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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Prof Karine Lacombe	None
Date	**November 2013**

Sixth Annual BHIVA Conference for the Management of HIV/Hepatitis Co-infection

in collaboration with BASL *and* BVHG

Wednesday 13 November 2013

HBV in HIV patients: is it still an issue?

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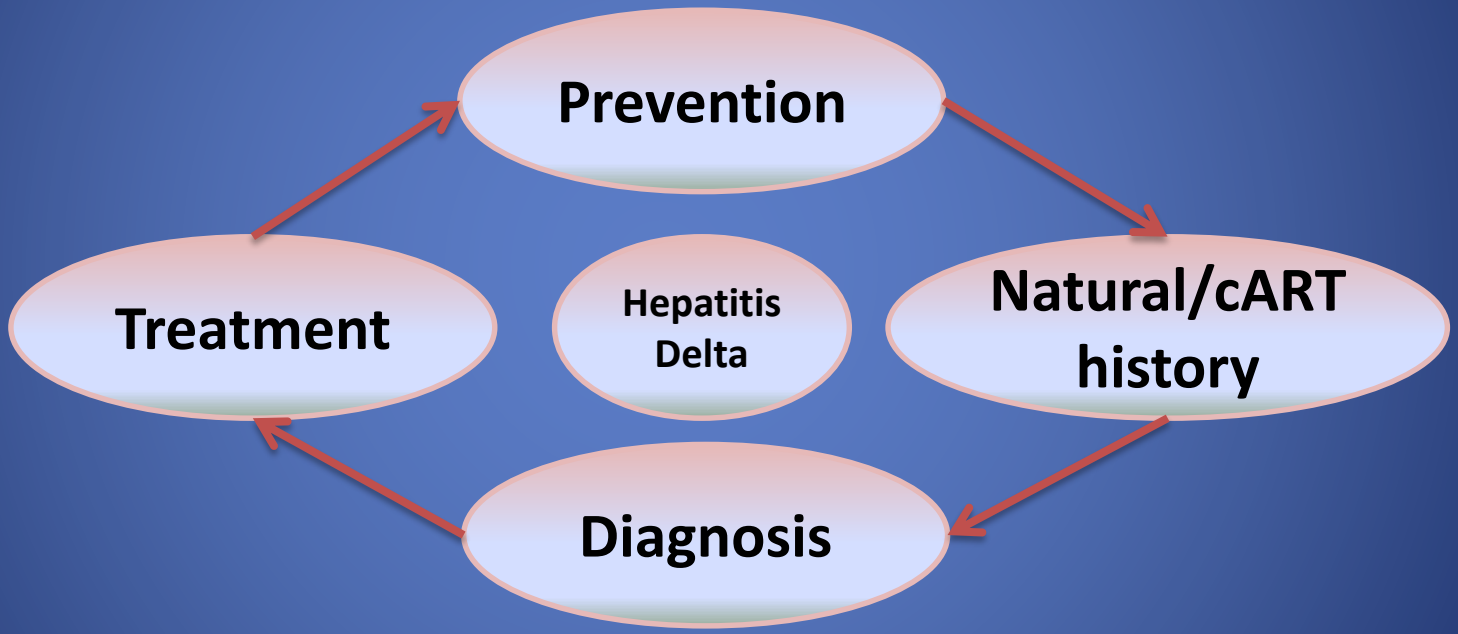
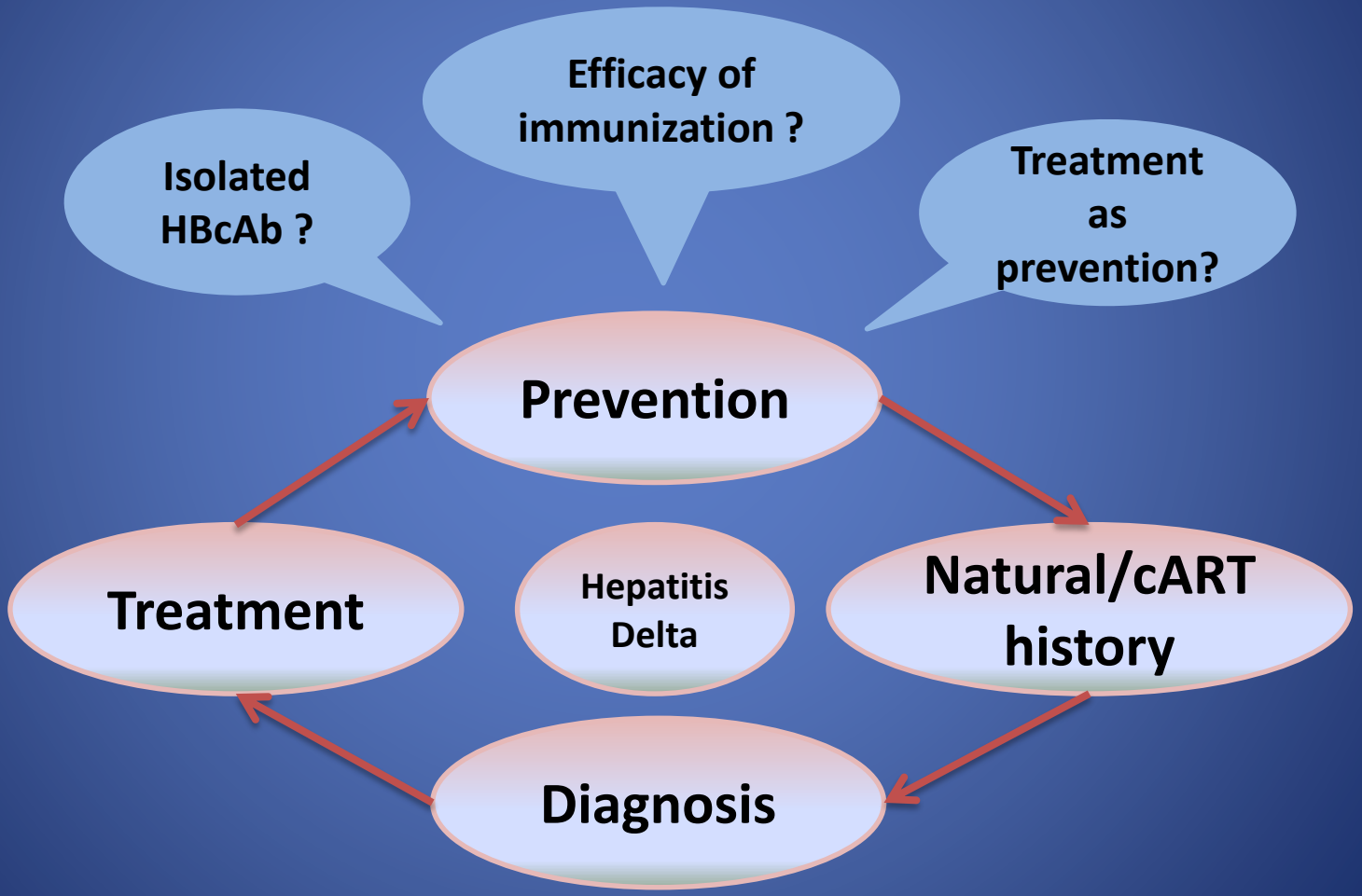
HBV in HIV patients: the continuum of care




Efficacy of immunization ?
Isolated HBcAb ?
Treatment as prevention?
Prevention
Treatment
Hepatitis Delta
Natural/cART history
Diagnosis

HBV immunization in HIV

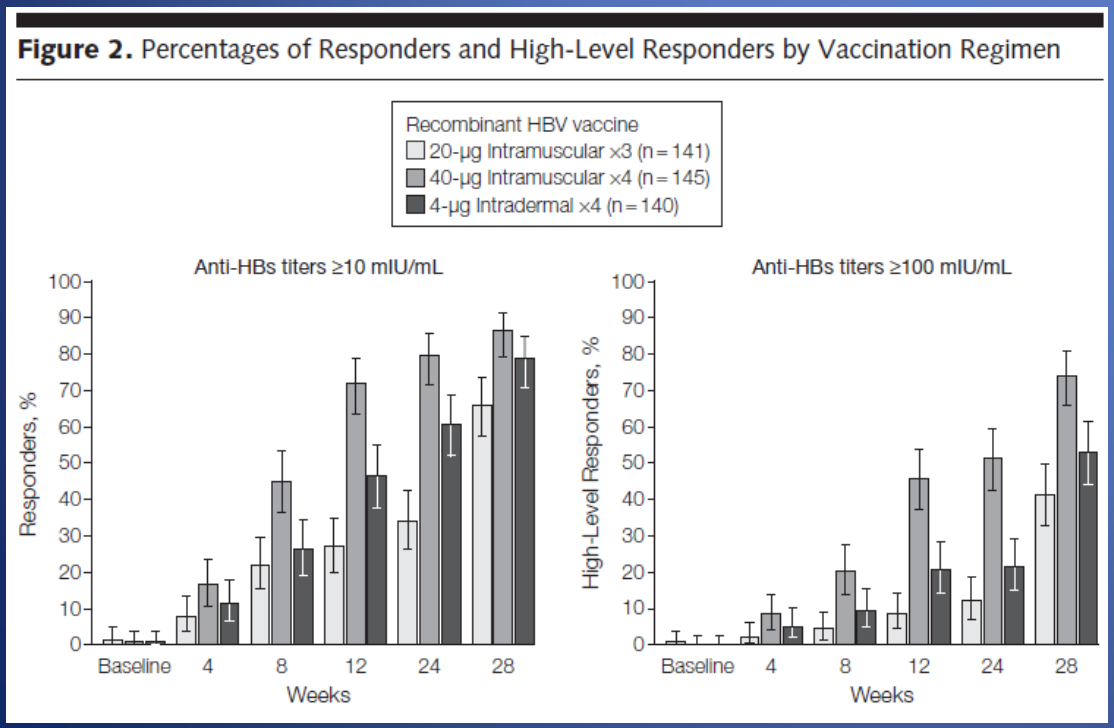
- Unsufficient HBV vaccine coverage and vaccine response[1]:
  - 32% of eligible patients were vaccinated
  - in those with one injection, immunization course completed in 57%
  - achivement of protective Ab titer in 37%

