Hepatitis masterclass 2024

Kliniek virale hepatitis A t/m C bij HIV

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UMC Utrecht

7 februari 2024

Doel

- Inzicht verkrijgen in de epidemiologie, diagnostiek, behandeling en preventie van infecties met hepatitis A t/m C bij mensen met HIV

- Geen disclosures

Casus

- Dhr. V (51 jaar)
- Bekend met HIV sinds 15 jaar
- Therapie: dolutegravir 50 mg 1dd + lamivudine 300 mg 1dd

- HIV RNA <50 kopieën/ml
- CD4 777 cellen/mm3

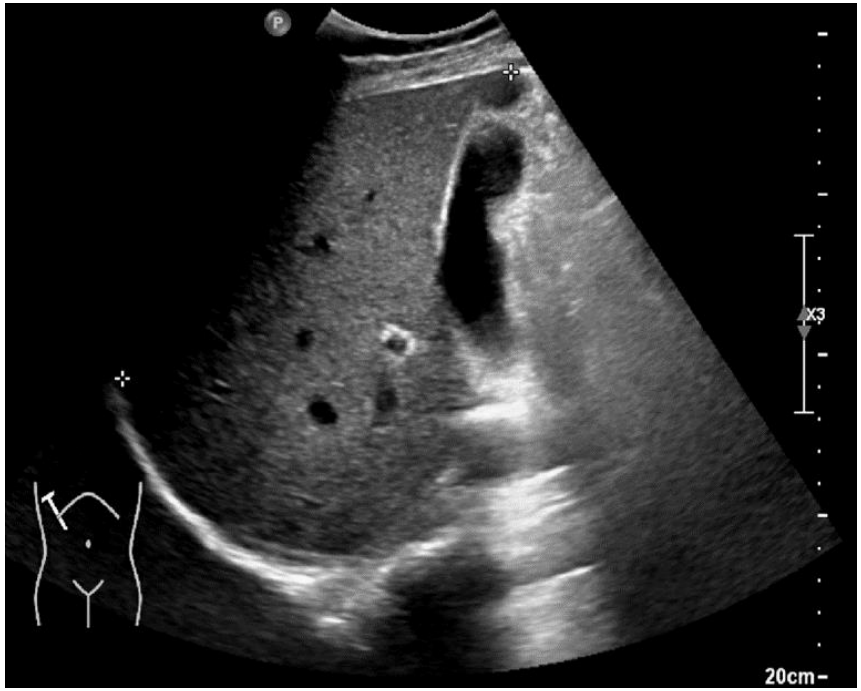
- Bij reguliere controle afwijkend laboratorium onderzoek

- Alcohol alleen in het weekend
- Geen over-the-counter medicatie, Chinese kruiden etc

- HBV vaccinatie non-responder. HAV niet gevaccineerd.

Test	06-07-2023 16:21 BWELZ2	
Bloedchemie		
Bilirubine Totaal	15	
Alkalische fosfatase	128	H
gamma-GT	200	H
ASAT	357	H
ALAT	582	H
LD	290	H

Verdenking acute virale hepatitis



Hepatitis A

Hepatitis B

Hepatitis C

Welke diagnostiek verricht U?

Aanvullende diagnostiek

Virologie uitslagen	
Hepatitis A virus IgM (CMIA)	0.19/Neg
Hepatitis A virus IgG (CMIA)	8.76/Pos
Hepatitis B virus HBsAg (CMIA)	0.21/Neg
Hepatitis B virus core IgG (CMIA)	0.10/Neg
Hepatitis C virus antistoffen (CMIA)	0.20/Neg
HEV virus IgM (VirClia)	0.066/Neg
HEV virus IgG (VirClia)	0.208/Neg

Virologie uitslagen	
HCV CORE en/of 5UTR/NS5B Conclusie (SEQ)	4D
Hepatitis C virus RNA QPCR (AM)	6.35E+04

Acute hepatitis C infectie bij een HIV-positieve man

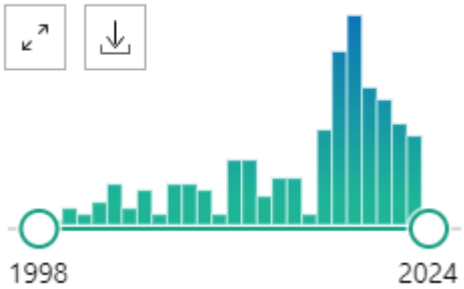
Hepatitis A

- RNA virus met faeco-orale transmissie
- Incubatietijd 2 – 7 weken (gemiddeld 4 weken)
- Jaarlijks 200 – 300 gevallen in Nederland. ~1% fulminant verloop
- Importziekte – MSM clusters - Voedsel gerelateerd

Kenmerk	Titel	Verwekker	Regio	Aantal Signalen	Publicatiedatum eerste signaal
3661	Opnieuw een cluster van hepatitis A-patiënten in het noorden en oosten van het land (vervolg)	Hepatitis A-virus	Binnenland	2	21-05-2021
3656	Cluster van hepatitis A-patiënten met voedsel als meest waarschijnlijke bron	Hepatitis A-virus	Binnenland	1	29-04-2021
3600	Uitbraak van hepatitis A in Zweden waarschijnlijk veroorzaakt door bevroren vruchten	Hepatitis A-virus	Buitenland	1	15-10-2020
3568	Waarschijnlijke transmissie van hepatitis A-virus bij rioleringswerkzaamheden	Hepatitis A-virus	Binnenland	1	07-08-2020
3506	Uitbraak van hepatitis A op een basisschool (vervolg)	Hepatitis A-virus	Binnenland	2	27-01-2020
3376	Moleculair hepatitis A genotype 1A cluster verspreid over meerdere GGD regio's (vervolg)	Hepatitis A-virus	Binnenland	2	16-05-2019
3347	Hepatitis A (Michigan-) stam 1B gevonden bij MSM in Nederland	Hepatitis A-virus	Binnenland	2	07-03-2019
2989	Hepatitis A uitbraak onder mannen die seks hebben met mannen	Hepatitis A-virus	Binnenland	12	23-01-2017
3286	Meerdere gezinsclusters hepatitis A na een reis naar Marokko	Hepatitis A-virus	Binnenland	1	18-10-2018
3217	Twee moleculaire clusters van hepatitis A in meerdere Europese landen	Hepatitis A-virus	Binnenland	1	07-05-2018

