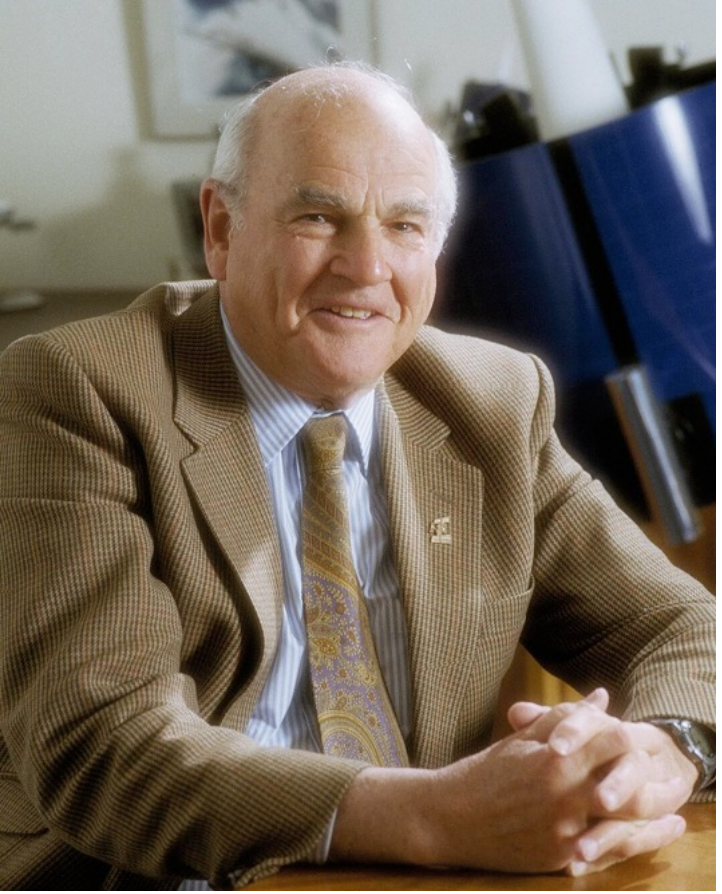
educational

Hepatitis B serology: rules and exceptions

prof.dr. Hans Zaaijer h.zaaijer@sanquin.nl
emeritus prof. of Blood-borne Infections,
Sanquin & University of Amsterdam, NL

no conflict of interests
no paid consultancy, no shares or other financial interests



Baruch (Barry) Blumberg, 1925-2011

1950s	study of genetic variation in blood samples worldwide
1964	he finds 'Australia antigen', shared by NY hemophilia patient and an Australian aboriginal person
1967	link to 'serum hepatitis' established (Sutnick)
1969	experimental vaccine (heat treated virus)
1976	Nobel prize for his work on hepatitis B

Hepatitis Carriers Called A New York School Peril

New York Times 1979

1979	children with chronic hep B excluded from NY schools. Blumberg advises children's lawyers, policy reversed
1981	first commercial vaccine (Heptavax-B, inactivated, plasma derived)
2025	CDC ends recommendation for universal hepatitis B vaccination at birth

Hepatitis B serology: the rules of thumb

HBsAg = pos	HBV infection	≥ 6 months: chronic
anti-HBcore = pos	HBV infection: now or in the past	
anti-HBs = pos	immunity to HBV	≥ 10 IU/L = positive
IgM anti-HBcore = pos	recent HBV infection or chronic hep B with flare	
IgM anti-HBcore = neg	*no* recent HBV infection	
HBeAg = pos	probably highly viremic and infectious	

Advanced hepatitis B serology

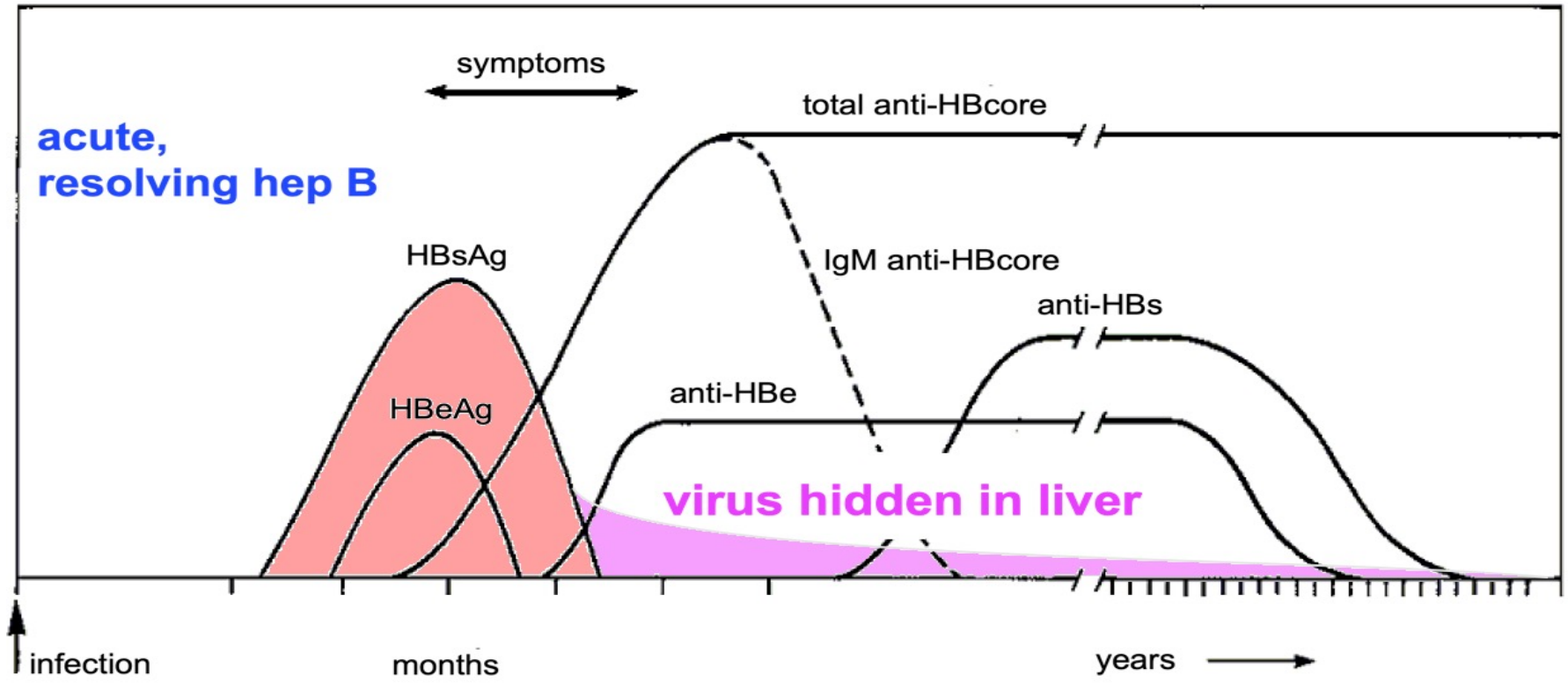
HBsAg and anti-s	both positive in ~10% of chronic hep B infections
HBsAg positive	in weeks after HBV vaccination
HBsAg negative	but there is HBV infection: 1) latent/occult infection = common 2) vaccine suppressed infection = common 3) HIV co-infection 4) delta flare or acute delta 5) HBV genotype G mono-infection
anti-core negative	and chronic HBV infection: HIV+ persons ; after stem cell Tx. even healthy, latently infected person may loose aHBcore (rare)