[1]Tedaldi EM, Clin Infect Dis 2004

Increasing HBV immunization

➔2 options:

- increasing the dosing (40µg instead of 20µg)
- increasing the number of injections (4 instead of 3)

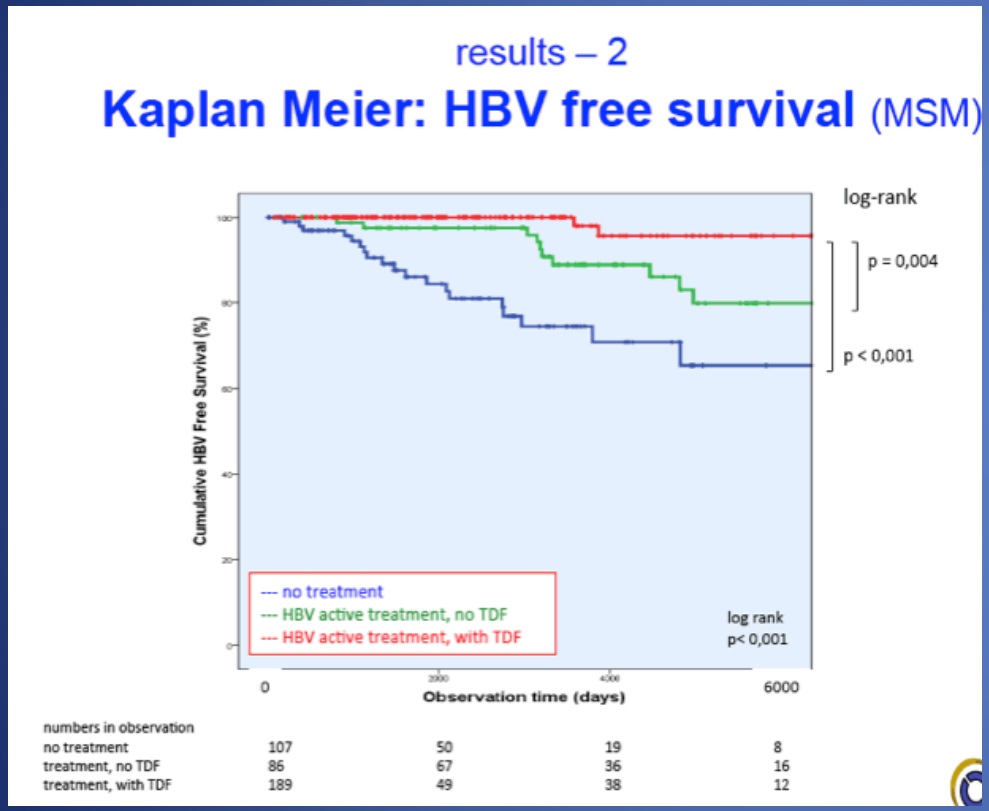


Confirmed by a meta-analysis of 5 trials (883 patients):
OR = 1,82 (1,47 – 2,61) of higher HBsAb titer in 4-doses v. 3-doses schedule

Ni JD, et al. Int J STD AIDS 2013

Launay O. et al, JAMA 2011

Treatment as prevention in HBV



- Dutch HIV cohort of 2942 patients[1]
- 871 « HBV susceptible »
- 35 HBV-infected during follow-up
- Treating non protected patients with TDF prevented transmission
- Same results in the study by Gatanaga[2]

➔ **Should TDF be used within « treatment for prevention » paradigm?**

[1]Heuft M, et al. CROI 2013. [2]Gatanaga, Clin Infect Dis 2013

Management of isolated HBcAb

SHOULD WE TREAT?

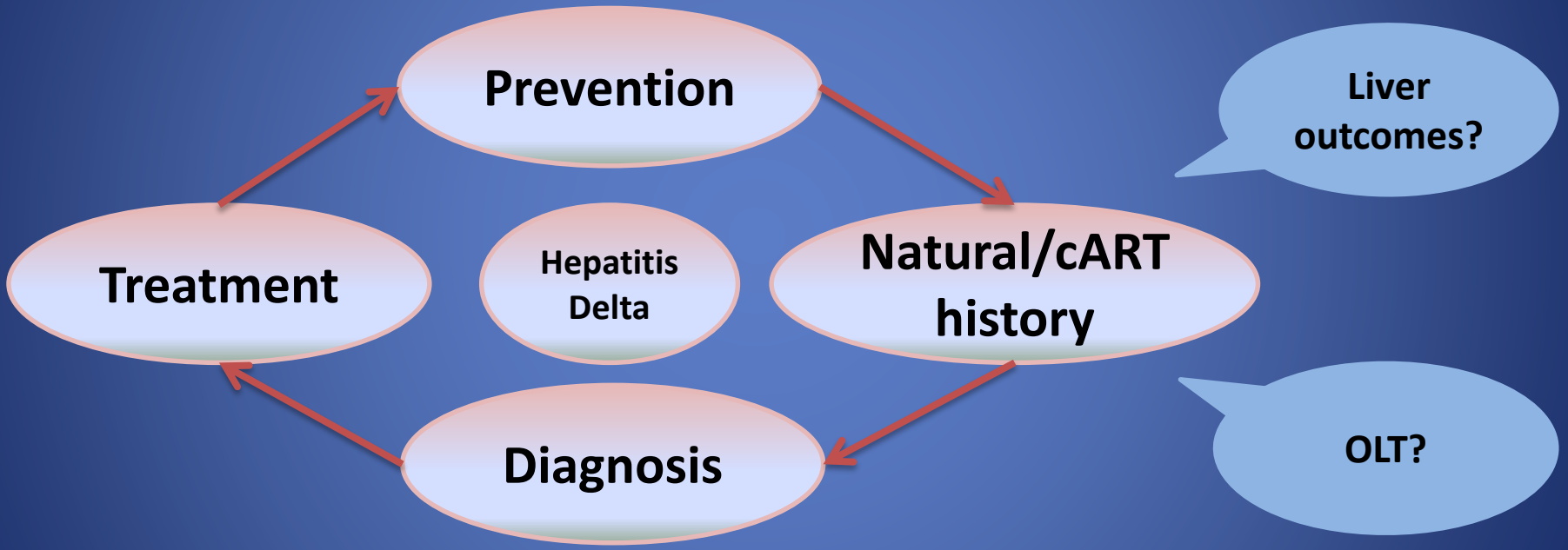
- Frequency of occult HBV differing regarding geographical origin: <1% in Europe[1], ≈5% in Africa[2]
- Most patient on TDF in Europe: controled « occult HBV »?
- High risk of reactivation at treatment interruption[3]

SHOULD WE IMMUNIZE?

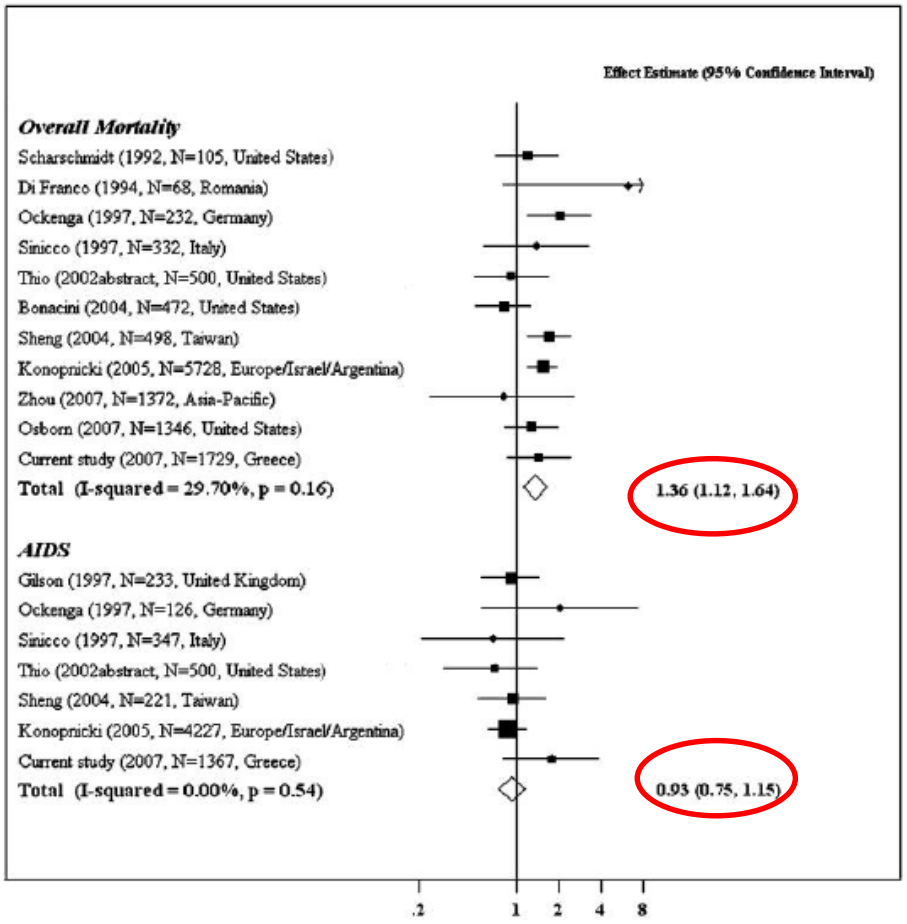
- **In 40 patients vaccinated with 1 to 6 vaccine doses[4]:**
  - anamnestic response: 32%
  - Vaccine response:74%
  - Durability of response: 74% of patients with median titer = 61UI at 1 year
- **In 37 patients vaccinated with 1 to 3 vaccines doses[5]**
  - anamnestic response: 22%
  - Vaccine response: 60%
  - Durability of response: 52% of patients at 2 years

➔ **anti-HBV treatment is indicated, immunization is not recommended**

[1]Liang SH, J AIDS 2010. [2]N'Dri Yoman T. Antivir Ther 2010. [3]Bloquel B, J Med Virol 2010.
[4]Chakvetadze C, et al. CID 2011. [5]Kaech C, et al. J Infect 2012


Prevention
Liver outcomes?
Treatment
Hepatitis Delta
Natural/cART history
Diagnosis
OLT?