Hepatitis A virus uitbraken

RESULTS BY YEAR



RAPID COMMUNICATIONS

Outbreak of hepatitis A associated with men who have sex with men (MSM), England, July 2016 to January 2017

RAPID COMMUNICATIONS

Hepatitis A outbreak among men who have sex with men (MSM) predominantly linked with the EuroPride, the Netherlands, July 2016 to February 2017

BRIEF DEFINITIVE REPORT

WILEY Liver INTERNATIONAL

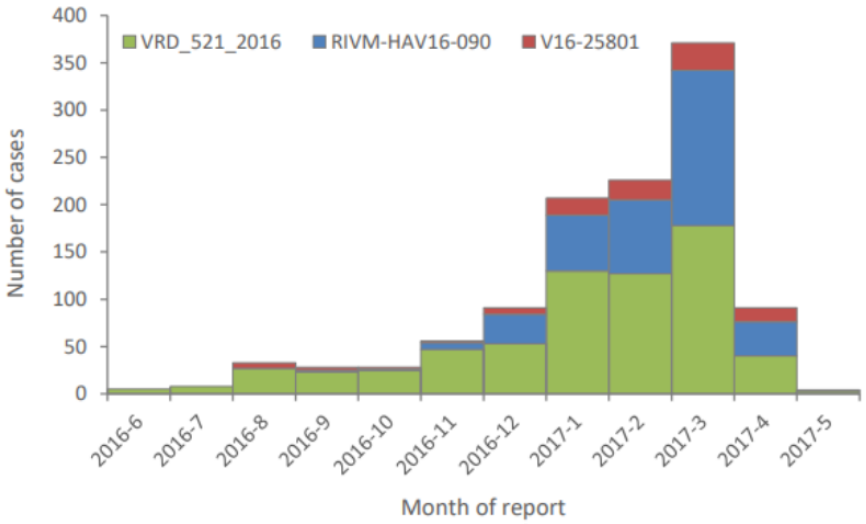
Hepatitis A outbreak in Barcelona among men who have sex with men (MSM), January-June 2017: A hospital perspective

Rodriguez-Tajes et al Liver Int 2017
Freidl et al. Euro surveillance 2017
Beebeejaun et al. Euro surveillance 2017

Transmissie route HAV bij (HIV+) MSM

- Rimming – fisting – gedeeld gebruik van sekspeeltjes
- ~ 60% van gehele populatie heeft anti-HAV antistoffen
- Phylogenetische analyse ter identificatie clusters

Figure 1. Distribution of hepatitis A cases, by month of report and genetic sequence, June 2016, as of 15 May 2017, EU/EEA (n=1 148)



Preventie HAV

- Hygiëne maatregelen
- Vaccineren – n.b. vergoeding
- 3x Twinrix
- 2x Monovalent HAV vaccin

GGD Amsterdam

You can help to prevent hepatitis A spreading any further by

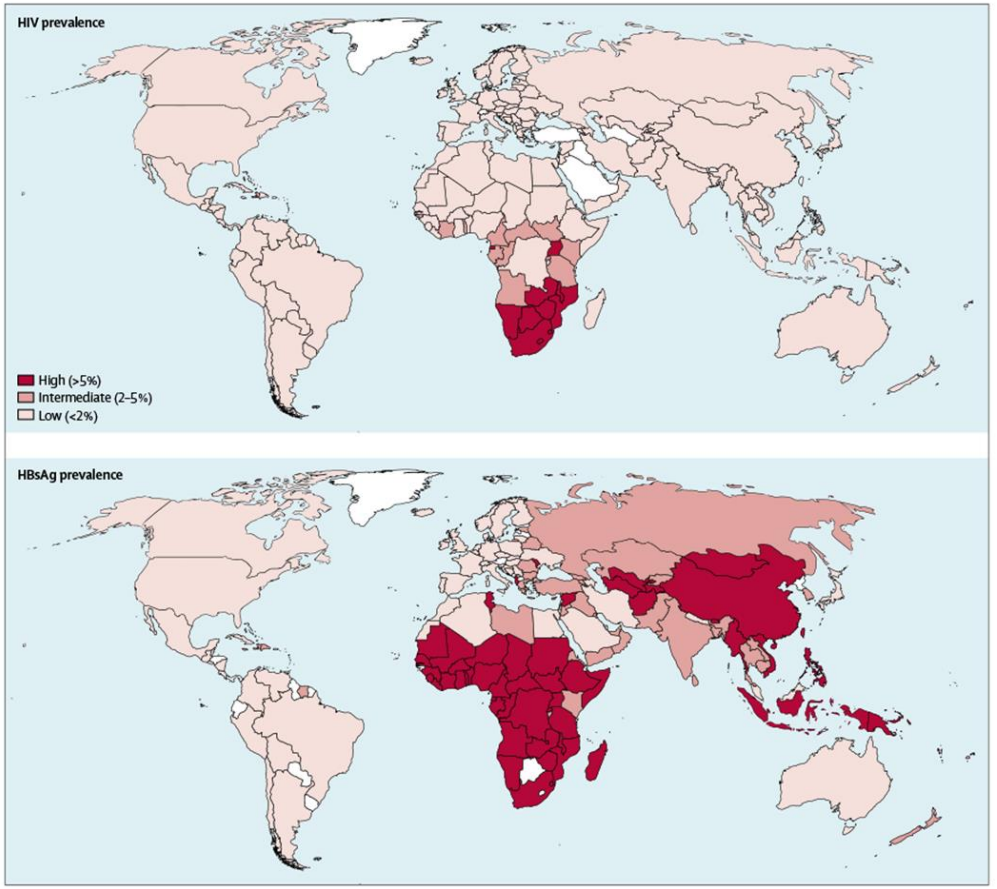
1. Washing your hands with soap and water after going to the toilet and before cooking/eating;
2. Washing your hands with soap and water before and after sex (or taking a shower);
3. Not sharing any sex toys;
4. Using condoms or latex gloves for anal sex, rimming, fingering, fisting, etc.