latent HBV infection

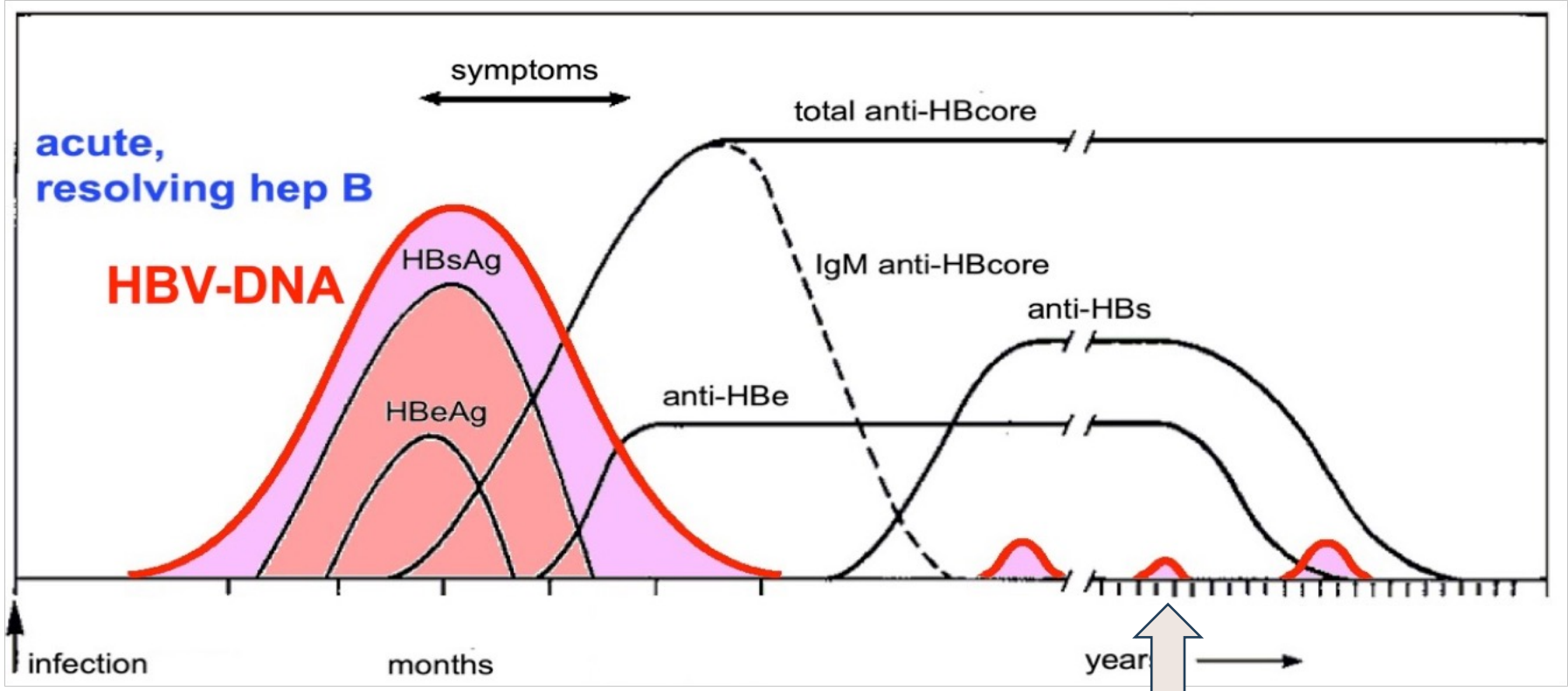
after resolved hepatitis B:

HBV often hides in the liver

sometimes for decades



latent HBV infection



HBsAg = negative,
HBV-DNA may be detectable:
"occult, OBI"

- not infectious via sex
- donations sometimes infectious
- chemo or organ Tx: risk of severe hep B reactivation

and now some pitfalls

- weird serology in patients
- HBsAg+ but no infection
- infection but no HBsAg
- vanishing anti-HBcore

passive transfer of donor antibodies to patient

erroneous serology
following transfusion of
platelets, ivig, FFP, SD-plasma,

but not or hardly via red blood cells

some (Dutch) blood components	approximate plasma content
Red cell concentrate in SAGM ('blood transfusion')	**5 - 10 ml**
Apheresis platelets in plasma/PAS-E for pediatric use	**21 - 70 ml**
Apheresis platelets in plasma /PAS-E	**53 - 140 ml**
Pooled platelets in plasma/PAS-E from buffy coats or interim platelet units	**93 – 124 ml**
S/D treated plasma (octaplasLG)	**200 ml**
Quarantine fresh frozen plasma	**310 ml**
Apheresis platelets in plasma	**150 - 400 ml**

with help from Ed Slot

passive transfer of donor antibodies to patient

serology in a toddler:

- 1 day after transfusion of platelets

- and 12 weeks later

	12-5-2015 13:54	4-8-2015 11:28
SEROLOGIE		
ANTI-HB CORE	Neg	Neg
ANTI-HBS IU/L	Pos 412	Pos 26.1
HBSAG IU/ML	Neg <0.030	Neg <0.030
ANTI-HCV	Neg	Neg
HIV-1/2 AG/AB	Neg	
CMV IGG U/ML	Pos 38.4	Neg <5.00
EBV ANTI-EBNA IGG	Pos	Neg
EBV VCA IGG	Pos	Neg
HSV IGG	Pos	Neg
VZV IGG	Pos	Neg
BOPVIRUS IGG	Pos	Neg
MAZELENVIRUS IGG	Pos	Neg
RUBELLAVIRUS IGG	Pos 38.5	Neg <3.00
PARVOVIRUS IGG		Neg