HBV infection and mortality risk (1)



- multicenter cohort + meta-analysis of 12 382 patients, either HIV+ or HIV/HBV
- 36% excess risk of dying (all cause) if HBs pos. compared to HBs neg.

➔ Higher mortality risk in HIV-HBV compared to HIV patients between 1992 and 2007

Nikolopoulos G, Clin Infect Dis 2009

HBV infection and mortality risk (2)

- MACS cohort: (337HBs+ - 343 HCV+) of whom 452 HIV+ ➔ 6728 person-years of F/U, 293 deaths

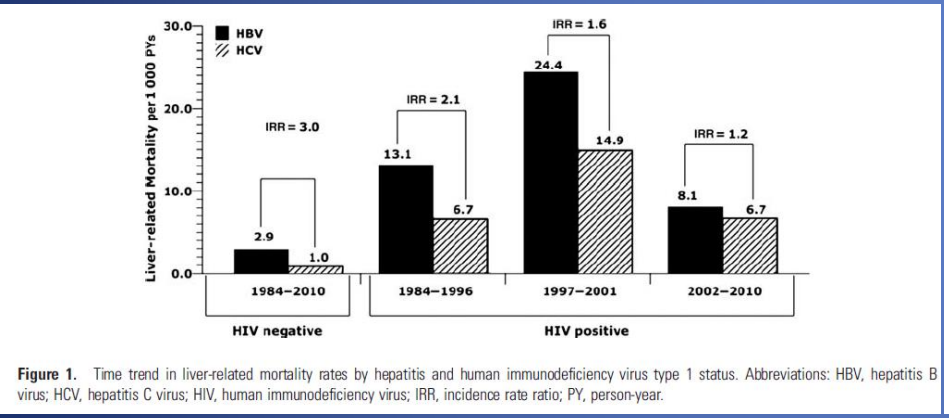


Figure 1. Time trend in liver-related mortality rates by hepatitis and human immunodeficiency virus type 1 status. Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IRR, incidence rate ratio; PY, person-year.

Table 3. Multivariable Analysis of Liver Death in HIV-Infected Individuals

Variable	IRR	95% CI	*P* Value
Hepatitis status			
HCV	1		
HBV	2.2	1.1–4.5	.03
Older age			
Per 10-year increase	1.6	1.1–2.3	.01
Latest CD 4 count			
>350 cells/mm^3	1		
200–350 cells/mm^3	7.0	2.4–20.1	<.001
<200 cells/mm^3	16.2	6.1–42.8	<.001

➔ **RR=2,2 [1,1 – 4,5] of dying of liver-related cause when HBs pos. V. HCV pos.**

➔ **No difference between HCV and HBV regarding all cause deaths**

Falade-Nwulia O, et al. Clin Infect Dis 2012

Impact of cART on liver-related deaths

Table 3. The adjusted IRR of cause-specific death by year longer on cART.

Cause of death	IRR	95% CI	*P*
All-cause	0.95	0.92–0.97	<0.001
AIDS	0.86	0.81–0.91	<0.001
Non-AIDS	0.97	0.95–1.00	0.061
NARI-death	0.97	0.90–1.05	0.417
LR-death	0.94	0.89–1.00	0.053
NADM-death	1.07	1.00–1.14	0.056
CVD-death	0.99	0.93–1.06	0.885
Violent death	0.90	0.81–0.99	0.027
Other death	1.01	0.94–1.09	0.725
Unknown death	0.94	0.86–1.01	0.096

CI, confidence interval; CVD, cardiovascular disease; IRR, incidence rate ratio; LR, liver-related; NADM, non-AIDS-defining malignancies; NARI, non-AIDS-related infection. Models' adjustment as in Table 2.

- Eurosida cohort: 12069 patients included in analysis

Kowalska, et al. AIDS 2012

Clinical outcomes in the era of cART

- 92 patients, 82% treated with FTC/TDFmedian f/u=39 months[1]

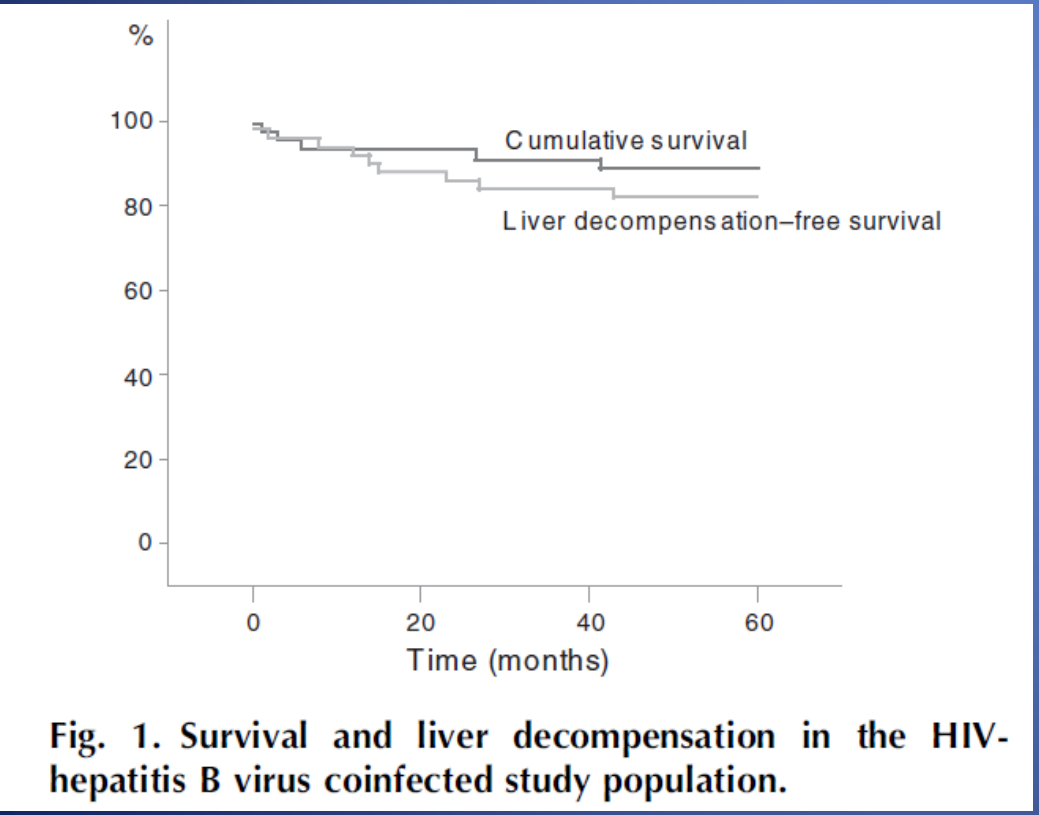


Fig. 1. Survival and liver decompensation in the HIV-hepatitis B virus coinfected study population.

- I(death): 2,2 / 100 p.y
- I(liver dec.) 2,9 / 100 p.y

➔Close to what is observed in HIV general population

- liver fibrosis stability in 75% of patients

Martin-Carbonero, et al. AIDS 2011

Survival rate in transplanted patients: data from France

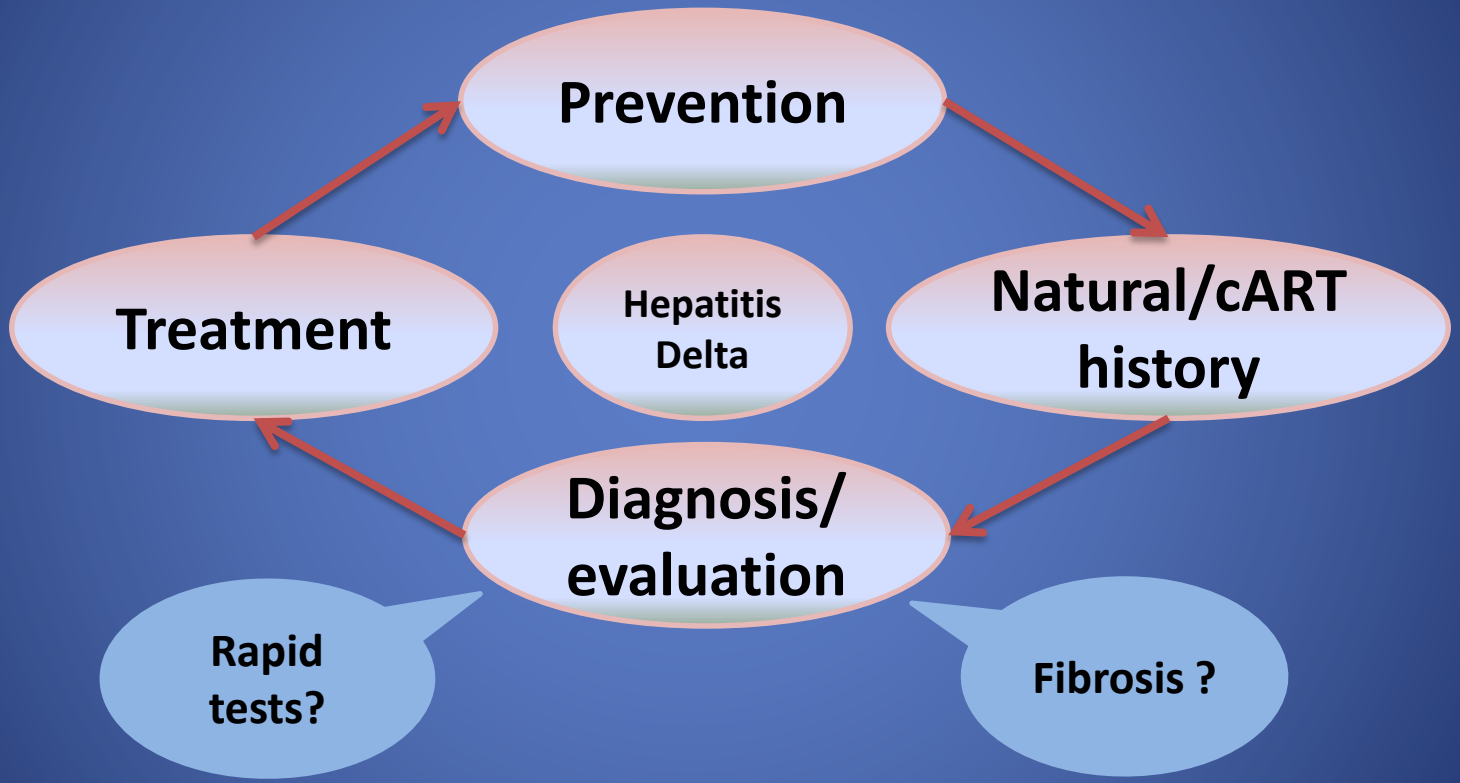
- 13 patients (1HDV+, 2 HCV+, 4 HCV-HDV+)
- Indication for OLT: decompensated cirrhosis (10) and HCC (3)
- Treatment after OLT: combination of TDF / 3TC + HBIg
- Overall survival rate at 32months: 100%
  - No mitochondrial toxicity
  - Controled HBV-DNA, HDV-RNA, HIV-RNA
  - Successful treatment with PR in 1/3 HCV-RNA+