Preventing hepatitis A

Getting vaccinated to prevent infection with hepatitis A is the best protection. Two vaccinations usually give lifelong protection, but the first vaccination will immediately protect you against the virus. You can make an appointment to get vaccinated at the GGD Amsterdam by calling 020-5555 464. Vaccination against hepatitis A is not free. But your health insurance may cover some of the costs.

Hepatitis B bij HIV

- Relevante co-infectie bij HIV
- Sterke geografische verschillen
- Snellere progressie naar fibrose
- Hogere lever-gerelateerde mortaliteit

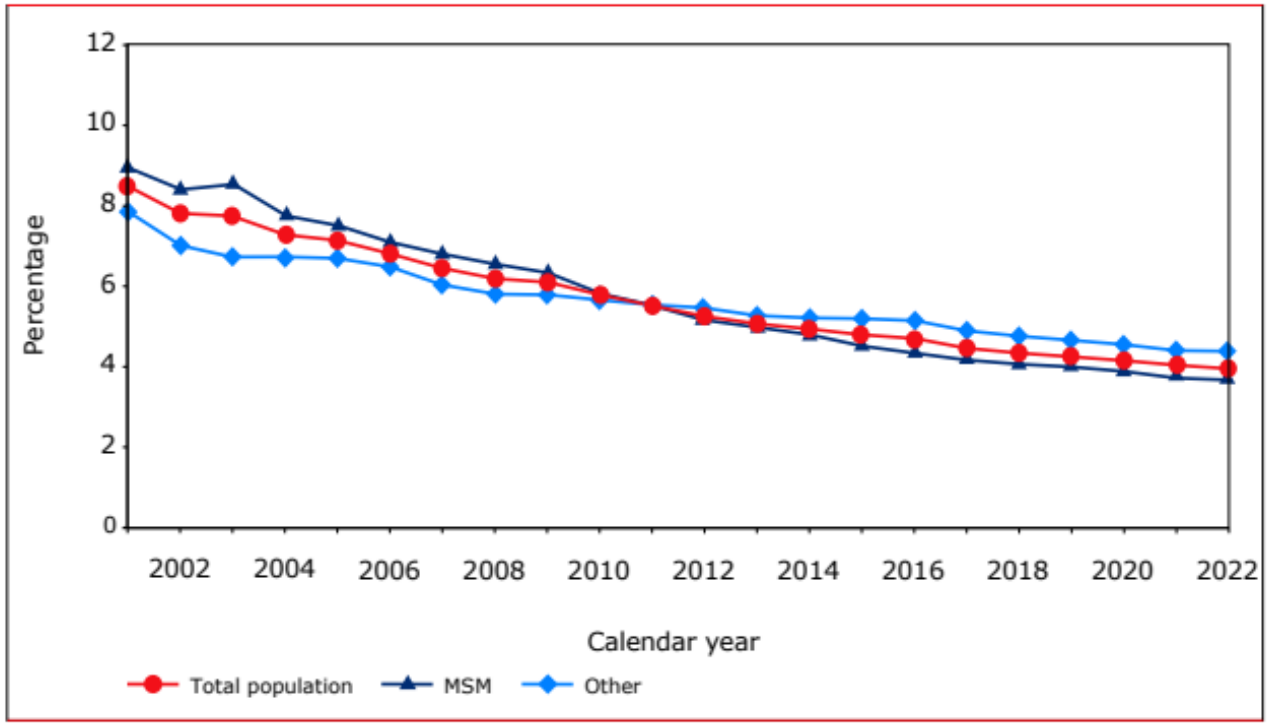


HIV/HBV in Nederland

- In NL ongeveer 1000 personen met HIV/HBV co-infectie

- Gestage afname over de tijd
- Vaccinaties, treatment as prevention and PrEP ‘avant la lettre’

Figure 4.12: Prevalence of HBsAg positive serology per calendar year.



Therapie bij HIV/HBV

- Because emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) have activity against both HIV and HBV, an ART regimen for patients with both HIV and HBV should be include (TAF or TDF) plus (3TC or FTC) as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive antiretroviral (ARV) regimen **(AI)**.
- Other HBV treatment regimens, including adefovir alone or in combination with 3TC or FTC and telbivudine, **are not recommended** for patients with HBV/HIV coinfection **(CII)**.