"past HBV infection" after ivig:
anti-HBs and anti-core positive

HBsAg positive after hep-B vaccination

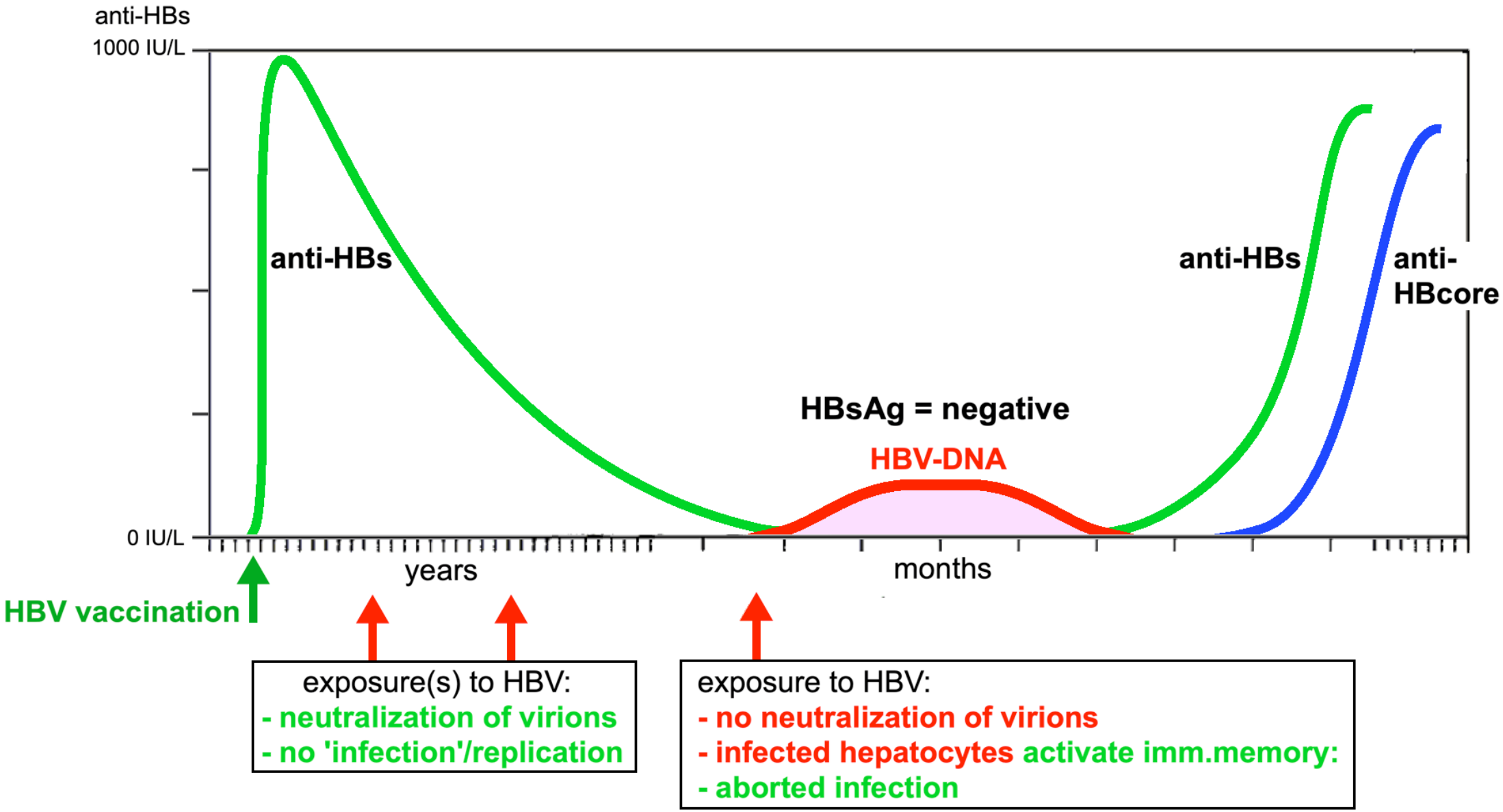
some blood donors
and patients seem HBV infected, but:

"oops, sorry,
last week I was vaccinated"

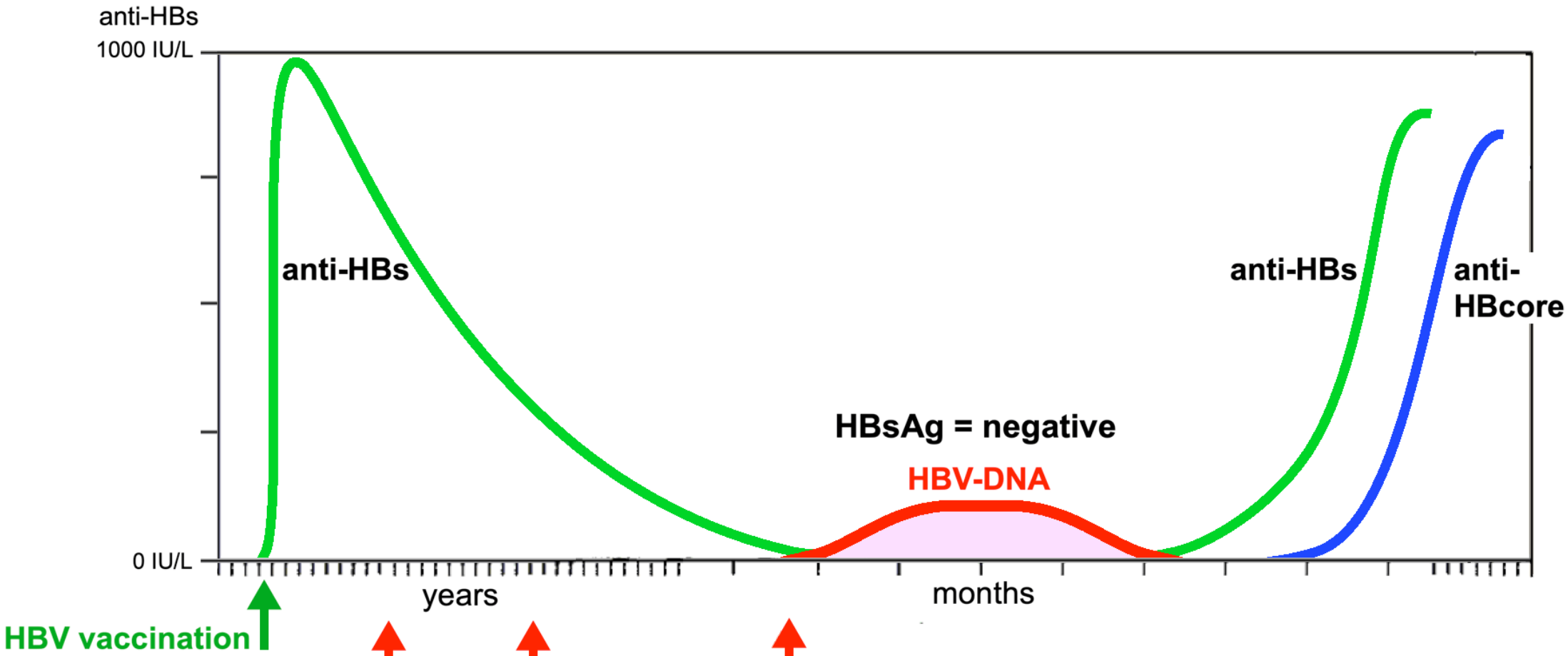
10 µg injected recombinant HBsAg
= detectable from few hours until
2-3 weeks after vaccination