Tatteo, et al. AIDS 2009

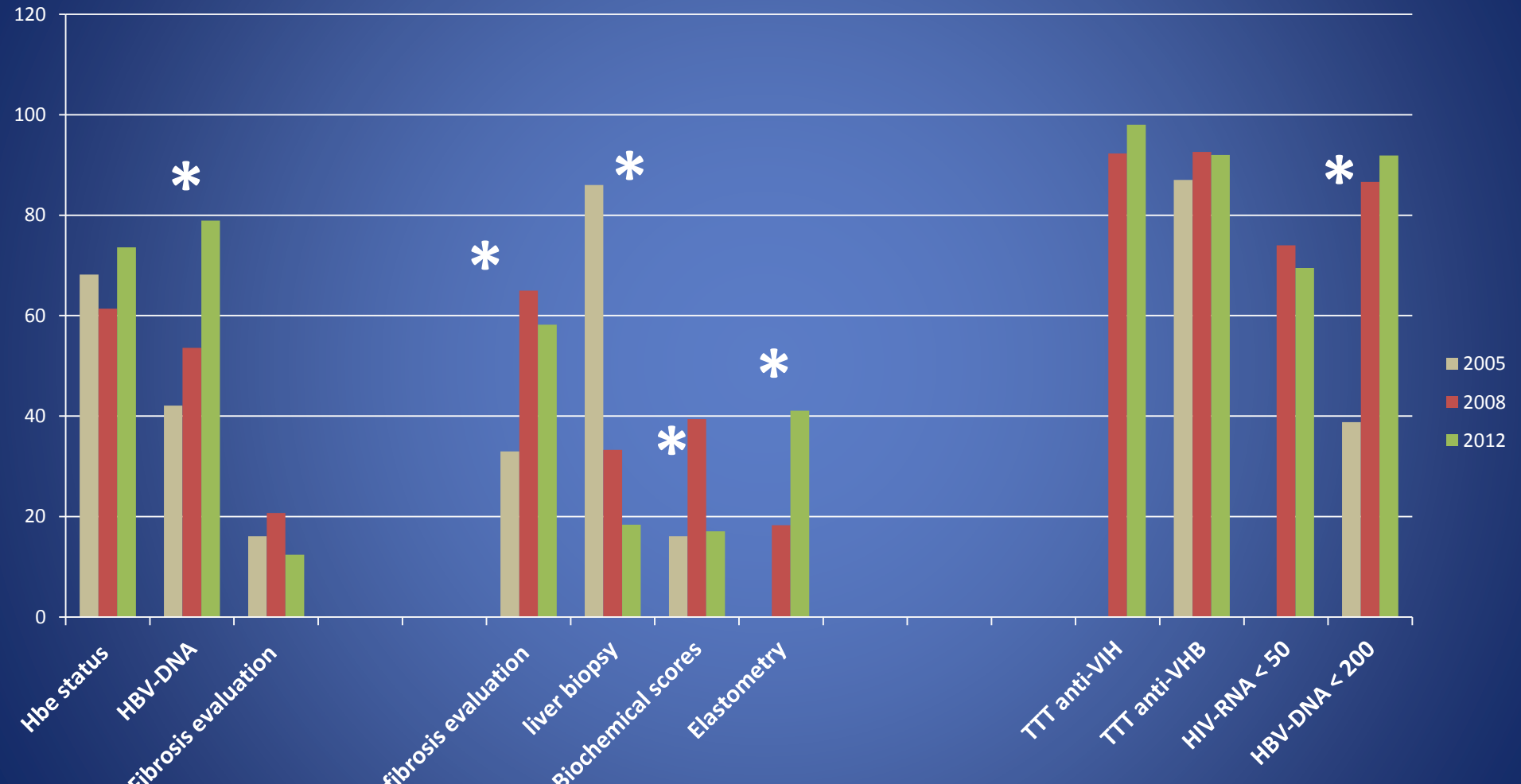
Survival rate in transplanted patients: data from the USA

- 22 patients (2 HCV+) matched with 20 HBV mono-infected patients
- Indication for OLT: decompensated cirrhosis (19), HCC (2), fulminant (1)
- Overall survival: 85% in HIV-HBV, 100% in HBV (p=0,09)
  - 3 deaths due to causes unrelated to HBV
  - Persistent low replicating HBV-DNA in 6/7patients with available HBV-DNA after OLT

Coffin, et al. Am J Transplant, 2010


Prevention
Natural/cART history
Diagnosis/ evaluation
Treatment
Hepatitis Delta
Rapid tests?
Fibrosis ?

Increasing screening in HIV patients



EPI-B studies, 2005, 2008, 2012 (AIDS 2007, J hepatol 2012, Submitted)

Can rapid tests increase screening efficacy?

Performance of 3 HBsAg rapid tests on capillar blood in the community[1]

	Patients	AUC, [95% CI]	Se	Sp
Vikia® HBsAg	3956	0.98 [0.96 - 1.00]	96.5	99.9
Quick Profile™ HBsAg	3950	0.95 [0.92 - 0.98]	90.5	99.7
Determine™ HBsAg	2478	0.97 [0.93 - 1.00]	93.6	100

- **In African rural settings[2], performance of Determine test: Se=96% / Sp=100%**
- **Are rapid tests reliable in the HIV settings?**
  - **YES[3] → κ correlation coefficient = 1 / Se=100% and Sp=100% in study done in Liverpool on 300 sera from HIV+ patients from Malawi (CD4 = 175)**

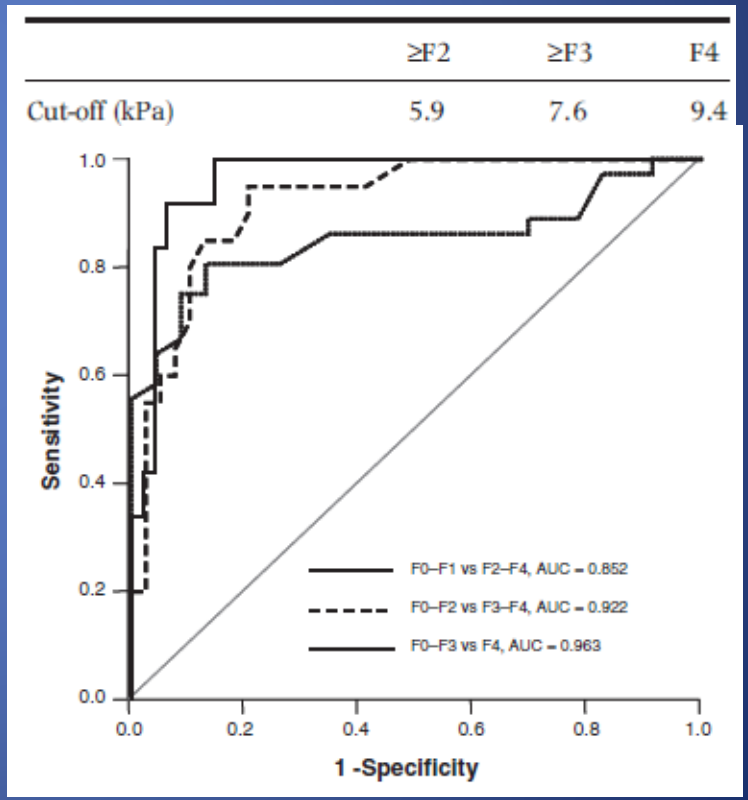
[1]Bottero J, et al. J Hepatol 2013. [2]Franseck FC, et al. PlosOne 2013. [3]Davies J, et al. Trans R Soc Med Hyg 2010