The anti-HIV antiviral activity of entecavir: The loss of a trusted friend? ☆

Joe Sasadeusz*

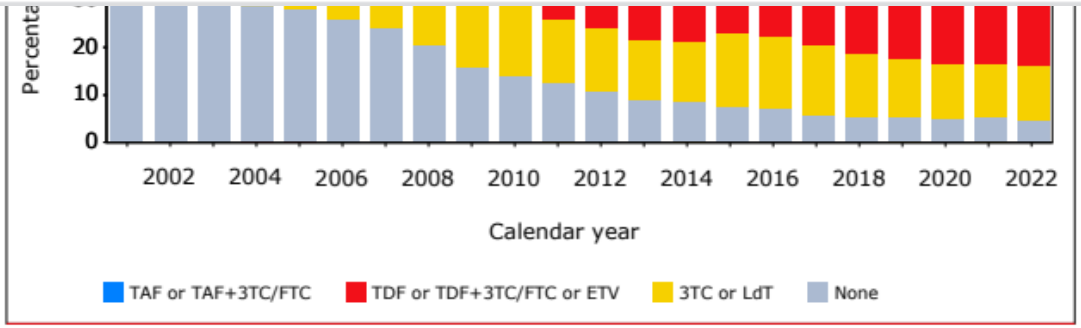
Sasadeusz et al. J of Hepatology 2007

‘The tenofovir era’

- Tenofovir disoproxil in 2003
- Sindsdien sterke afname van all-cause en lever-gerelateerde mortaliteit
- Tenofovir effect en minder hepatotoxiciteit (ddI, d4T)

Table 2. Unadjusted and Adjusted Hazard Ratios of Underlying Cause of Death per Time Era of HIV Diagnosis

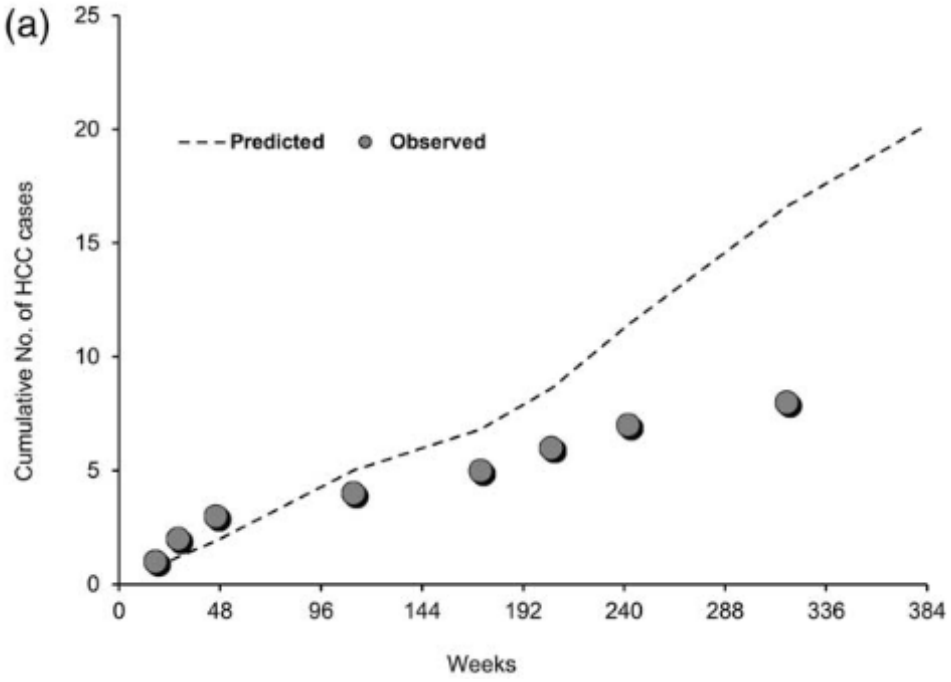
		Two-Period Analysis
	<2003 (Reference)	≥2003
All-cause (n = 198)		
• Nonadjusted	1.0	0.55 (0.38–0.78)
• Adjusted[a]	1.0	0.50 (0.35–0.72)
Liver-related (n = 38)		
• Nonadjusted	1.0	0.30 (0.13–0.78)
• Adjusted[a]	1.0	0.29 (0.11–0.75)

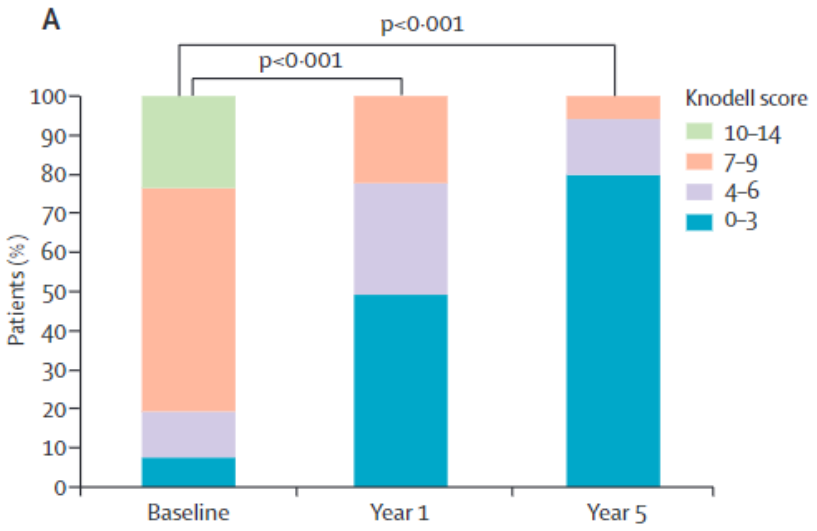


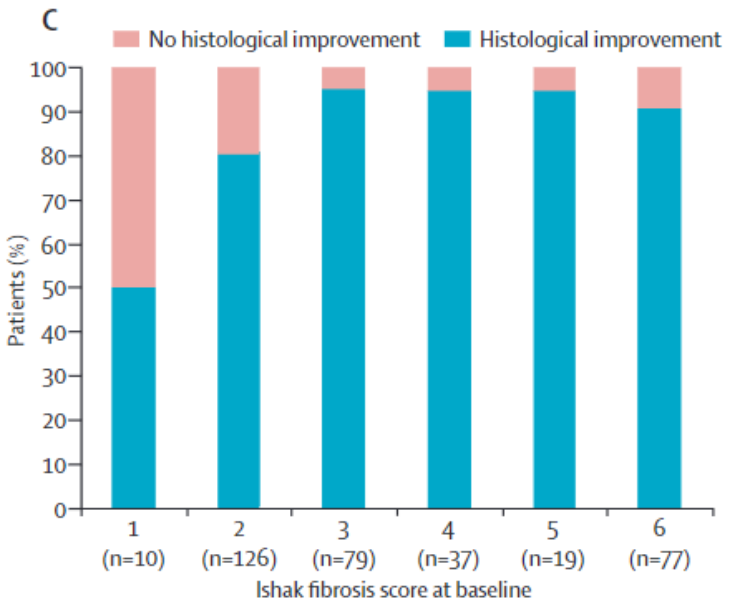
SHM monitoring report 2023; Van Welzen et al. OFID 2020

