in HIV-infected patients

- Compared to HBV mono-infected patients
  - higher HBV DNA load
  - higher HBe antigenemia (Oshitani et al. Trans R Soc Trop Med Hyg. 1996)
  - higher incidence of HCC (Puoti et al. AIDS. 2004)

- 18-fold increased risk of liver mortality

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	..

Table 3: **Comparison of liver-related mortality by HIV-1 and HBsAg status**

Thio et al. Lancet 2002

TDF-based cART negatively affects the natural history of HBV in HIV+ patients

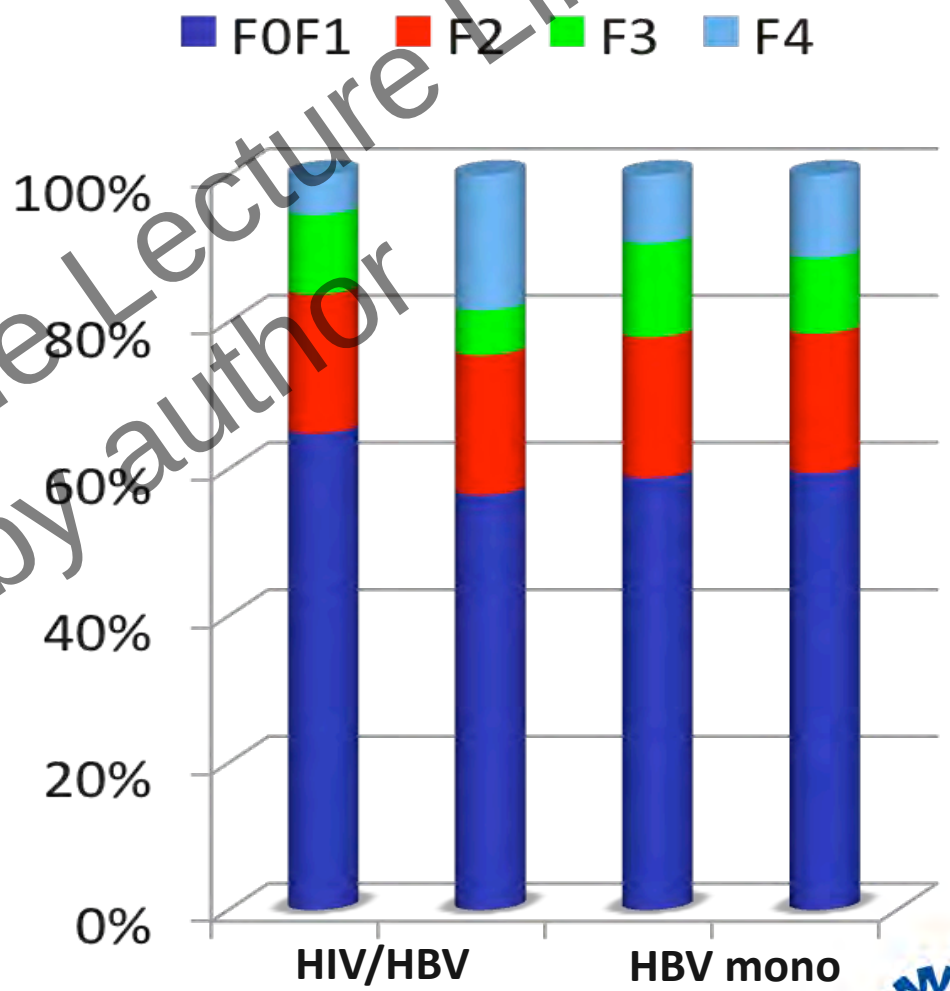
Table 1. Characteristics of chronic hepatitis B infection in HBV–HIV co- and in HBV-mono-infected patients

	HIV-positive patients (n = 299)	HIV-negative patients (n = 410)	P*
Age, (mean ± SD, years)	42.9 +/− 10.6	40.9 +/− 14.5	0.04
Male gender, n (%)	209 (69.9%)	243 (59.3%)	0.004
Geographic origin, n (%)†			
France	137 (45.8%)	88 (21.5%)	$<10^{-3}$
Europe	7 (2.5%)	55 (13.4%)	
Africa	134 (44.8%)	171 (41.7%)	
Asia	9 (3.0%)	85 (20.8%)	
Other/Unknown	12 (4.0%)	11 (2.7%)	
HDV seropositivity, n/N (%)†	21/216 (9.7%)	18/358 (5.0%)	0.03
Positive HDV RNA, n/N (%)†	7/19 (36.8%)	4/14 (28.5%)	0.62
HCV seropositivity, n/N (%)†	37/297 (12.5%)	14/405 (3.5%)	$<10^{-3}$
Positive HCV RNA, n/N (%)†	10/32 (31.3%)	3/14 (21.4%)	0.51
Daily alcohol intake >40gr, n/N (%)†	73/293 (24.9%)	54/387 (14.0%)	0.0003
Time from first HBV diagnosis (mean ± SD, years)	12.3 +/− 7.3	9.8 +/− 7.6	$<10^{-3}$
Time from first visit (mean ± SD, years)	11.3 +/− 8.8	8.6 +/− 6.9	$<10^{-3}$
HBV transmission route, n (%)†			
Blood transfusion	10 (3.3%)	13 (3.2%)	$<10^{-3}$
IVDU	27 (9.0%)	13 (3.2%)	
Sexual	142 (47.5%)	16 (3.9%)	
Mother to Child	22 (7.4%)	121 (29.5%)	
Other/Unknown	98 (32.8%)	247 (60.2%)	
HBV genotype, n (%)**			
A	11 (45.8%)	11 (17.7%)	$<10^{-3}$
B	3 (12.5%)	7 (11.3%)	
C	0 (0.0%)	10 (16.1%)	
D	0 (0.0%)	26 (41.9%)	
E	9 (37.5%)	8 (12.9%)	
G	1 (4.2%)	(0.0%)	

Piroth et al. Liver International 2015

Result of the study

- fibrosis progression was increased in patients with HCV or HDV coinfection
- Less HCC development in HIV/HBV coinfected patients
- 18.5% anti-HBe seroconversion and 8.5% anti-HBs seroconversion