Non invasive Fibrosis Evaluation: still challenging

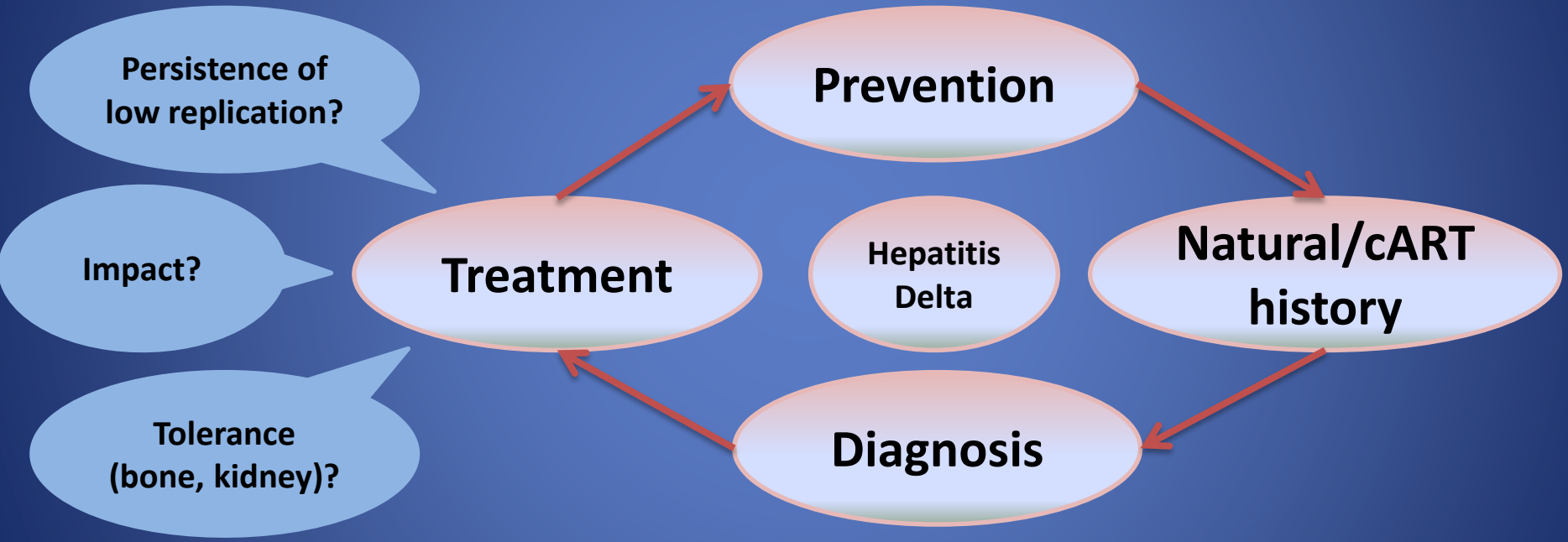
➔ *134 patients, 11 scores tested*[1]

scores	AUC	Cut-offs	(HCV)
Fibrometer®			
-≤ F2	0,74	0,46	0,5
- ≤ F3	0,83	0,69	
- F4	0,89	0,83	
Fibrotest®			
-≤ F2	0,77	0,43	0,49
- ≤ F3	0,80	0,59	0,59
- F4	0,87	0,74	0,75

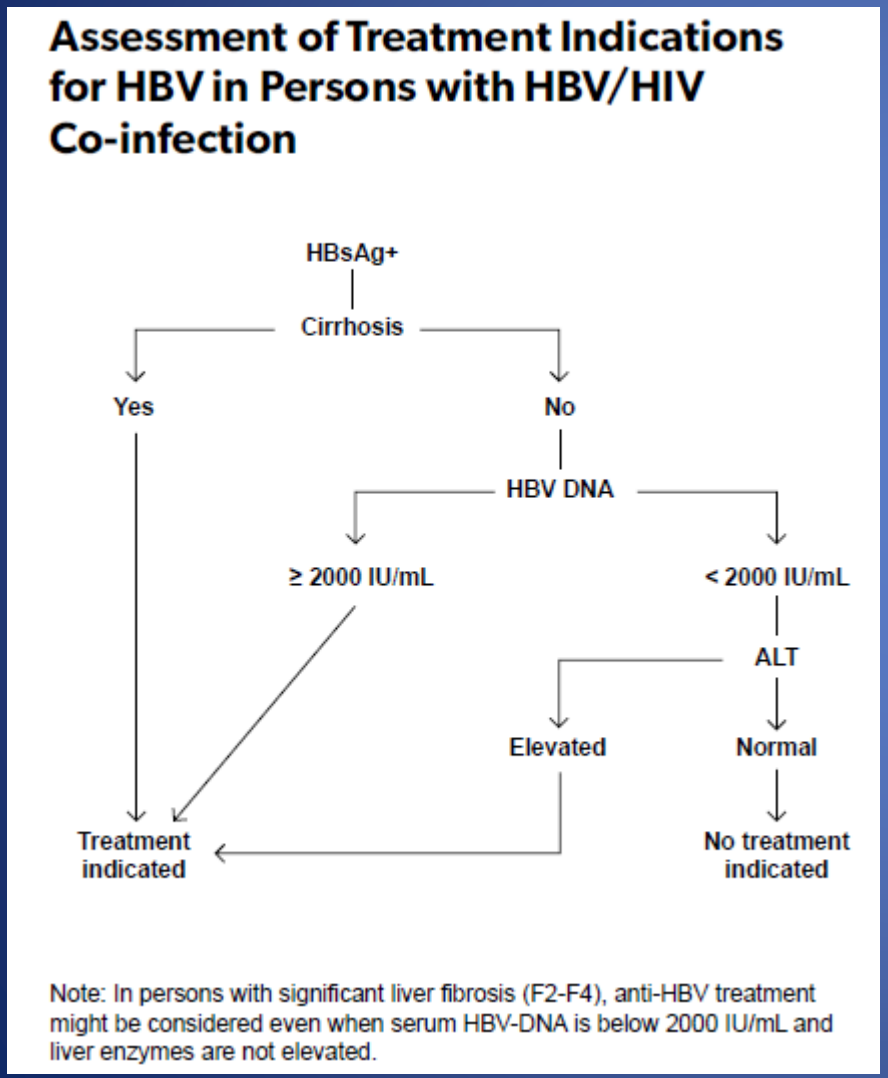
➔ *57 patients, elastmetry*[2]

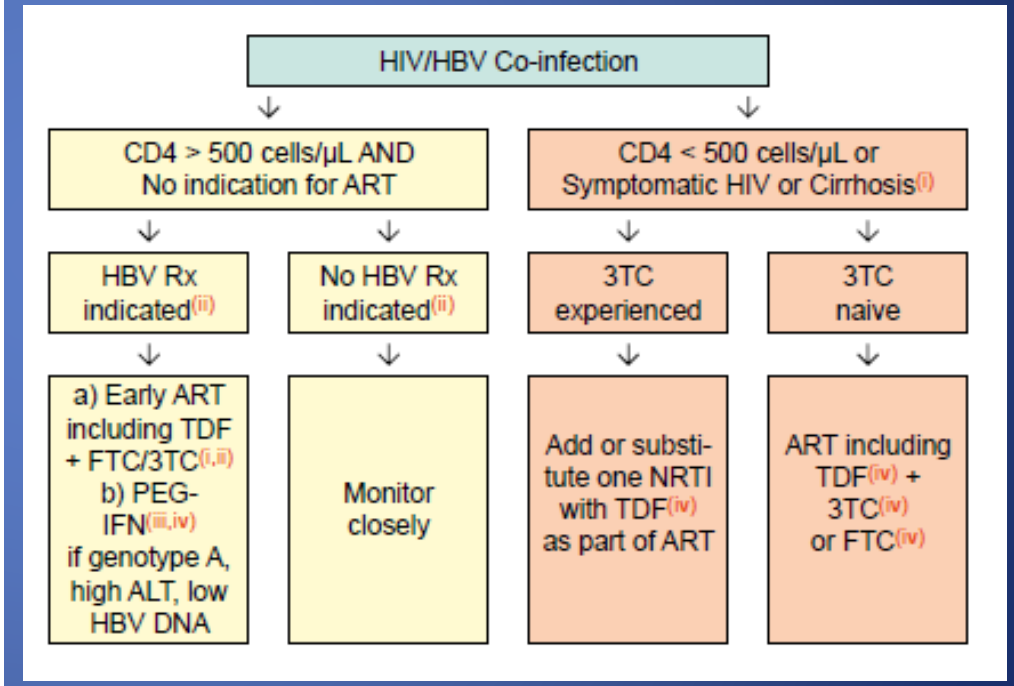


[1]Bottero J. J Hepatol, 2009. [2]Miailhes P. J Viral Hepat 2010


Persistence of low replication?
Impact?
Tolerance (bone, kidney)?
Prevention
Treatment
Hepatitis Delta
Natural/cART history
Diagnosis