	Donation	3 months later
SEROLOGIE		
ANTI-HB CORE	**Neg**	**Neg**
ANTI-HBS	**Neg**	**Pos**
HBSAG	**Pos**	**Neg**
HBSAG NEUTRAL.	**Pos**	
HBV-DNA	**Neg**	**Neg**

Vaccine suppressed HBV infection



Vaccine suppressed HBV infection



exposure(s) to HBV:
- neutralization of virions
- no 'infection'/replication

exposure to HBV:
- no neutralization of virions
- infected hepatocytes activate imm.memory:
- aborted infection

Normal and common.
- no disease
- no societal transmission
- threat to transfusion

HBV has 2 parasites in need of HBsAg

1) Delta virus

lost knowledge:
flair of Delta hepatitis → HBsAg temporarily negative
(see supplemental slides)

2) HBV genotype G

HBV-G has impaired HBsAg processing

Hepatitis B Virus Genotype G: The Odd Cousin of the Family

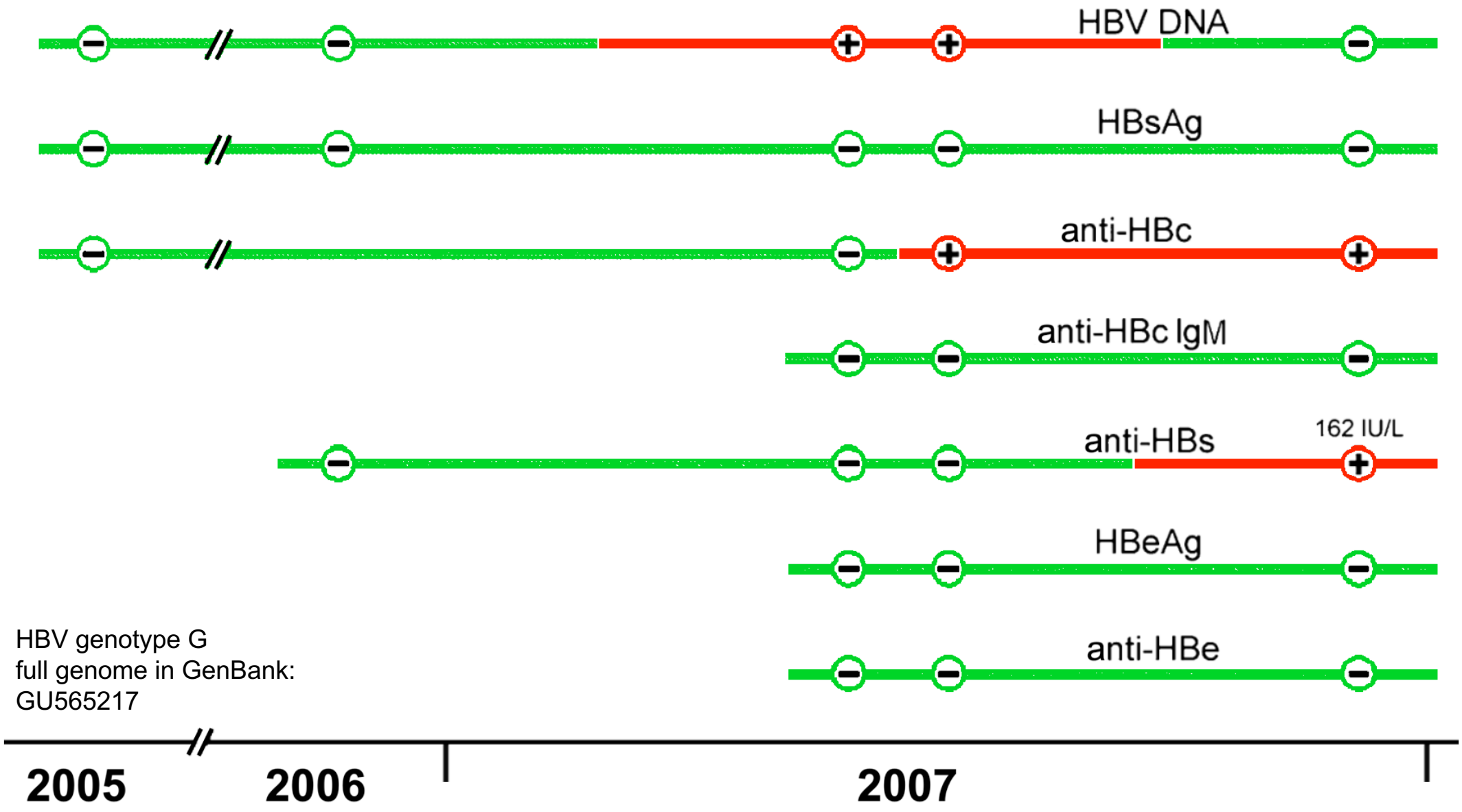
Araujo M.N., Osiowy C. Frontiers in Microb. 31 Mar. 2022

Often dual infection of 2 HBV genotypes:
genotype G+A, G+D, etc.

But HBV-G mono-infection does occur:

HBV genotype G mono-infection in donor: no HBsAg

J.Vir.Hep.2011, Zaaijer ea.