Piroth et al. Liver International 2015

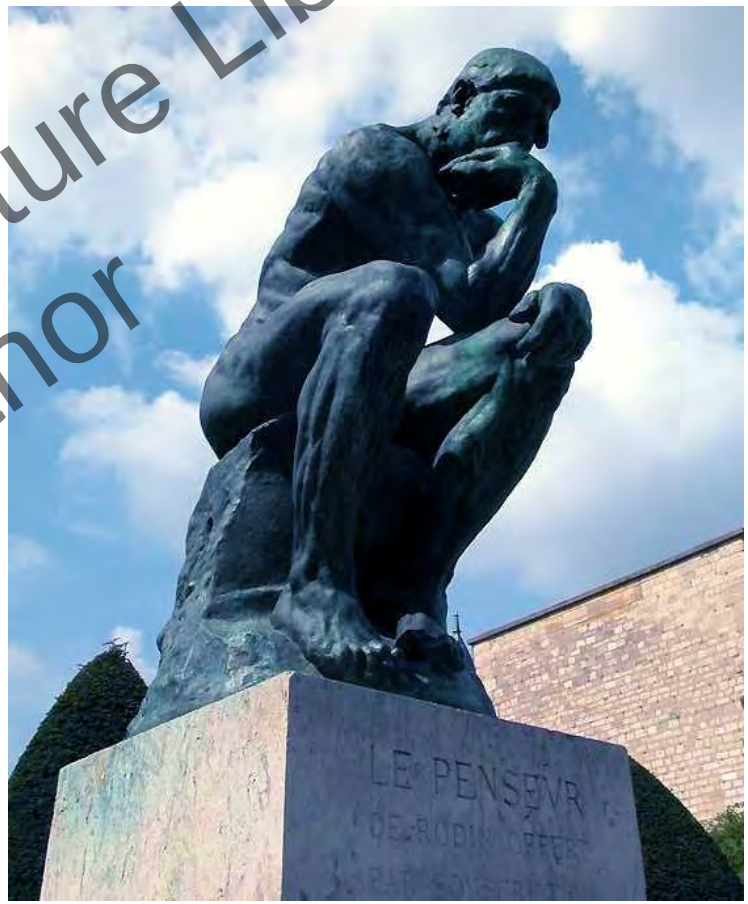
Treatment of hepatitis B is quite boring

1. **Truvada** (tenofovir/ emtricitabine)
2. **Truvada** (tenofovir/ emtricitabine)
3. **Truvada** (tenofovir/ emtricitabine)

.

.