Treatment algorithms





EACS Guidelines Nov 2013

Treatment efficacy with TDF

- 102 patients (61% HBeAg+) with a median 5 years of follow-up

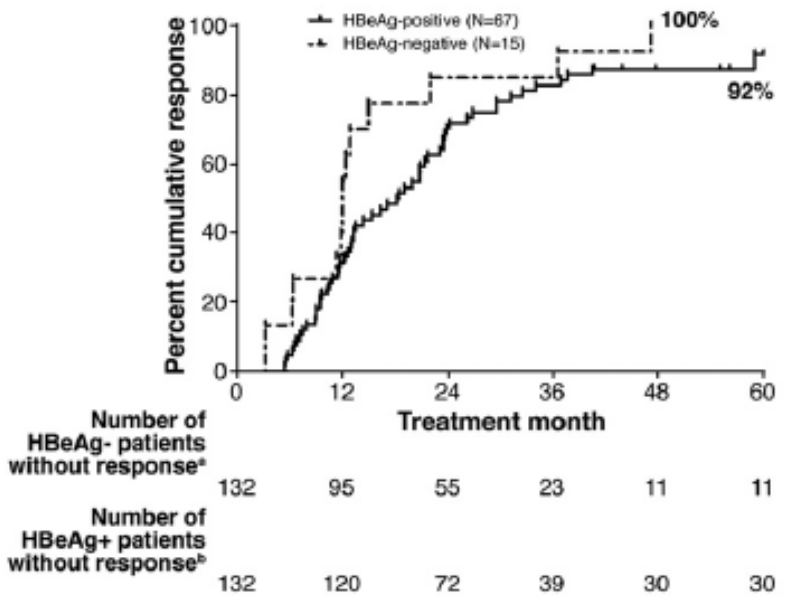
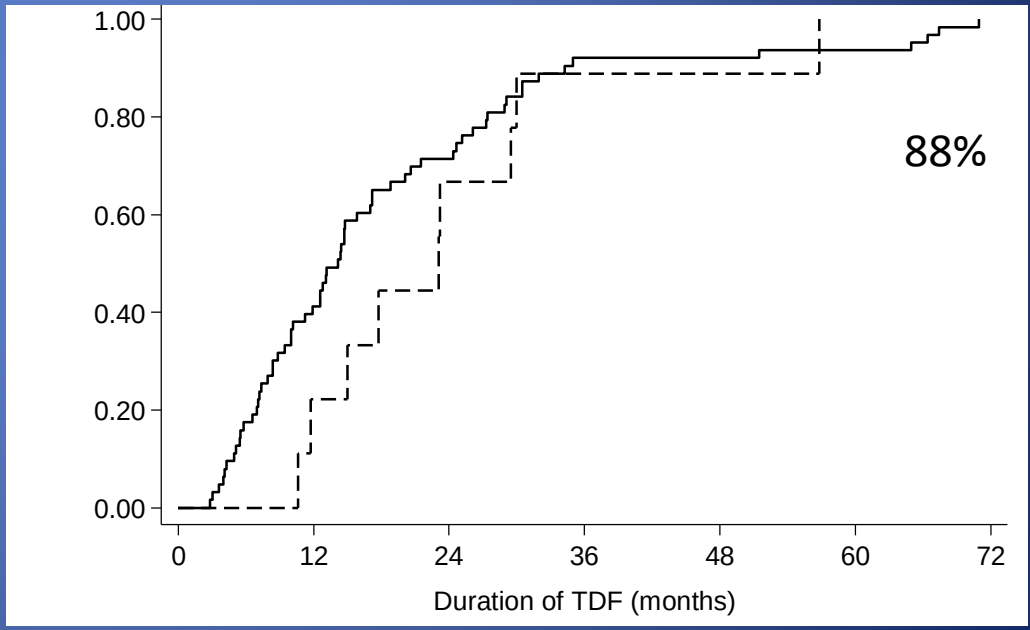


Figure 1. Kaplan–Meier curve for the cumulative probabilities of achieving virologic response, defined as HBV-DNA levels less than 20 IU/mL, for HBeAg-positive (n = 67) and HBeAg-negative (n = 15) HIV/HBV with patients with detectable HBV DNA at baseline (n = 82).

- 120 patients (63% HBeAg +) with a minimum of 1 year of TDF and a median 6 years (3 – 8) of follow-up



De Vries Suijs T, et al. Gastroenterol 2010

Boyd, et al. Submitted

Role of Peg-IFN in TDF-treated patients

EMVIPEG: pilot study evaluating the addition of Peg-IFN to TDF in HIV-HBV patients [1]

	On Peg-interferon + tenofovir + emtricitabine				On tenofovir + emtricitabine
Variables	W0 N=51	W12 N=50	W24 N=50	W48 N=50	W72 N=50
Patients with ALT < ULN [1]: [n(%)]	39 (76)	26 (52)	26 (52)	34 (68)	43 (86)
HBV DNA >100 copies/ml: [n(%)]	20 (39)	19 (38)	10 (20)	5 (10)	6 (12)
HBeAg loss: [n (%)] [3]	2 (4) [2]	2 (4)	8 (16)	10 (20)	10 (20)
Anti-HBe seroconversion: [n (%)] [4]	0	3 (6)	5 (10)	4 (8)	4 (8)
HBV sustained response : [n (%)]	0	NA	NA	NA	4 (8)
HBsAg loss [n(%)]	0				2 (4)
% CD4 : [médian(range)]	29 (11-45.3)	32 (11-46)	34 (10-51)	31.5 (12-49.6)	31.8 (14-47.2)
CD4 cell count : [médian (range)]	506 (175-1316)	369 (139-955)	368 (102-879)	372 (149-834)	516 (176-1292)
HIV RNA <50 copies/ml: [n (%)]	49 (96)	45 (90)	49 (98)	45 (90)	44(88)

↳No benefit of adding Peg-IFN regarding antiHBe seroconversion or HBs loss rate

1 Miailhes P, et al. CROI 2013

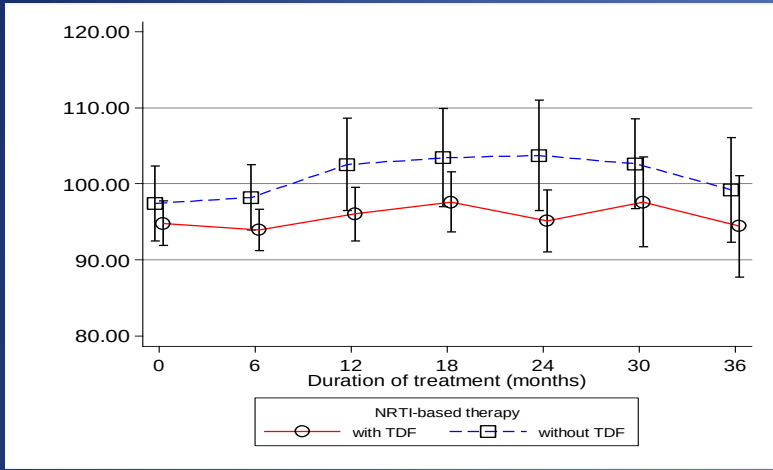
Persistent HBV replication

- **MAGNITUDE:** 5 to 10% of patients on TDF after > 3 years[1,2]
- **PATTERNS:** blips, persistent viremia, rebound[2,3]
- **CAUSES:**
  - suboptimal adherence: YES[2,3]
  - suboptimal treatment: NO[4] (maybe in pre-treated patients)[3]
  - resistant strains: NO[2,3,5]
  - failing immunological control?
- **IMPACT:**
  - no Hbe or HBs loss in patients w/ persistent replication, no clinical event[6]
- **MANAGEMENT:**
  - confliting results regarding addition of ETV[7,8,9]
  - check adherence[10]
  - stay on same therapy if regular decrease > 1 year[10]
  - add ETV only long-term stagnation of HBV-DNA [10]
  - reconsider after 6 months[10]

[1]de Vriis Sluijt 2010. [2]Boyd 2009. [3]Matthews 2013. [4]Matthews 2008. [5]Childs, AIDS 2013. [6]Boyd *submitted*. [7]Luetkemeyer, JAIDS 2011. [8]Ratcliffe, AIDS 2011. [9]Mikulska, J Med Virol 2012. [10]EACS/EASL Guidelines 2012 and 2013

Long term tolerance of TDF

Figure 1: MDRD clearance over time



- 240 patients with a 3year-time follow-up, normal eGFR at baseline[1]: no difference with other NUC
- **Available data on renal and bone impairment over time in HIV-infected patients on long-term use of TDF (> 6 years)**
- **TDF- associated tubular nephropathy very rarely described in HBV-infected patients[2,3]**

MANAGEMENT:

- Check the imputability of TDF in alteration of renal Cl. (send to kidney specialist and biopsy)
- Decrease TDF dosage(1cp/2-3 days)
- No place for ADV
- Add probenecide ?
- Switch for ETV if no previous exposure to 3TC?

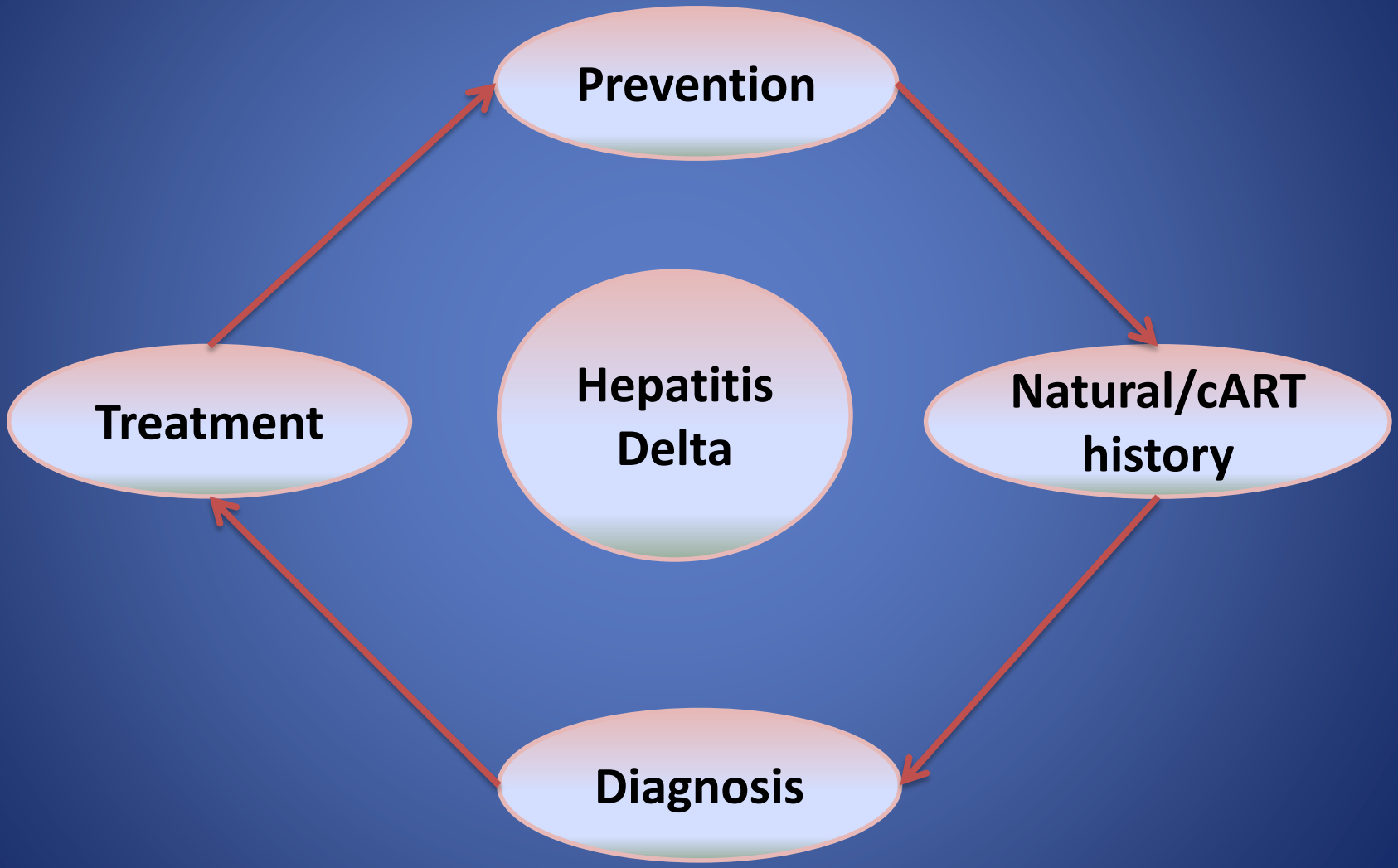
1Lacombe K, EASL 2008. 2Si-Ahmed SN, Antiviral Res 2011. 3Gish RG, Clin Gastroenterol Hepatol 2012