Vanishing anti-HBcore

anti-HBcore is reliable marker for past or ongoing HBV infection, but it may disappear:

- in HIV/HBV co-infection	not uncommon example
- in stem cell transplantation patients	not uncommon
- in healthy persons	rare example

Vanishing anti-HBcore in HIV/HBV co-infected patient

2001:

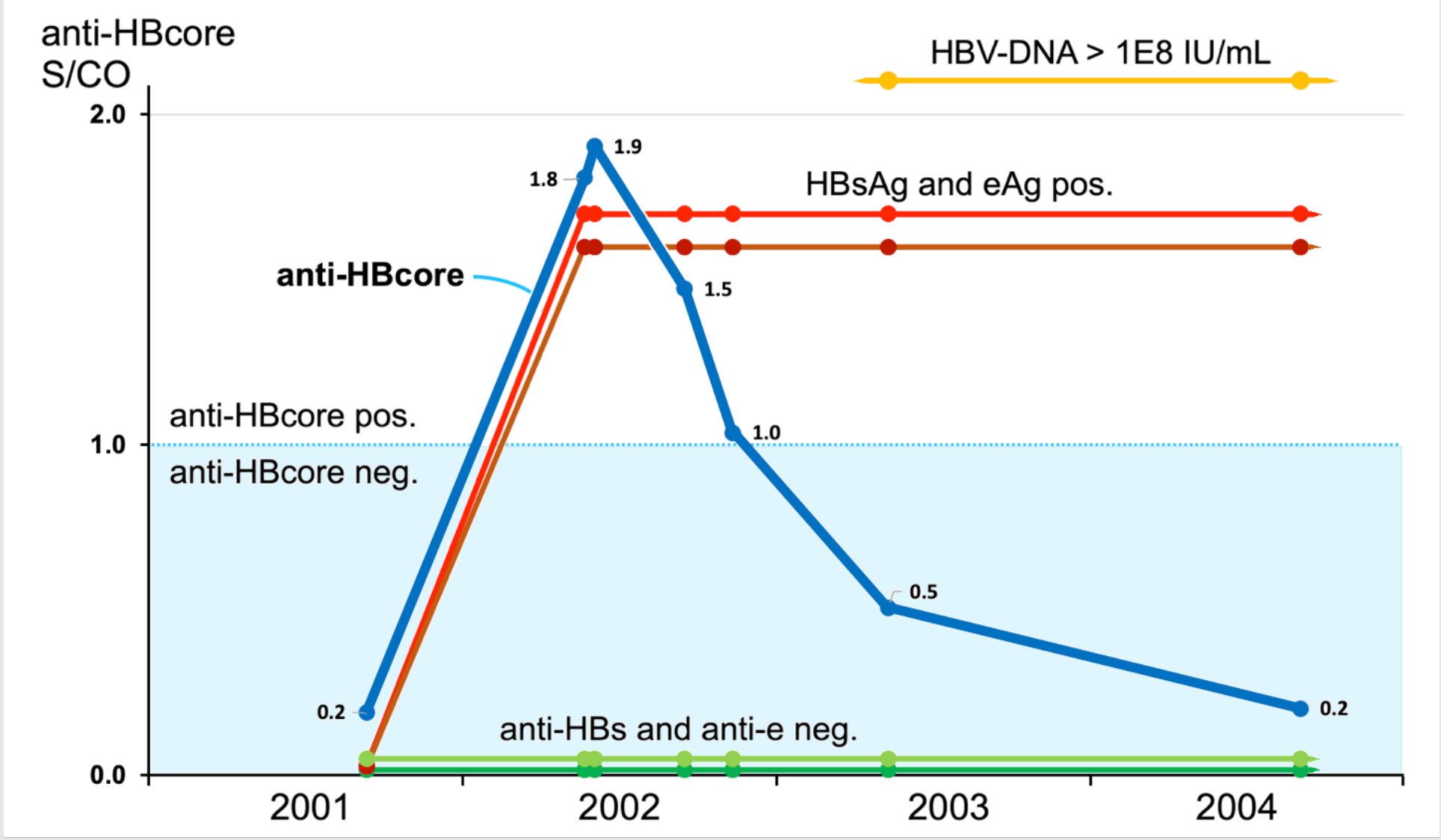
mr. X, HIV-infected

no HAART at that time

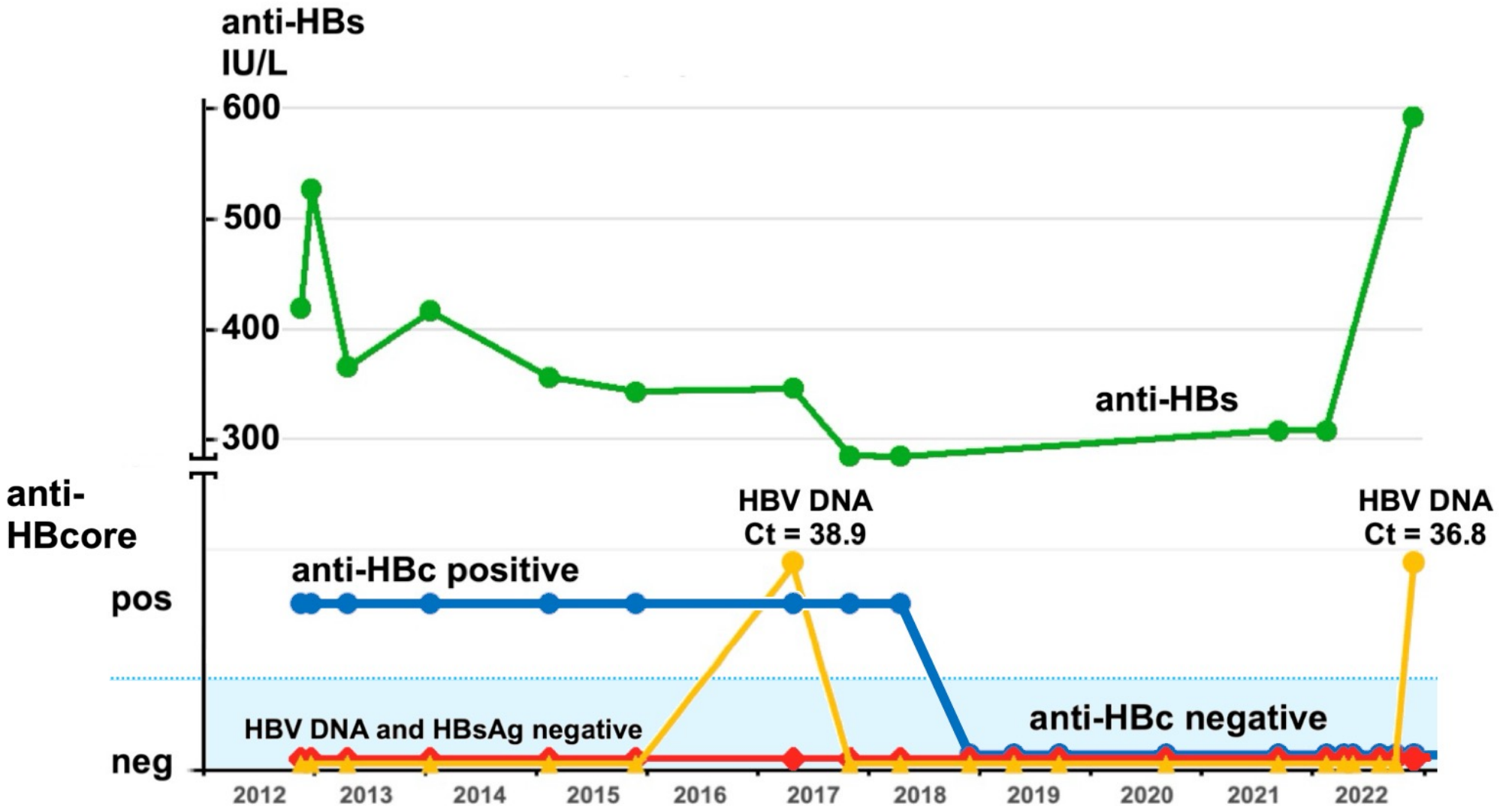
2002:

acute hep B → chronic,

anti-HBcore disappears



Vanishing anti-HBcore in healthy Dutch donor



Advanced hepatitis B serology

HBsAg and anti-s	both positive in ~10% of chronic hep B infections
HBsAg positive	in weeks after HBV vaccination
HBsAg negative	but there is HBV infection: 1) latent/occult infection 2) vaccine suppressed infection 3) HIV co-infection 4) delta flare or acute delta 5) HBV genotype G mono-infection
anti-core negative	and chronic HBV infection: HIV+ persons ; after stem cell Tx. even healthy, latently infected person may loose aHBcore (rare)

QUIZ: Your interpretation please…

mr. X, 46 y: slightly elevated transaminases

	HBsAg	anti-HBs	anti-core	eAg	anti-e
16-7-2018	neg <0,03	45 IU/L	neg 1,97		
15-3-2019 Liaison values	neg <0,03	45 IU/L	neg 1,35	neg 0,01	neg 1,77

HBV serology indicates:

1. HBV vaccination in the past
2. HBV infection cleared long ago
3. Chronic HBV infection

QUIZ: Your interpretation please…

mr. X, 46 y: slightly elevated transaminases

	HBsAg	anti-HBs	anti-core	eAg	anti-e
16-7-2018	neg <0,03	45 IU/L	neg 1,97		
15-3-2019 Liaison values	neg <0,03	45 IU/L	neg 1,35	neg 0,01	neg 1,77

HBV serology indicates:

1. HBV vaccination in the past
2. HBV infection cleared long ago
3. Chronic HBV infection

QUIZ: Your interpretation please…

mr. X has chronic HBV infection

	HBsAg	anti-HBs	anti-core	eAg	anti-e	HBV-DNA	HIV	CD4
16-7-2018	neg <0,03	45 IU/L	neg 1,97			**75** **IU/mL**	**pos**	
15-3-2019 Liaison values	neg <0,03	45 IU/L	neg 1,35	neg 0,01	neg 1,77	**86** **IU/mL**	**pos**	110 xE6/L

3 pecularities in one patient:

- ✶ HBsAg often absent in HIV/HBV co-infection
- ✶ anti-HBcore sometimes absent in HIV/HBV co-infection
- ✶ anti-HBs detectable in 10% of chronic hep-B

Thank you for your attention

supplemental slides:

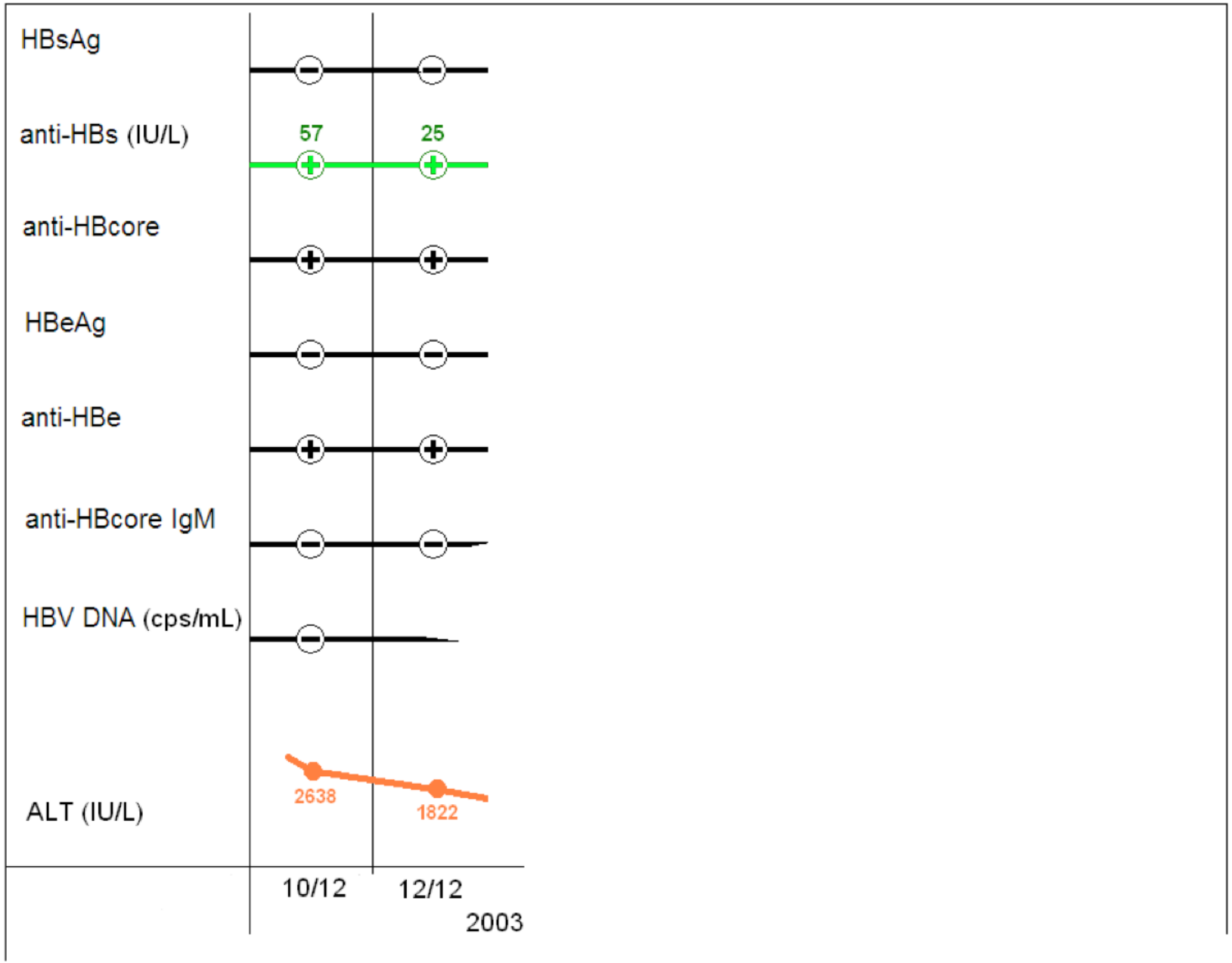
a patient with temporary loss of HBsAg due to acute (or a flaire of) hepatitis delta