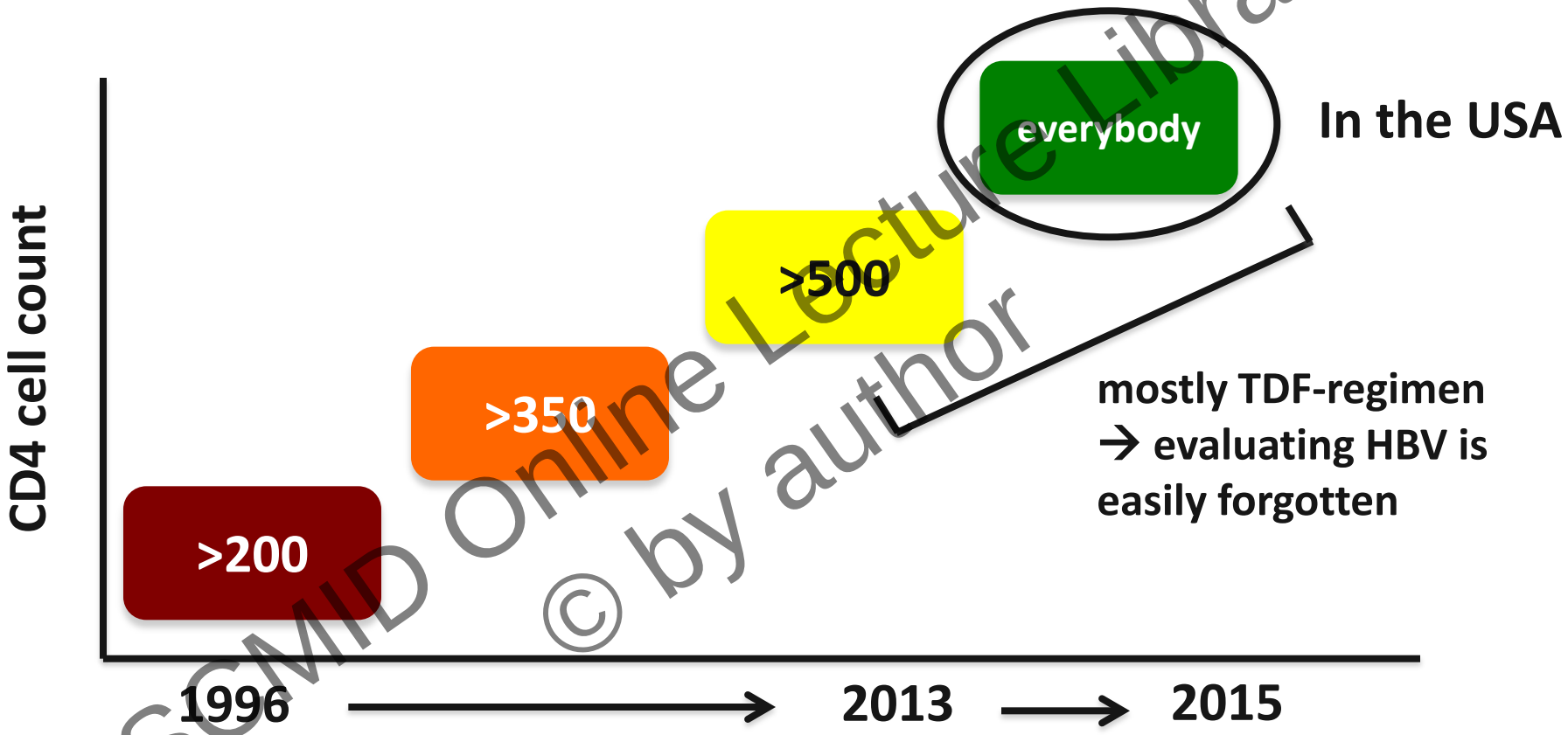
10. **something else**



- TDF-toxicity
- HBV-vaccination

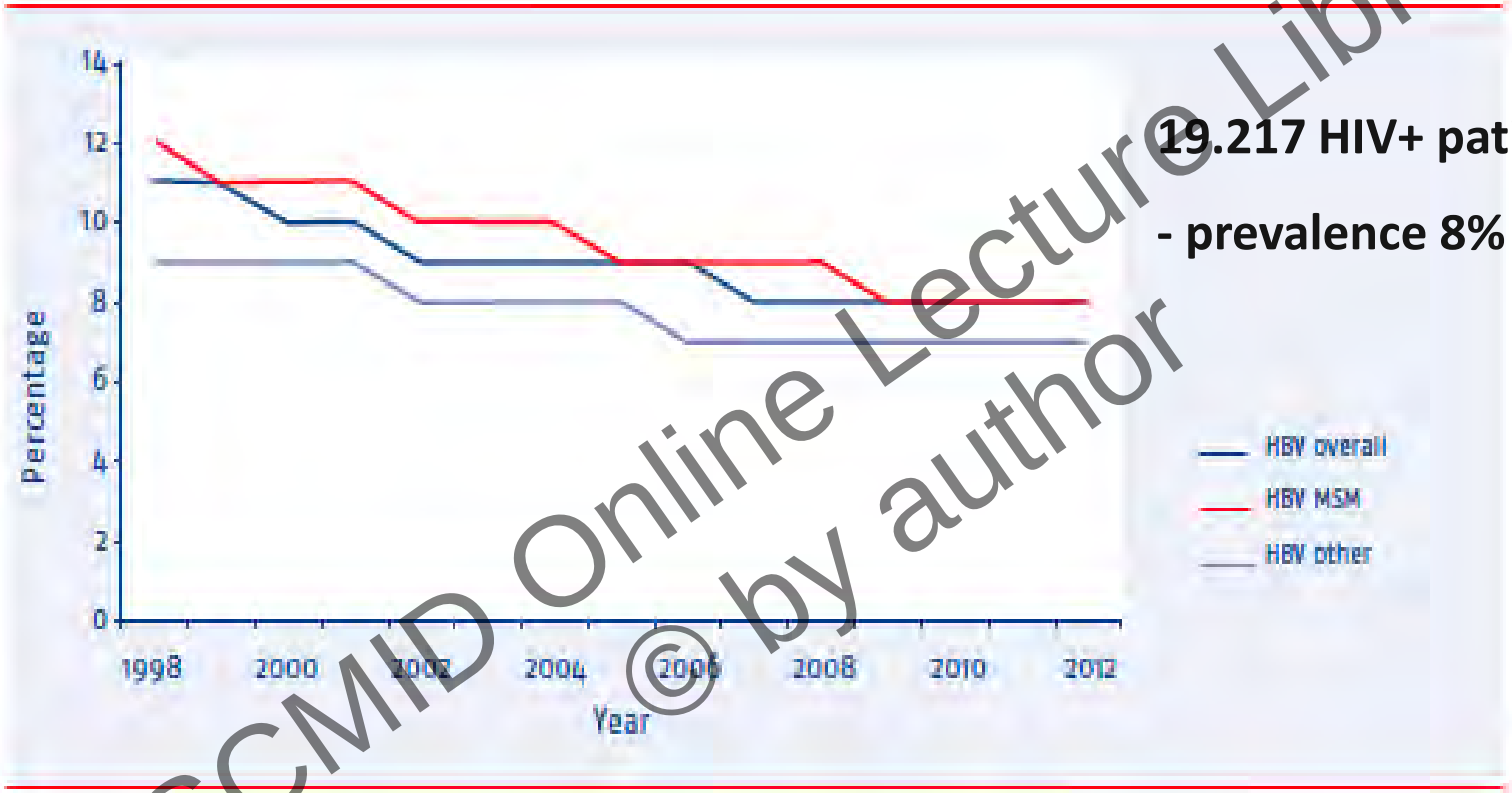
- introduction of TAF

CD4 cell count used to determine cART initiation



- used arguments
  - patient health, immune activation, public health, drug toxicity and cost