‘The tenofovir era’

- Regressie van fibrose
- Reductie HCC incidentie
- Geen data voor HIV/HBV co-infecties





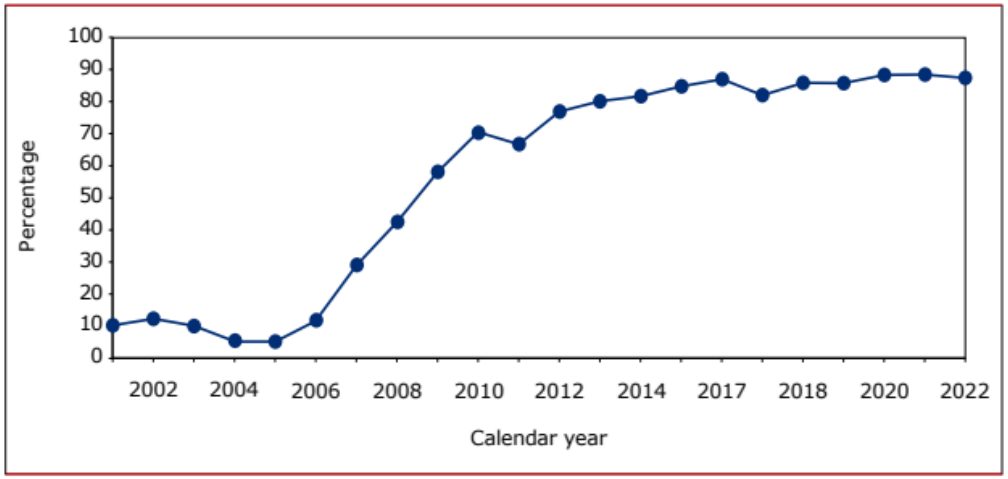


Kim et al. Cancer 2015, Marcellin et al. Lancet 2013

Monitoring HBV DNA bij HIV/HBV

- Na het eerste jaar, elke 12 maanden HBV DNA
- ~10% met persisterende viremie bij goede spiegels
- Bij PV minder vaak HBeAg en HBsAg klaring.
- Geen duidelijke associatie met klinische uitkomsten
- Consequenties?

Figure 4.14: Percentage of individuals with undetectable hepatitis B virus (HBV) DNA levels by assay, with a detection limit of <20, <100, <200, <400, <1,000, or <2,000 IU/ml HBV DNA per calendar year, regardless of HBeAg status.



Persistent Viremia in Human Immunodeficiency Virus/ Hepatitis B Coinfected Patients Undergoing Long-Term Tenofovir: Virological and Clinical Implications

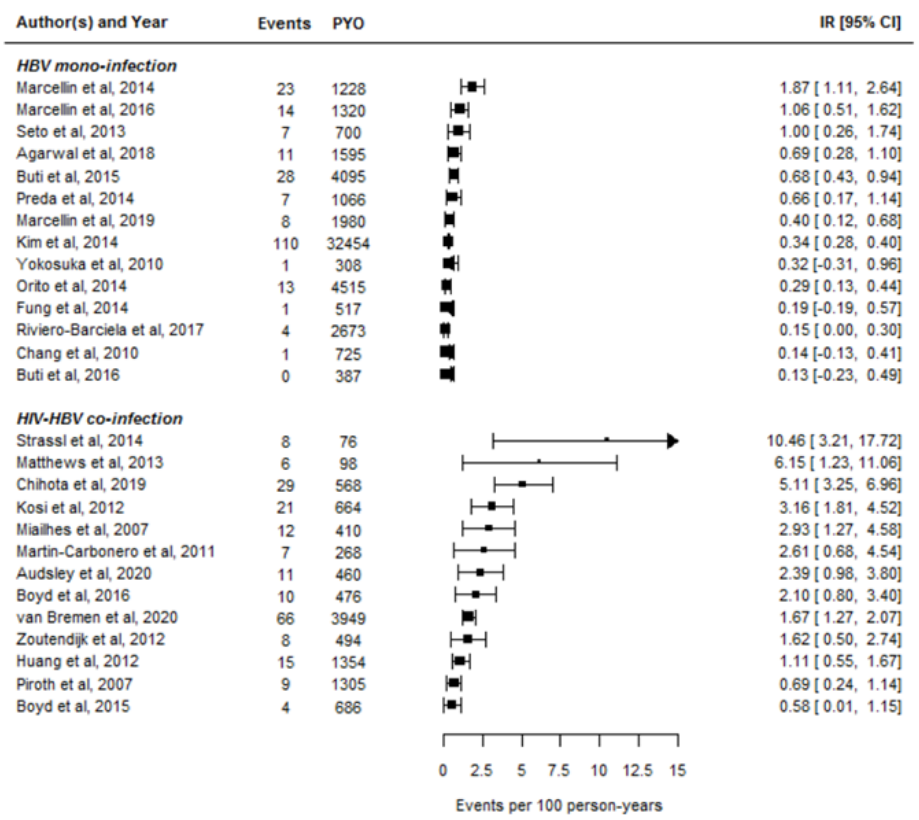
Anders Boyd,[1] Joël Gozlan,[2,3] Sarah Maylin,[4,5,6] Constance Delaugerre,[4,5,6] Gilles Peytavin,[7] Pierre-Marie Girard,[1,8,9] Fabien Zoulim,[10,11,12] and Karine Lacombe[1,8,9]