Temporary loss of HBsAg in hep delta patient

Dec. 2003, emergency dept. of uni hospital:

a middle aged man with fulminant hepatitis

hep.B serology indicates: resolved HBV infection in the past.

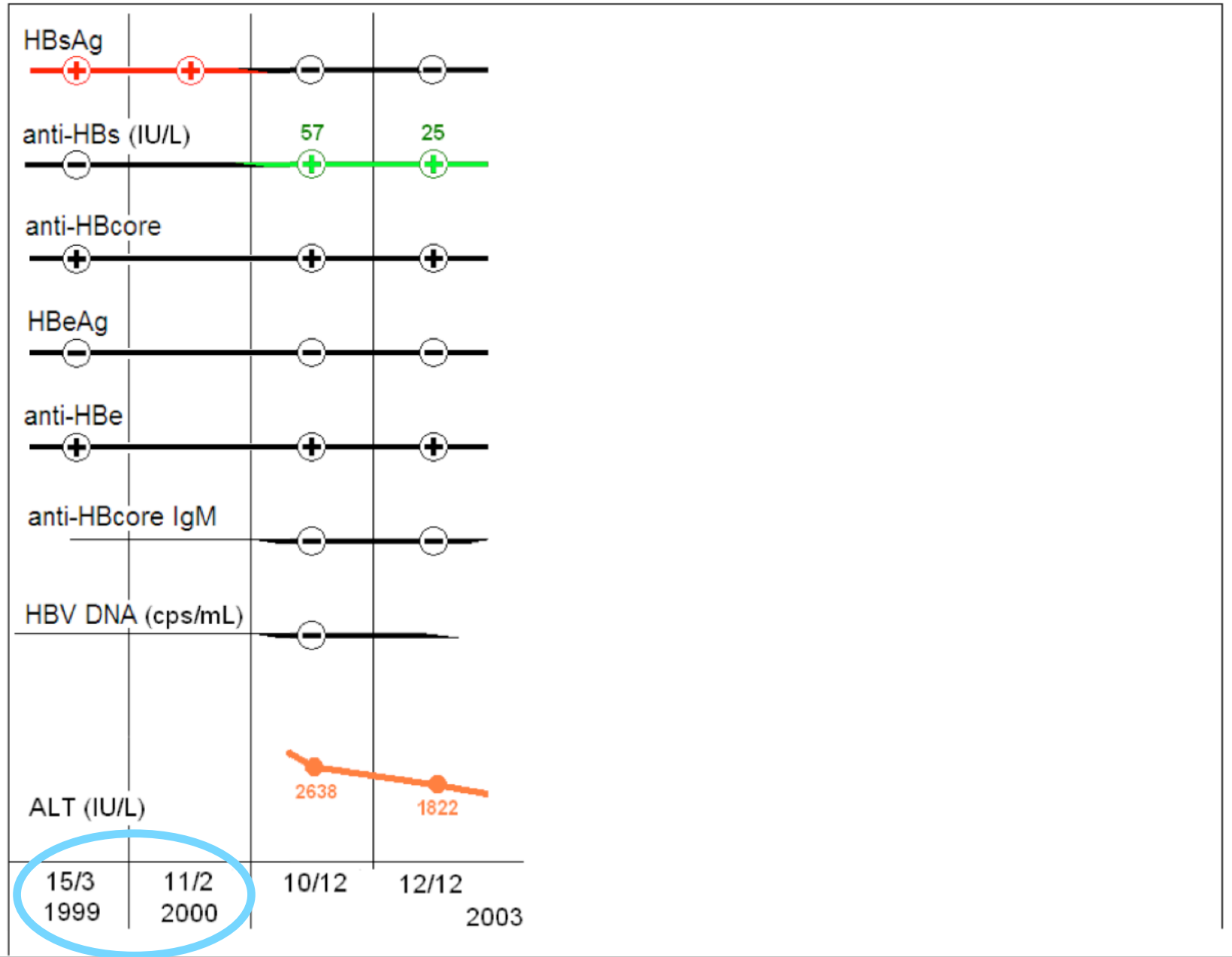


Temporary loss of HBsAg in hep delta patient

hep.B serology indicates: resolved HBV infection in the past.