HIV/ HBV the Netherlands



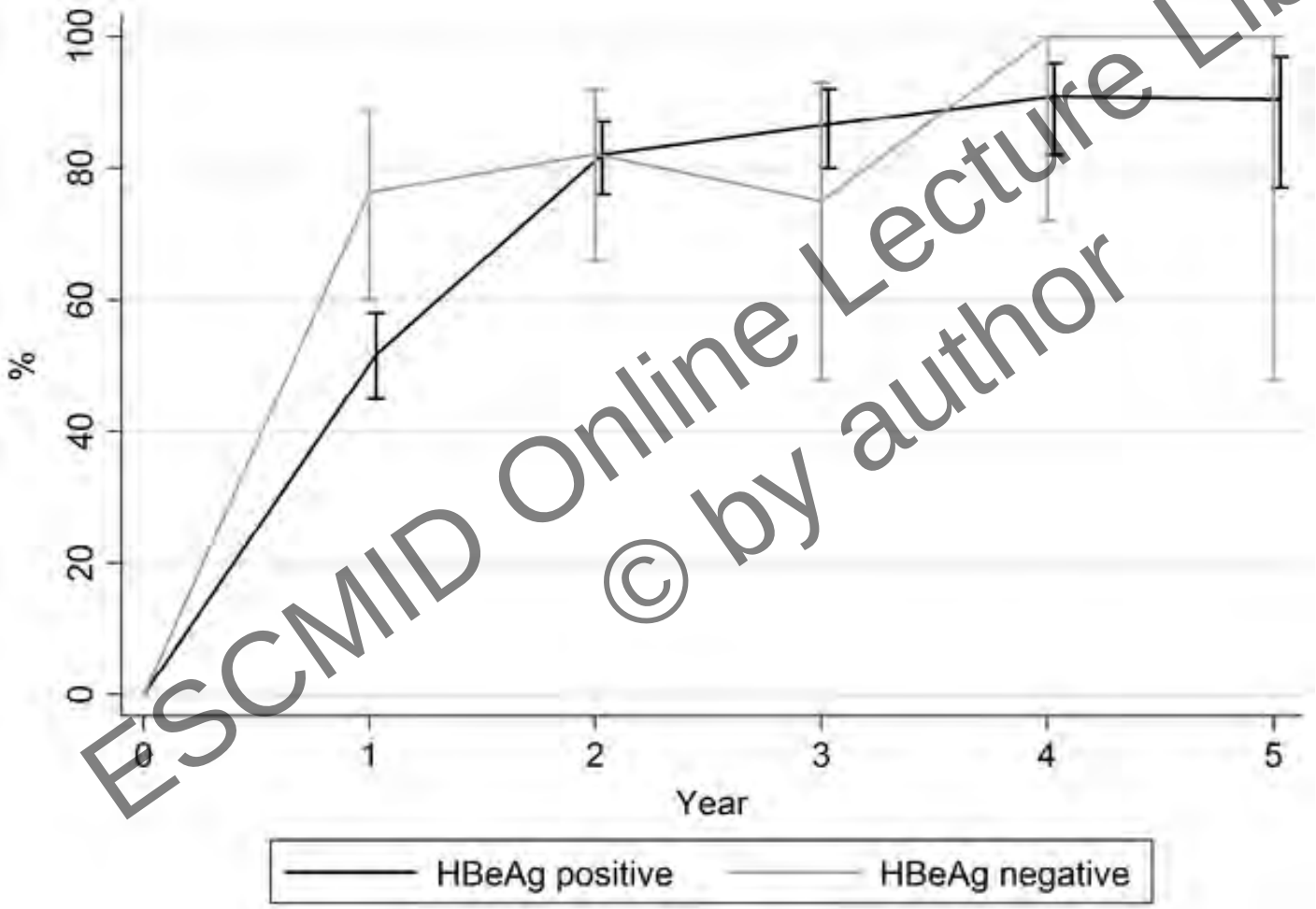
19.217 HIV+ patients screened

- prevalence 8% (n=1.739)

- **70% of all HIV+ patients is on tenofovir/ emtricitabine backbone**

HIV Monitoring Foundation report 2013

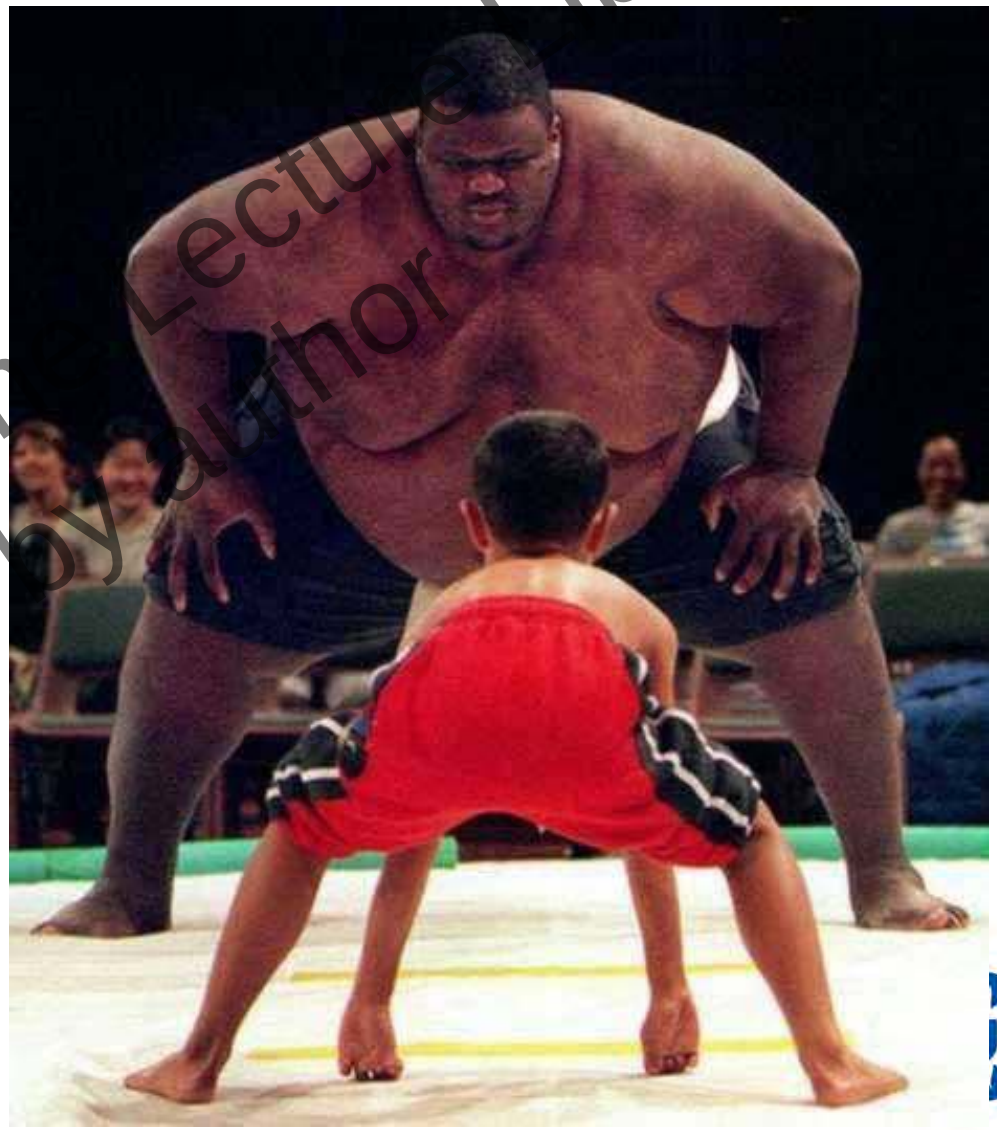
HBV DNA undetectability under TDF in HIV/HBV coinfected patients