SHM monitoring report 2023; Boyd et al. Hepatology 2014

Monitoring HBsAg bij HIV/HBV

- EACS: HBsAg elke 12 maanden
- “In those on ART where the nucleoside backbone needs changing, anti-HBV therapy may be stopped cautiously after confirmed HBsAg-seroconversion”
- Seroclearance rate 16.5% na 5 jaar tenofovir-bevattende cART
- Rol van immunologisch herstel?
- In UMCU: ~10% seroclearance

(b)



Boyd et al. Viruses 2021, Oomen et al. Int J STD AIDS 2023

HCC surveillance bij HIV/HBV

SHORT COMMUNICATION

JVH WILEY

Low compliance with hepatocellular carcinoma screening guidelines in hepatitis B/C virus co-infected HIV patients with cirrhosis

- Gebrek aan awareness bij behandelaren
- Populatie soms moeilijk in zorg te houden
- Idealiter betere risico stratificatie met predictie modellen zoals mPAGE B

Patiënten die in aanmerking komen voor HCC surveillance zijn:

1. Alle patiënten met chronische hepatitis B en cirrose.
2. De volgende groepen patiënten met chronische hepatitis B zonder cirrose [1]:
   1. Oost-Aziatische mannen ≥40 jaar
   2. Oost-Aziatische vrouwen ≥50 jaar
   3. Patiënten afkomstig uit sub-Sahara Afrika ≥20 jaar
   4. Positieve familieanamnese voor HCC

Research Article
Viral Hepatitis

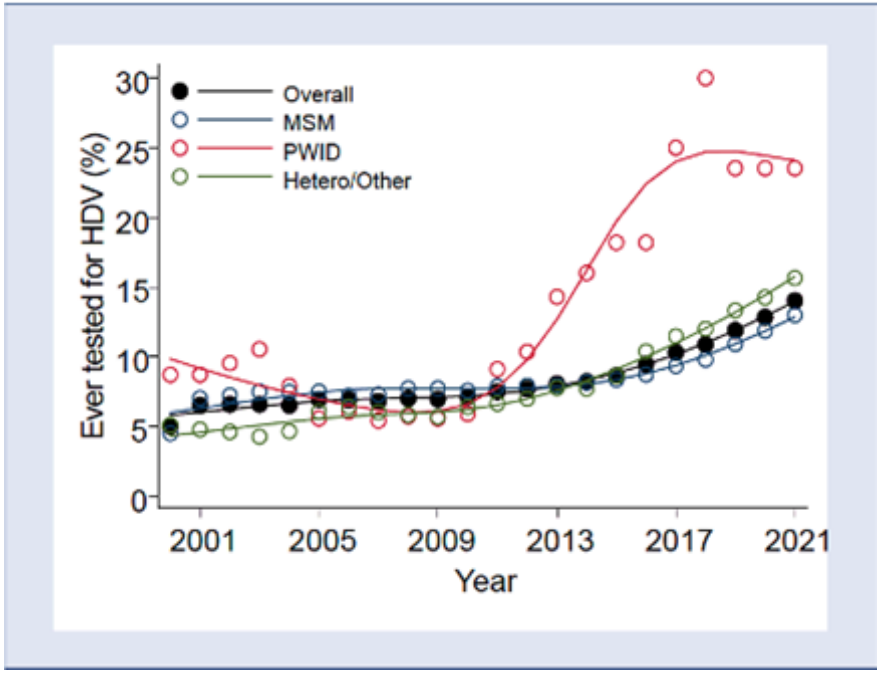
JOURNAL OF HEPATOLOGY

External validation of the PAGE-B score for HCC risk prediction in people living with HIV/HBV coinfection

Willemse et al. J Viral Hepat 2018; Surial et al. J Hepatol 2023

Hepatitis delta bij HIV/HBV

- In toenemende mate aandacht voor hepatitis delta virus (HDV)
- Diagnostiek wordt slecht beperkt verricht (~ 15- 25%)
- Bij ~10% anti-HDV antistoffen aanwezig
- UMCU retrospectief testen: 4 patiënten met anti-HDV antistoffen



Boyd et al. EASL 2023; Oomen et al. INT J STD AIDS 2023

Preventie HBV bij HIV

- Safe seks en vaccinaties (3x HBvaxPro 20 µg of Engerix 40 µg)

CD4 ≥ 350 cellen / mm3

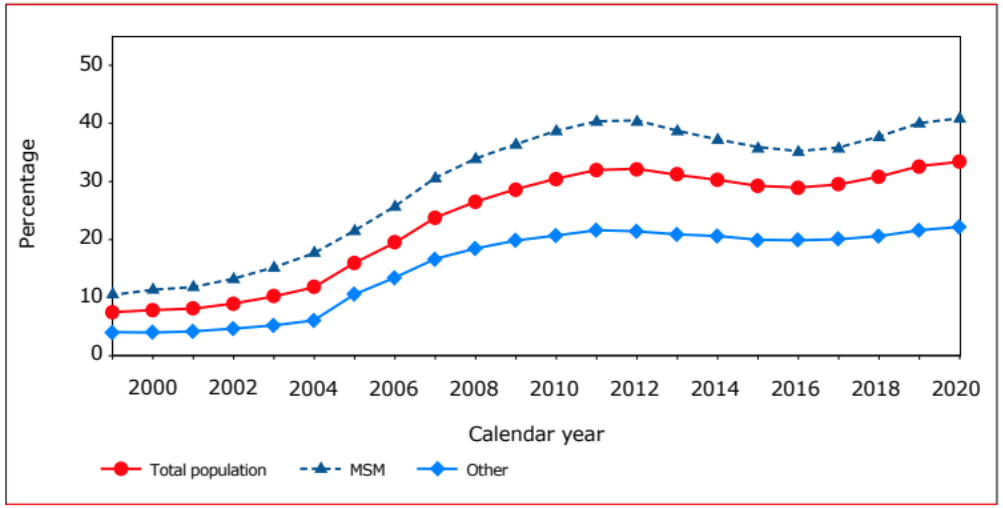
- Start hepatitis B-vaccinatieschema met dubbele dosis