Emergence of treatment and immune escape mutants

Groups of mutations	% of patients with incident mutations	
	TDF±LAM/FTC	numerous switchs
	% (*n*)	% (*n*)
Alkyl phosphonate-associated *pol*-gene	(*n*=49)	(*n*=15)
	6.1%	6.7%
Immune-associated *S*-gene	(*n*=73)	(*n*=18)
	1.4%	5.6%
L-nucleoside-associated *pol*-gene/antiviral-associated *S*-gene	(*n*=64)	(*n*=15)
	9.4%	33.3%

➔ **Emergence of antiviral-associated S mutations conferring resistance to current NUCs and potential vaccine escape strains[1]**

Lacombe K, Hepatology 2013


Prevention
Natural/cART history
Diagnosis
Treatment
Hepatitis Delta

Prevalence of HDV markers in HIV

Manesis EK. EASL Monothematic Conference Delta Hepatitis. Sept 2010. Istanbul

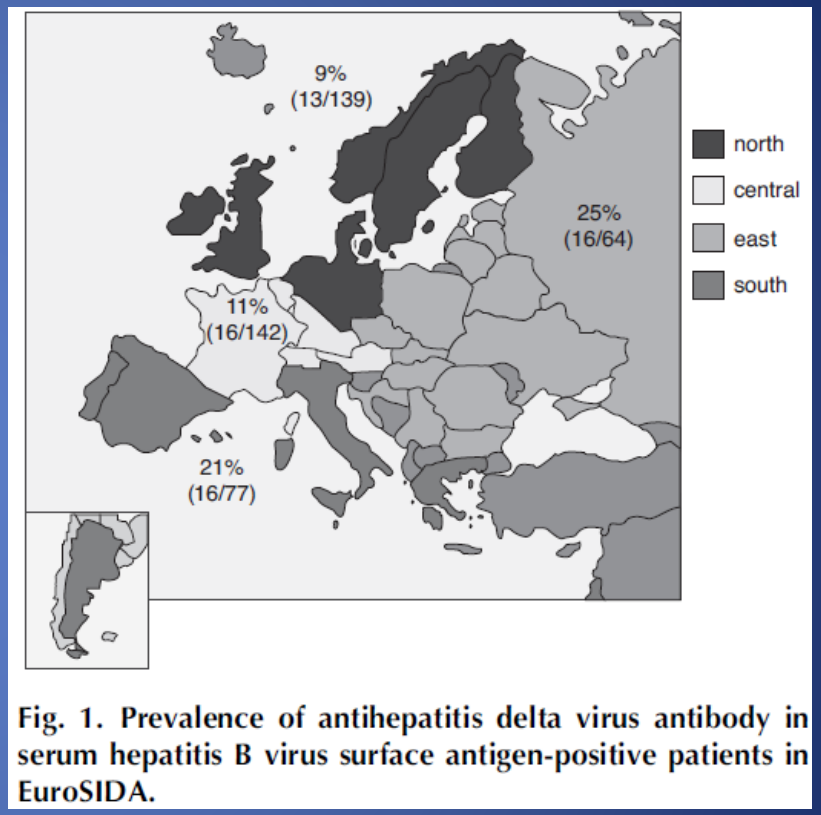
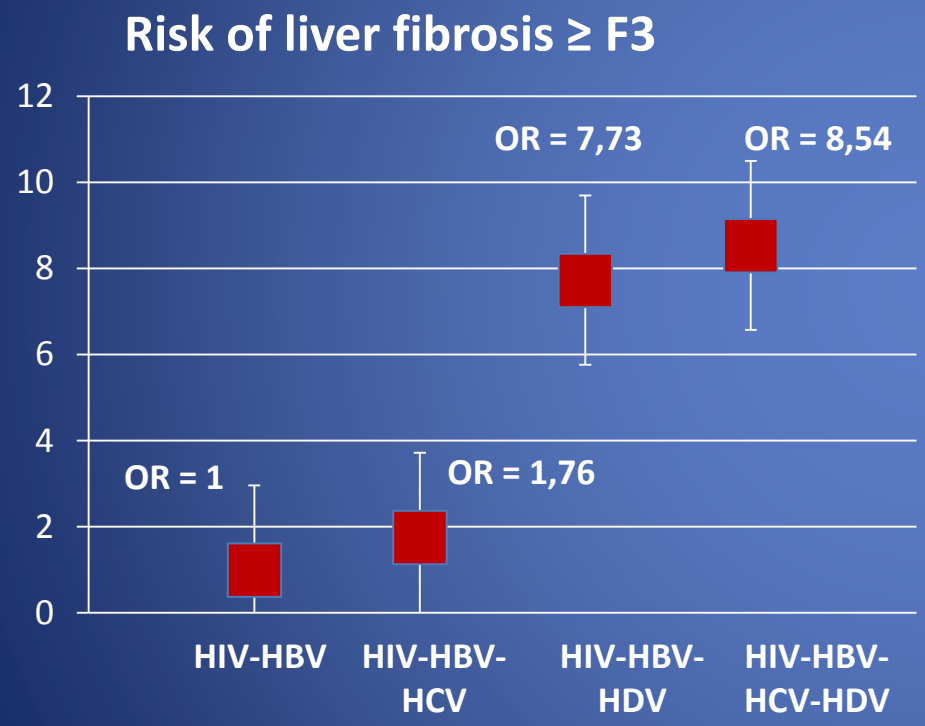


Fig. 1. Prevalence of antihepatitis delta virus antibody in serum hepatitis B virus surface antigen-positive patients in EuroSIDA.

Soriano V. et al. AIDS 2011

➔ P(HDV/HIV-HBV) = x2 (P(HDV/HBV)

Increased fibrosis in HDV-infected patients



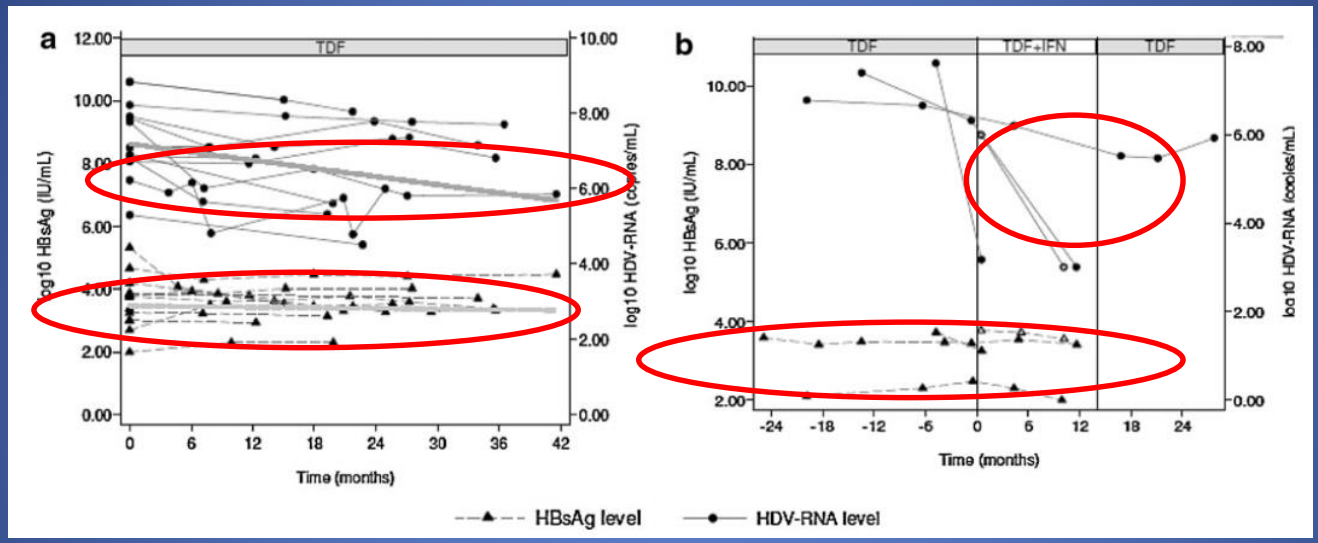
Lacombe K, et al. AIDS 2007

Predictors of clinical outcomes in HDV-infected patients, EUROSIDA

Clinical outcomes	IRR (95%CI)
Progression to death	2,23 (1,17-4,28)
Progression to liver related events	4,44 (1,46-13,55)
Progression to AIDS	1,60 (0,56-4,56)
Progression to AIDS or death	2,17 (1,22-3,87)