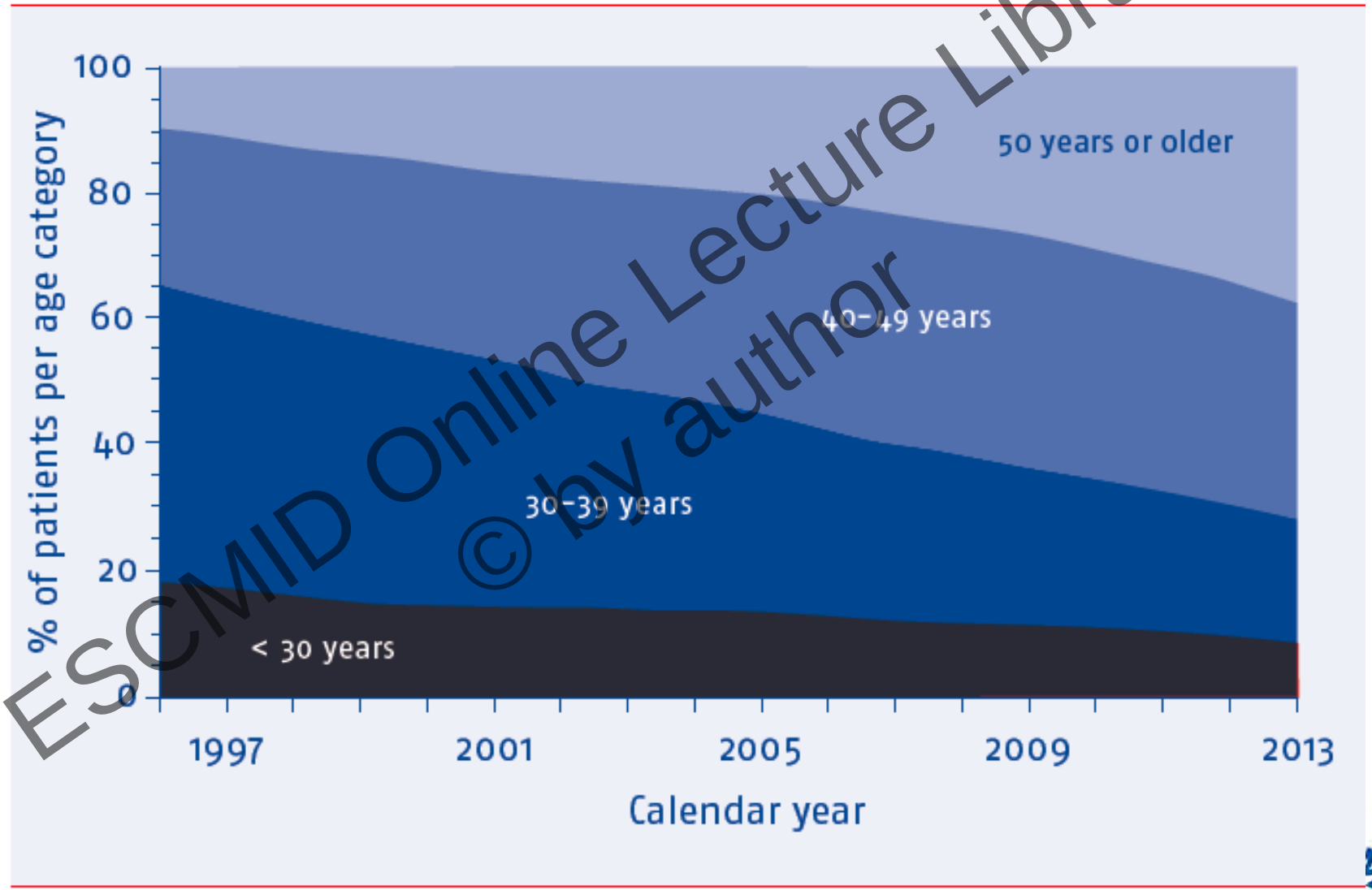
- meta-analysis of 23 studies including 550 HBV/HIV coinfected patients treated with TDF
- no effects of prior and concomitant 3TC/FTC on virological suppression

de Vries-Sluijs et al. Gastroenterology 2010
Martín-Carbonero et al. AIDS 2011
Price et al. PLoS ONE 2013