However: he is known with chronic hep.B at municipal health service

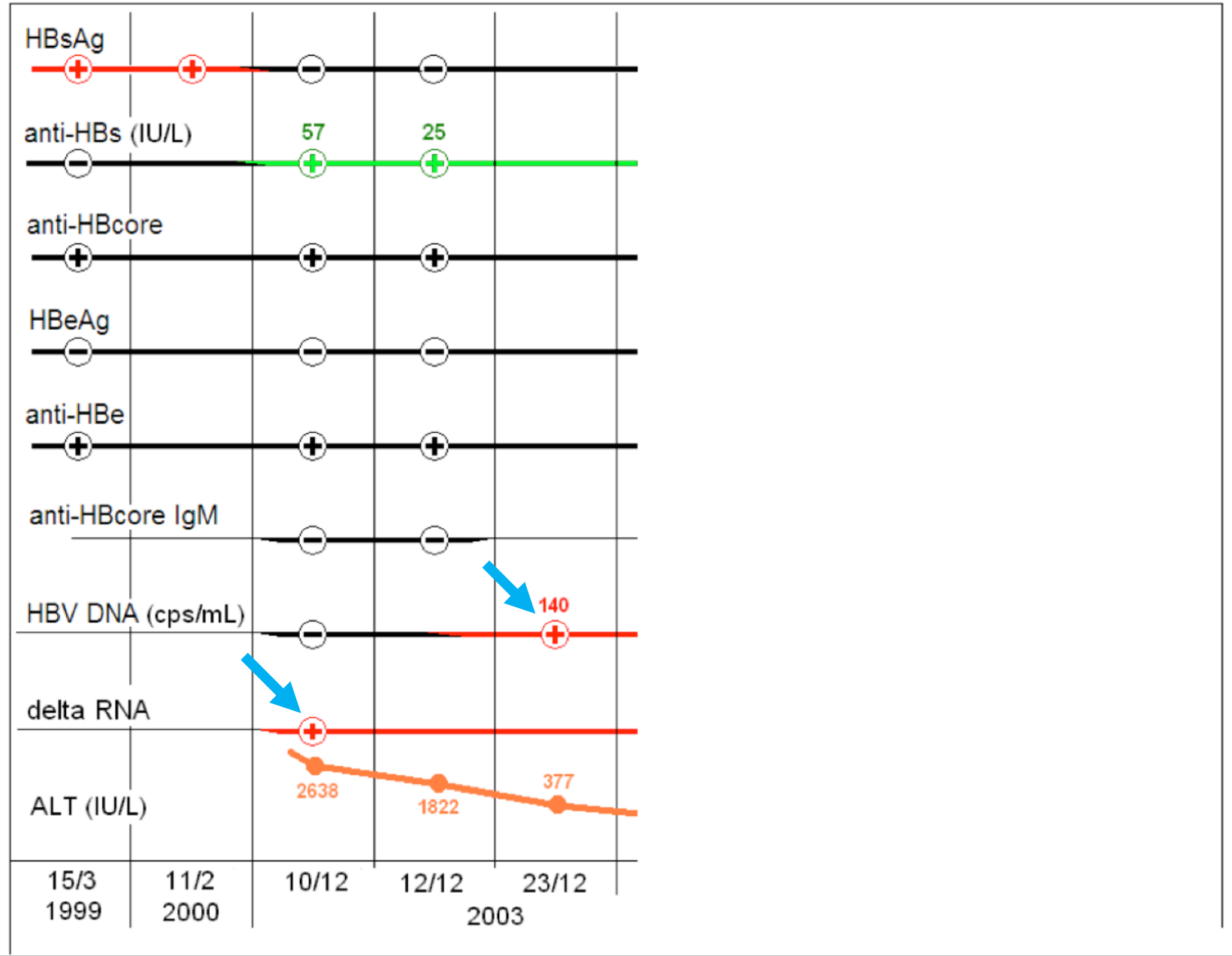
chronic hep B ! ➡



Temporary loss of HBsAg in hep delta patient

hepatitis improves spontaneously

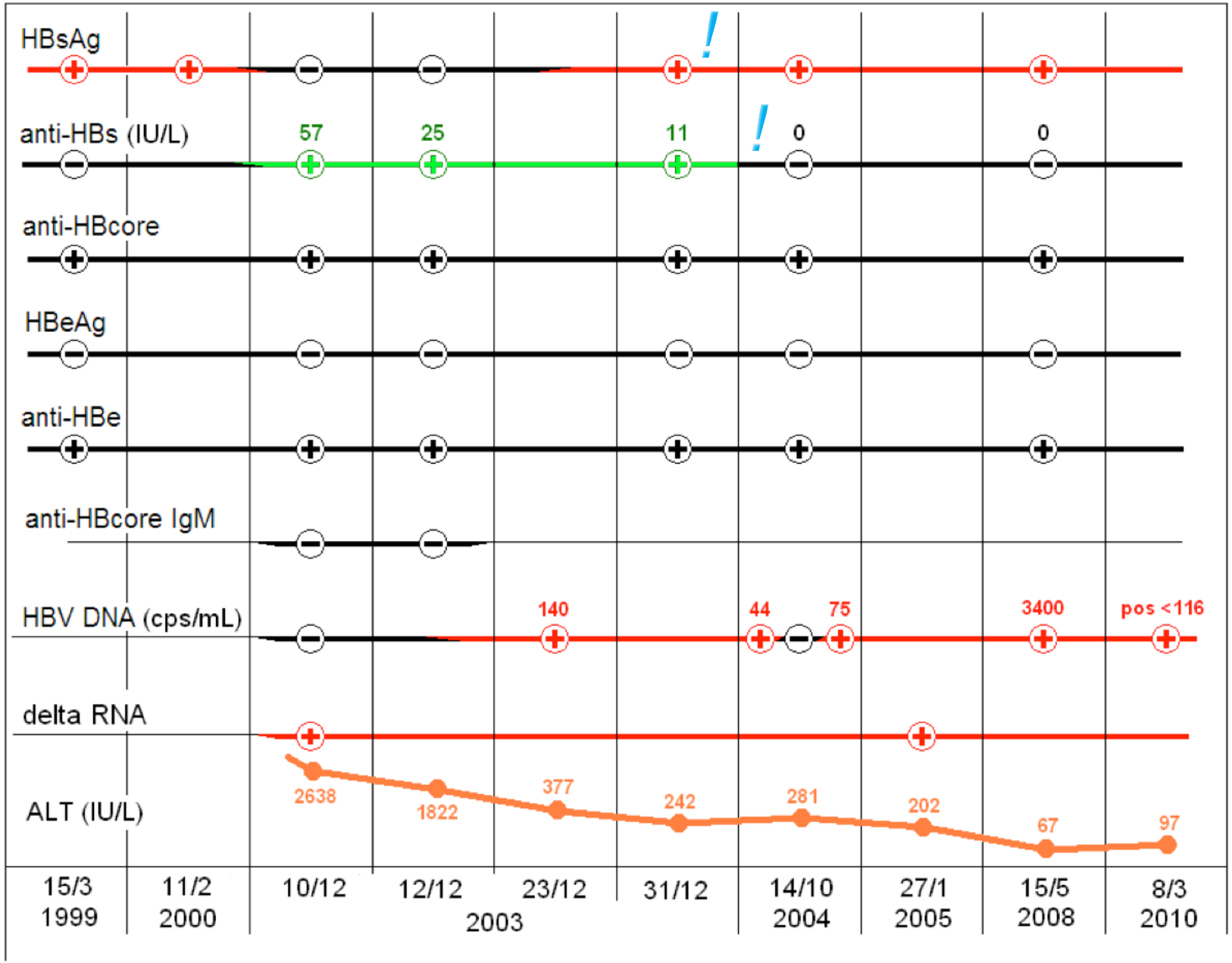
additional lab results come in:
HBV-DNA = positive
Delta-RNA = positive



Temporary loss of HBsAg in hep delta patient

hepatitis improves spontaneously

HBsAg re-appears
anti-HBs disappears



Thank you for your attention