Soriano V, et al. AIDS 2011

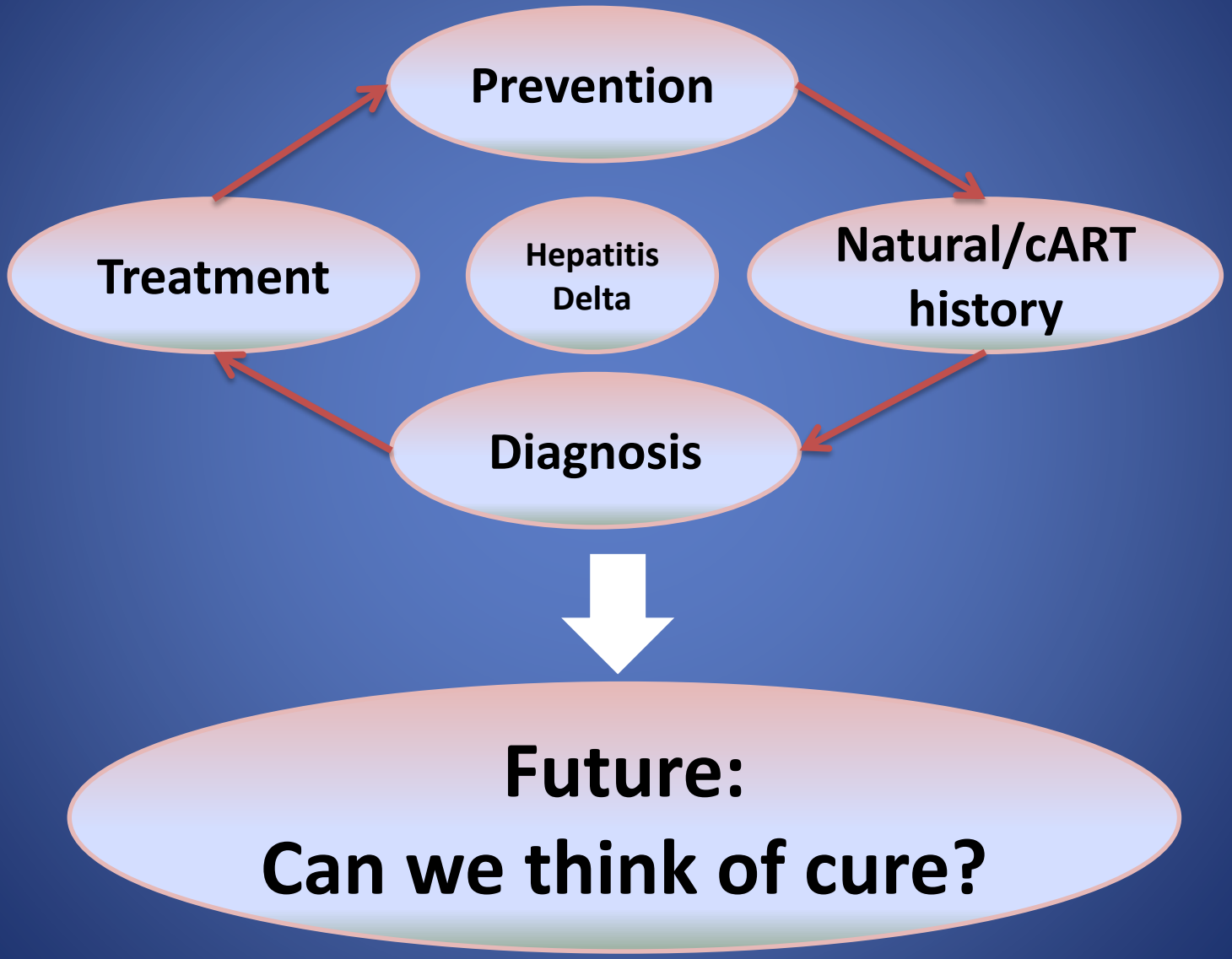
Treatment options for HDV in HIV



➔ **Persistent HDV-DNA replication in all 17 patients (including those treated with Peg-IFN + TDF after Peg-IFN interruption**

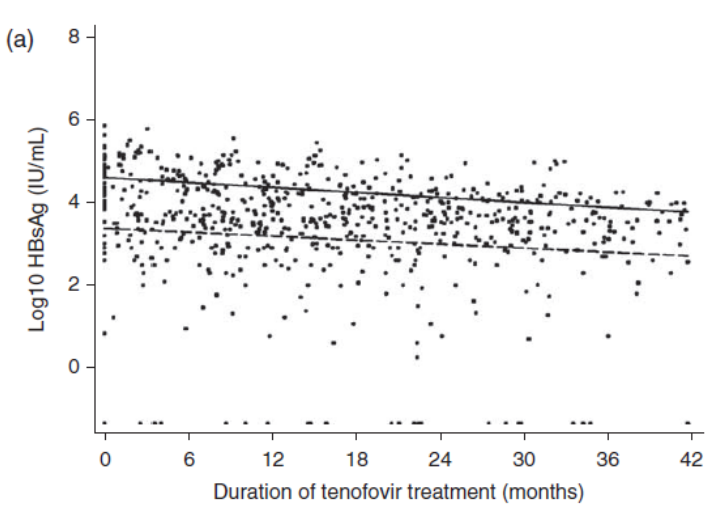
➔ **Sequential treatment with Peg-IFN ? (normalisation of transaminases, stabilization of liver fibrosis?)**

Boyd A, et al. AIDS Res Hum Retroviruses 2013


Prevention
Treatment
Hepatitis Delta
Natural/cART history
Diagnosis
Future:
Can we think of cure?

HBs loss with current treatment

Studies	Duration of F/U	Hbe loss	HBs loss
Treatment experienced			
De Vriis Sluijt, 2010 (n=102)	5 years	46%	12%
Maylin, 2013 (n=143, Hbe+=67%)	3 years	43%	4%
Treatment naive			
Matthews, 2013 (n=47, Hbe+=57%)	2 years	48%	13%



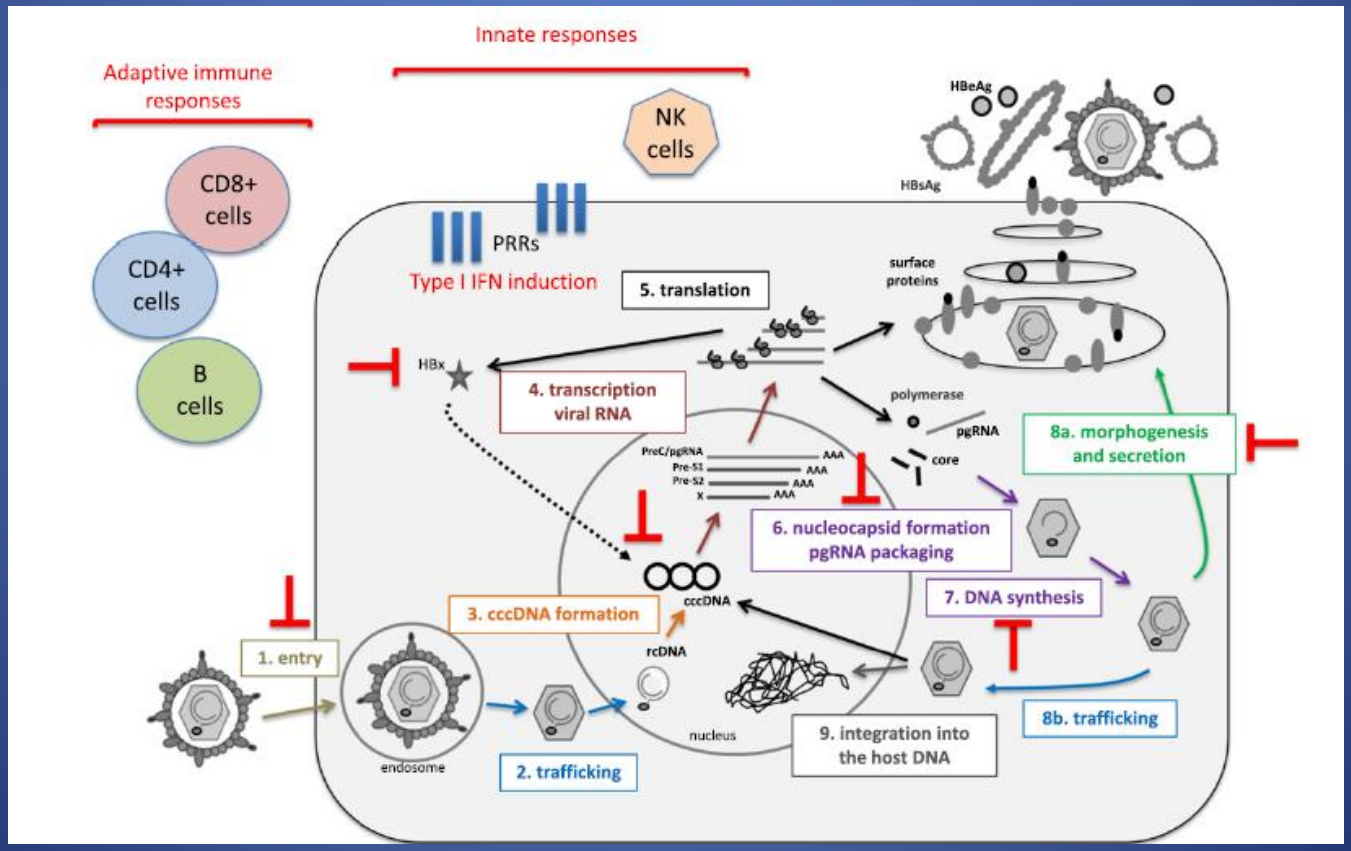
➔ **HBs loss is low with NUCs, HBs seroconversion is even lower…**

Maylin S. AIDS 2012

New therapeutic strategies

Drugs targeting virus or host[1]

New targets for « functional cure »[2]



[1]Zoulim F, Expert Opin Emerg Drugs 2013. [2]Zoulim F. Antivir Res 2012

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