Problems might get bigger in the future

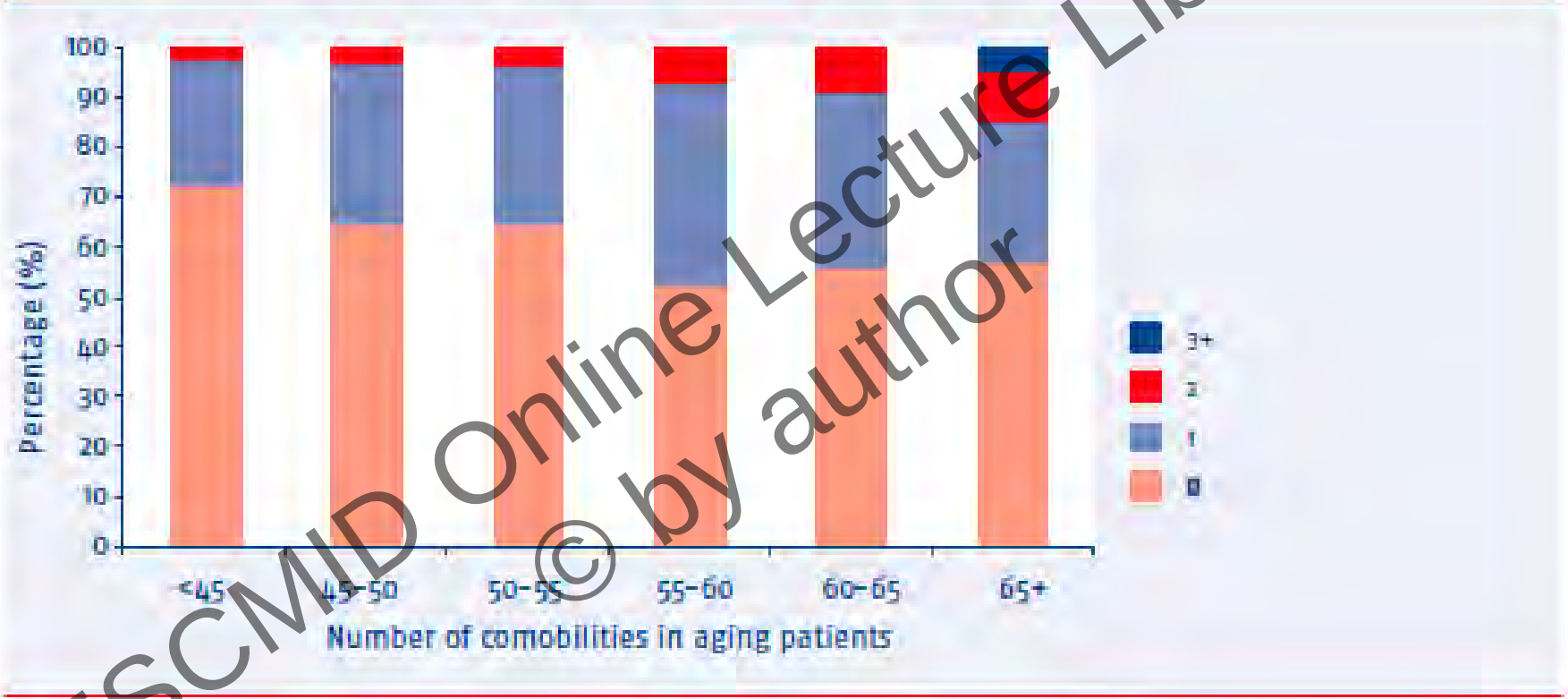


HIV-infected patients are increasing in age



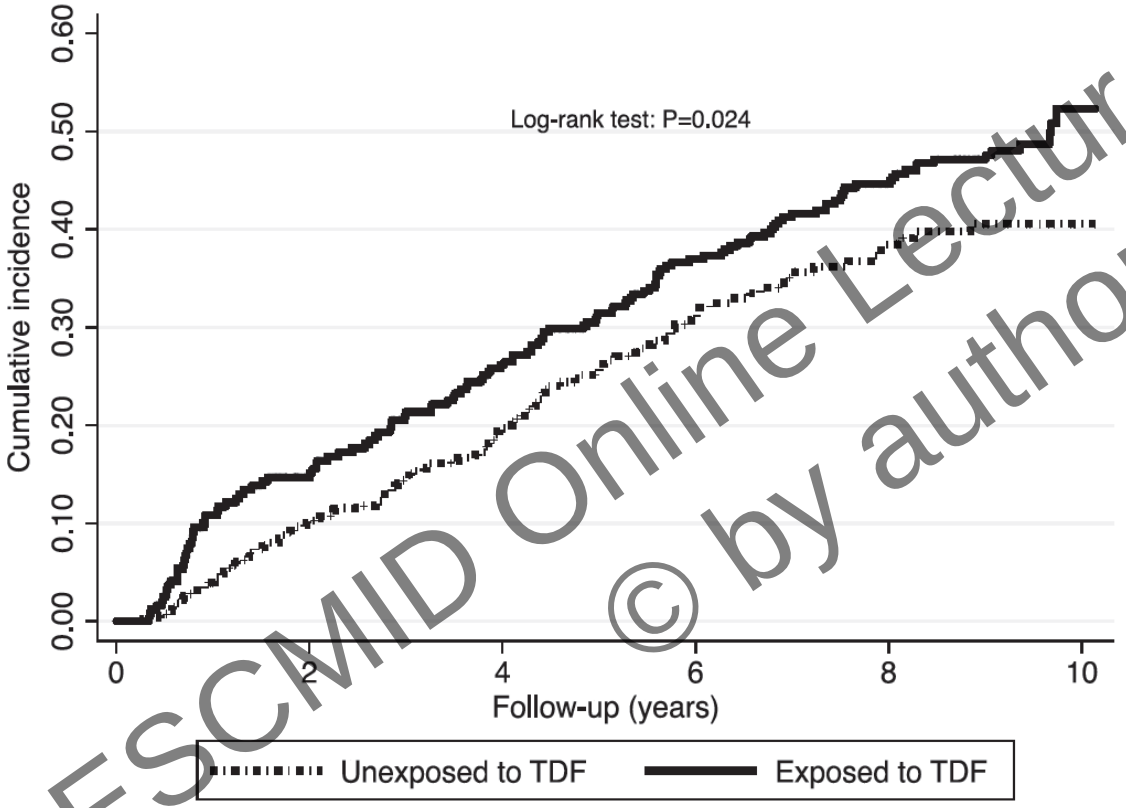
Dutch HIV Monitoring Foundation report 2013

More comorbidities in older patients



*Age at diagnosis of an event, or current age (as of 1 June 2013) if no comorbidities were diagnosed.

Therapy with tenofovir is associated with increased nephrotoxicity



- 10 year follow-up in 1,043 HIV+ pt
- kidney dysfunction defined as eGFR <90mL/min/1.73m^2
- HR=1.63 (95% CI:1.26–2.10)

TDF-nephrotoxicity associated with older age, alcohol and previous renal dysfunction

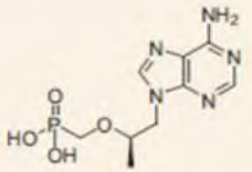
Laprise et al. Clin. Infect. Dis. 2012 Nov

Problems and opportunities ahead

- effective HBV treatment is mandatory in HIV-infected patients
  - increasingly more HIV-patients on TDF-regimen
- however…..
  - not all patients achieve undetectable HBV DNA
  - TDF-toxocity is loming
- so what are the opportunities
  - non-nephrotoxic TDF
  - no HBV-infections

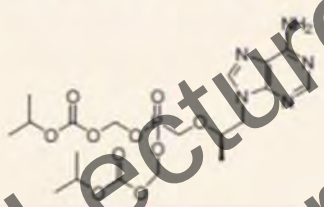
What is TAF

Tenofovir Alafenamide Fumarate



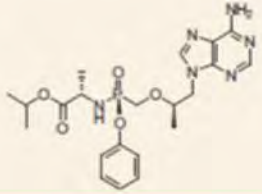
TFV

Tenofovir



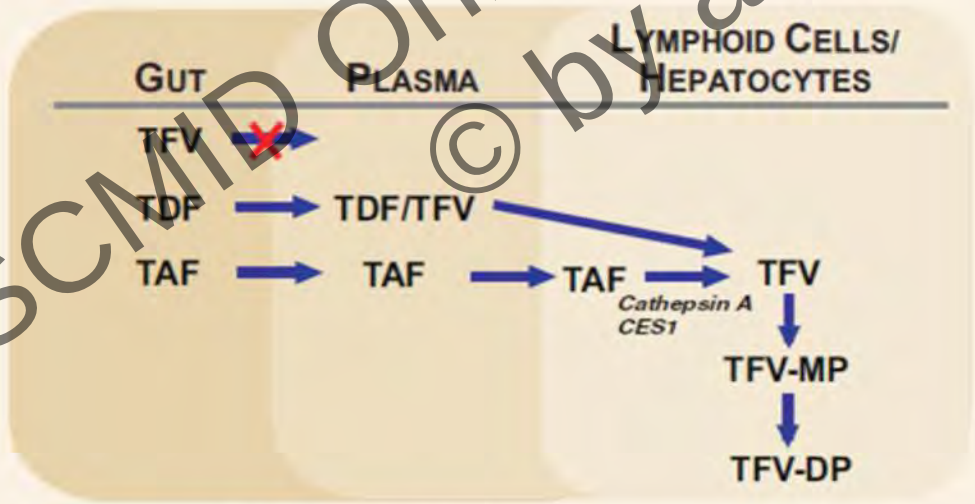
TDF

Tenofovir Disoproxil Fumarate



TAF

Tenofovir Alafenamide Fumarate



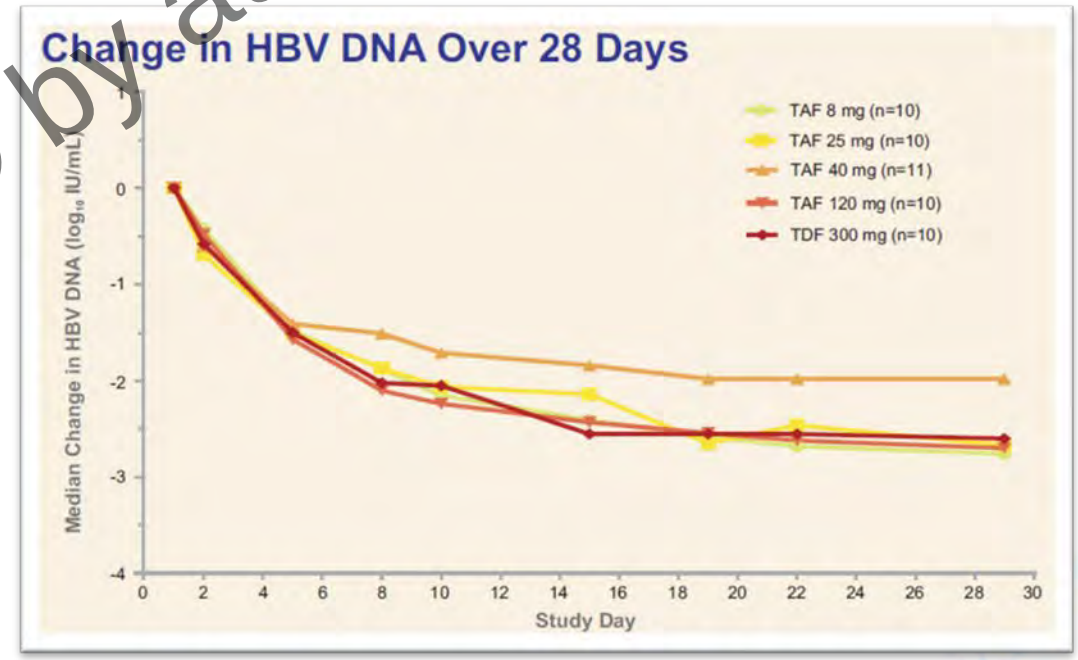
- Improved stability of TAF in plasma:
  - Enhances delivery of active TFV-DP into hepatocytes
  - Lower doses required/systemic TFV exposures greatly reduced

CES1, carboxylesterase 1; MP, monophosphate.

Agarwal et al. AASLD 2013

Efficacy of TAF on HBV DNA

- in phase 3 evaluation for HIV treatment
- dose-finding study in chronic HBV patients (8-25-40-120 mg with n=10 per group)
- randomized open-label study
- 4 week treatment period



Agarwal et al. AASLD 2013

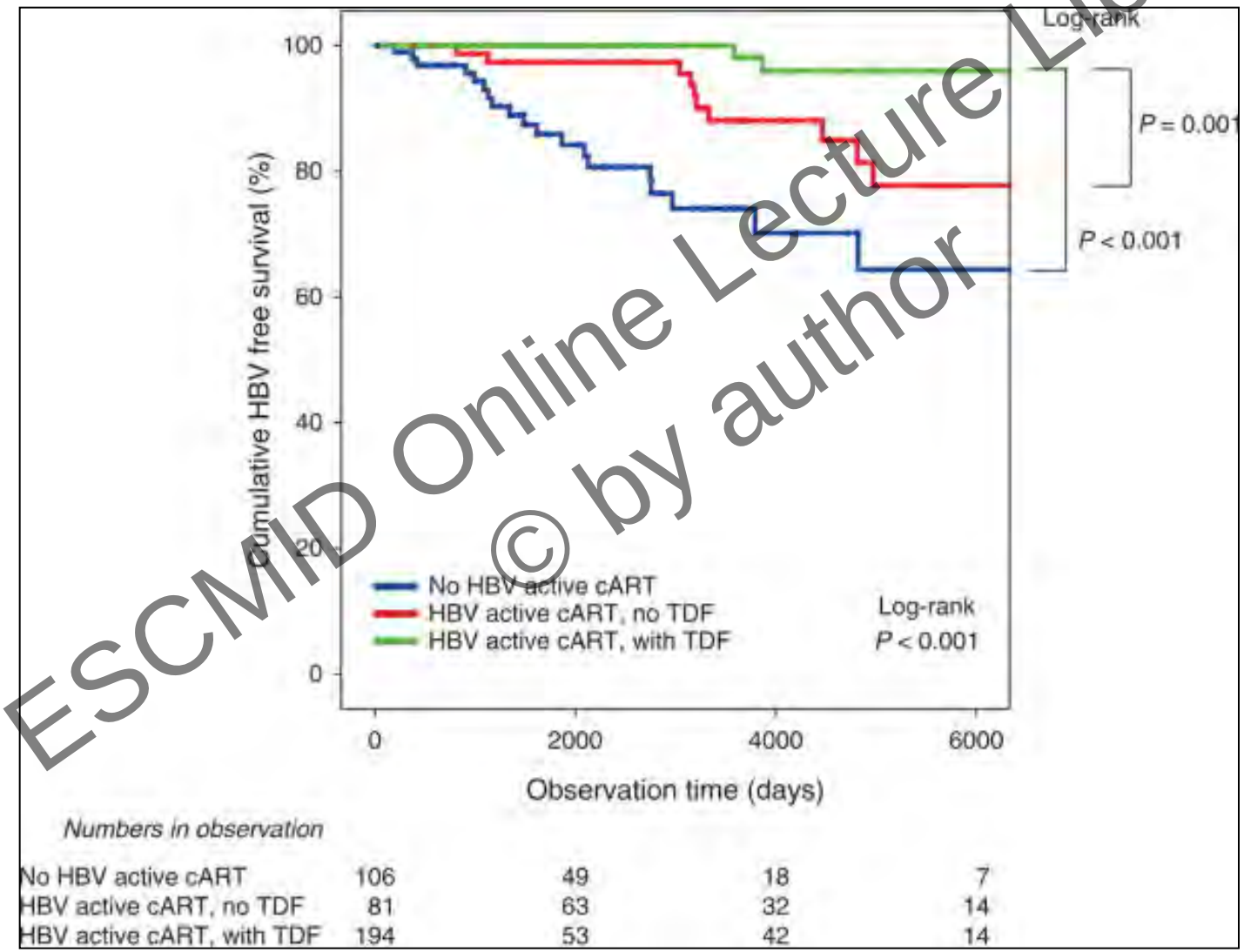
TDF as PrEP versus HBV vaccination

Is HBV vaccination necessary in HIV+ patients?

- in low endemic countries large part of HIV+ patients has never been exposed to HBV

- HBV vaccination is not effective in patients with very low CD4 cell counts

HBV-active cART protects against the occurrence of de-novo HBV infection



Numbers in observation

No HBV active cART	106	49	18	7
HBV active cART, no TDF	81	63	32	14
HBV active cART, with TDF	194	53	42	14

Brinkman et al. AIDS 2014

TDFas PrEP

Figure 1A. STB Study Designs
Studies 104 (Ph 2), 102 (Ph 3), and 103 (Ph 3)

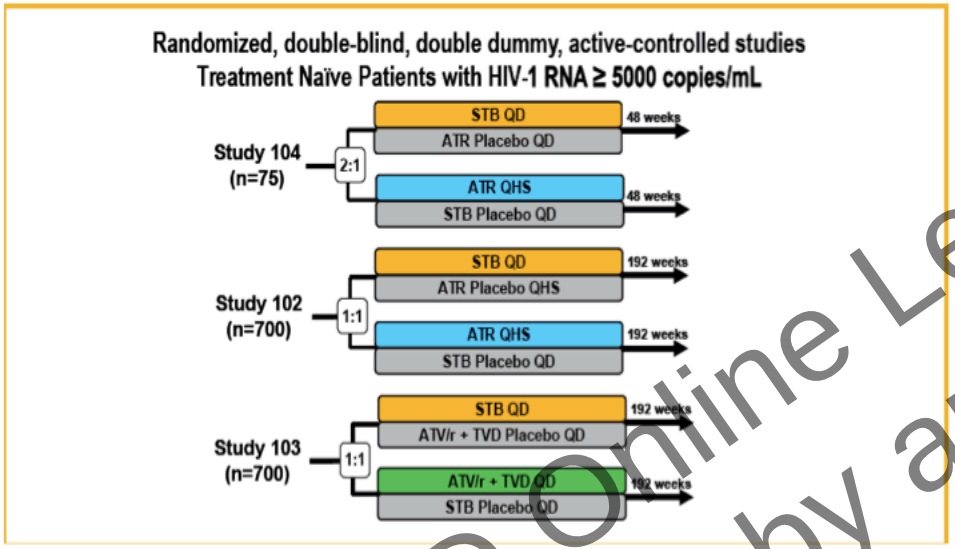
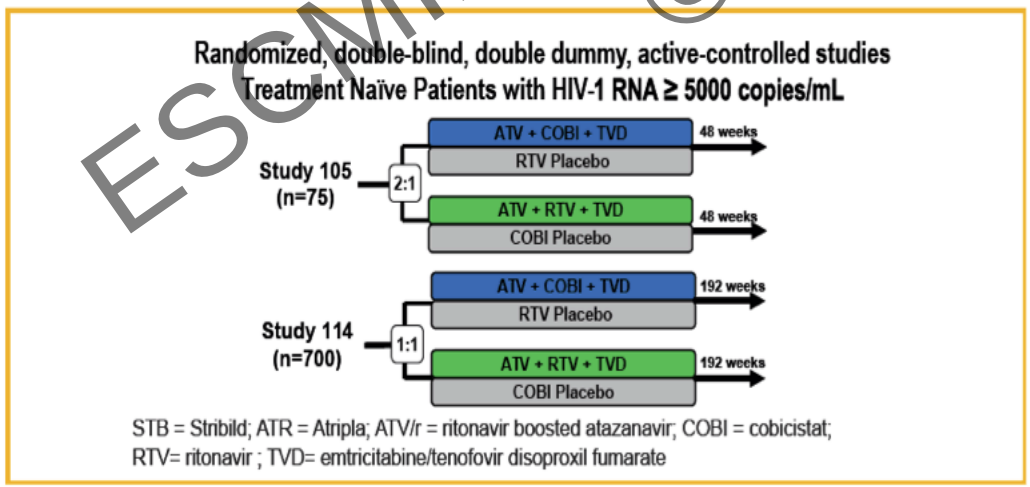


Figure 1B. STB Study Designs
Studies 105 (Ph 2) and 114 (Ph 3)



STB = Stribild; ATR = Atripla; ATV/r = ritonavir boosted atazanavir; COBI = cobicistat; RTV= ritonavir ; TVD= emtricitabine/tenofovir disoproxil fumarate

- Gilead-study:
  - evaluation of 5 TDF-containing studies
    - n=2250 subject
  - 20 acute HCV found but no acute HBV cases reported

Quirk et al. EACS 2013

Two possible strategies

HBV vaccination	
positive	• once protected then life long • cheap
negative	• not effective with low CD4 cells • consider double dose and accelerated schedule

TDF treatment	
positive	• possible in low CD4 counts
negative	• costly • remember when stopping TDF

Conclusions

- with adequate and potent cART (TDF-containing) liver fibrosis progression (and liver related complications) seem less severe
- due to older age and comorbidities TDF-toxicity will increase
- TAF seems promising to replace TDF also for HBV
- vaccination of TDF als PrEP deserves further tought

Questions?