CD4 < 350 cellen / mm3*

- Bij voorkeur start HAART en wacht totdat virale load ondetecteerbaar is (< 50 kopieën/ml)
- Start vervolgens met een hepatitis B-vaccinatieschema met dubbele dosis

**NB: Als de patiënt een hoog risico loopt op hepatitis B, dan kan de hivbehandelaar overwegen om toch te starten met vaccineren.*

Figure 4.16: Prevalence of hepatitis B vaccination per calendar year.



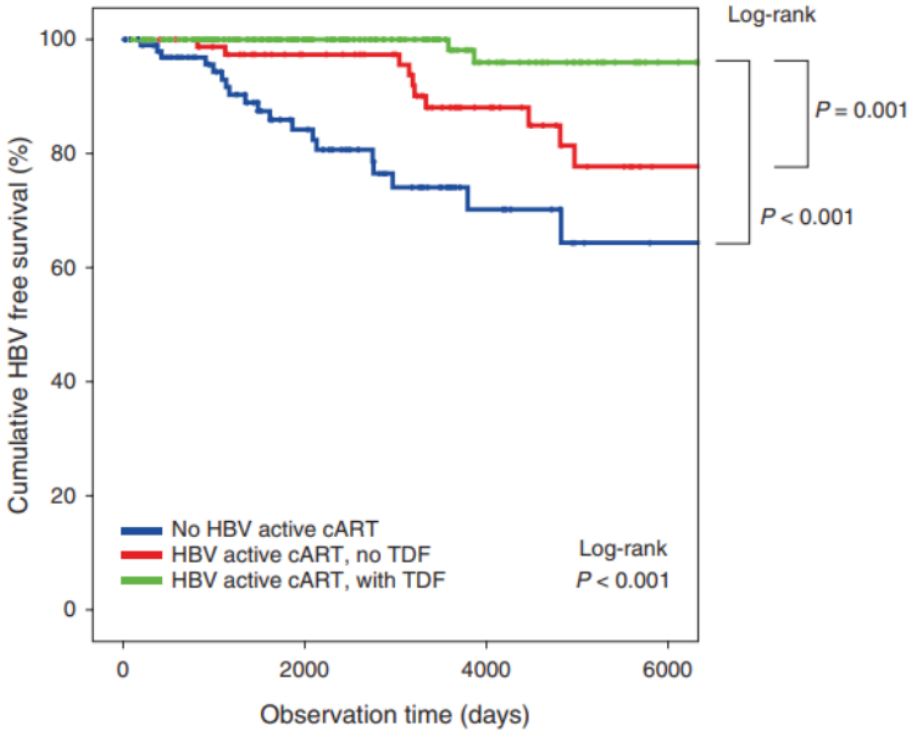
SHM monitoring report 2021; Richtlijn HBV vaccinatie bij HIV 2013

Tenofovir als HBV profylaxe

Protective effect of hepatitis B virus-active antiretroviral therapy against primary hepatitis B virus infection

Merel M. Heuft[a], Sanne M. Houba[a], Guido E.L. van den Berk[a], Tessa Smissaert van de Haere[a], Alje P. van Dam[b], Lea M. Dijksman[c], Rosa M. Regez[a] and Kees Brinkman[a]

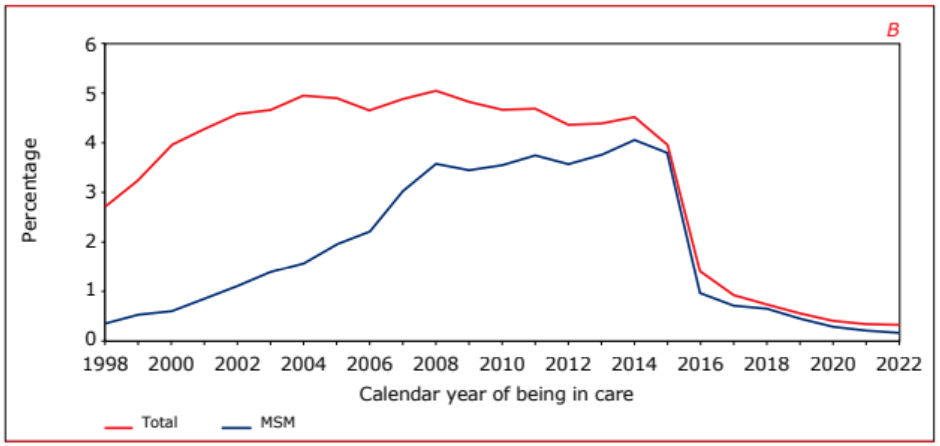
- N=381 at risk voor HBV
- Stratificatie naar gebruik van HBV-protectief cART
- HR tenofovir 0.07



Heuft et al. AIDS 2014

Hepatitis C bij HIV

- Traditioneel geassocieerd met i.v. drugsgebruikers en hemofilie
- Gaandeweg een verschuiving naar MSM populatie



Increase in diagnosed newly acquired hepatitis C in HIV-positive men who have sex with men across London and Brighton, 2002–2006: is this an outbreak?

Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic

Increase in HCV Incidence among Men Who Have Sex with Men in Amsterdam Most Likely Caused by Sexual Transmission

UMC Utrecht

Van de Laar et al. J Infec Dis 2007; Urbanus et al. AIDS 2009; Giraudon et al. Sex Transm Infect 2008

Hepatitis C bij HIV+ MSM

Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours

	Number participating (%)		
	Controls (%)	Cases (%)	*P*-value*
Sexual practice:			
Active oral sex (no ejaculation)	112 (94.1)	57 (96.6)	0.73
Active oral sex (ejaculation)	56 (47.1)	37 (62.7)	0.07
Active oral sex with condoms (safe)	12 (10.1)	5 (8.5)	0.94
Passive oral sex (no ejaculation)	109 (91.6)	52 (89.7)	0.89
Passive oral sex (ejaculation)	42 (35.3)	30 (50.9)	0.07
Passive oral sex with condoms (safe)	11 (9.2)	2 (3.4)	0.22
Receptive UAI (no ejaculation)	60 (50.4)	53 (89.8)	0.0001
Receptive UAI (ejaculation)	42 (35.3)	46 (78.0)	0.0001
Receptive AI with condoms (safe)	83 (69.8)	44 (74.6)	0.62
Insertive UAI (no ejaculation)	57 (47.9)	49 (83.1)	0.0001
Insertive UAI (ejaculation)	39 (32.8)	34 (57.6)	0.003
Insertive AI with condoms (safe)	82 (68.9)	40 (69.0)	1.00
Passive rimming	92 (77.3)	58 (98.3)	0.0007
Active rimming	92 (77.3)	54 (91.5)	0.03
Insertive fisting	31 (26.3)	44 (74.6)	0.0001
Receptive fisting	15 (12.6)	34 (57.6)	0.0001
Use of sex toys	51 (42.9)	46 (78.0)	0.0001
Lifetime sexually transmitted infection (%)	78 (78)	51 (92)	0.005
Group sex participation (group of >2 individuals):	63 (52.5)	52 (88.1)	0.0001
Group sex practices			
Receptive UAI	26 (41.3)	49 (94.2)	0.0001
Insertive UAI	30 (47.6)	44 (84.6)	0.0001
Receptive fisting	9 (14.3)	29 (55.8)	0.0001
Insertive fisting	10 (15.9)	35 (67.3)	0.0001
Group sex by number of sex practices			
0–1	94 (78.3)	11 (18.6)	
2	14 (11.7)	15 (25.4)	
3–4	12 (10.0)	33 (55.9)	0.0001

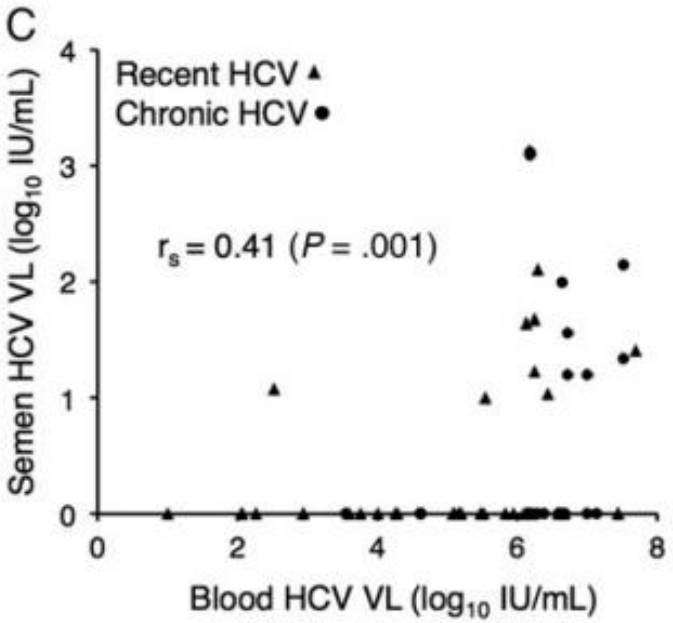
*The proportions who have ever had each type of sex were compared using chi-squared tests (or Fisher's exact test if appropriate). anal intercourse (AI)Unprotected anal intercourse (UAI);

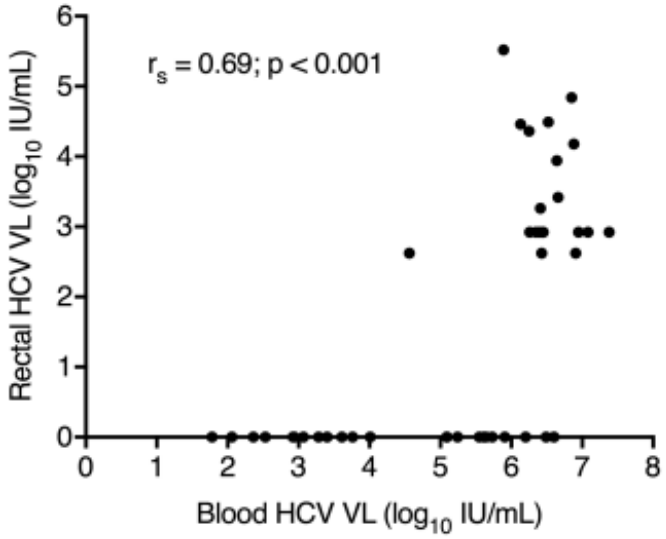
UMC Utrecht

Danta et al. AIDS 2007

Pathofysiologie HCV bij HIV+ MSM

- Associatie met seksuele technieken met risico op ‘microtraumata’
- Receptief contact: HCV+ semen icm kwetsbare mucosa
- Insertief contact: Lagere kans, maar gebied bij meatus is kwetsbaar





Turner et al. OFID 2016; Fowler et al. Clin Inf Dis 2017

Natuurlijk beloop HIV/HCV co-infectie

- Minder spontane klaring HCV
- Snellere progresssie naar leverfibrose
- Hogere incidentie hepatocellulair carcinoom

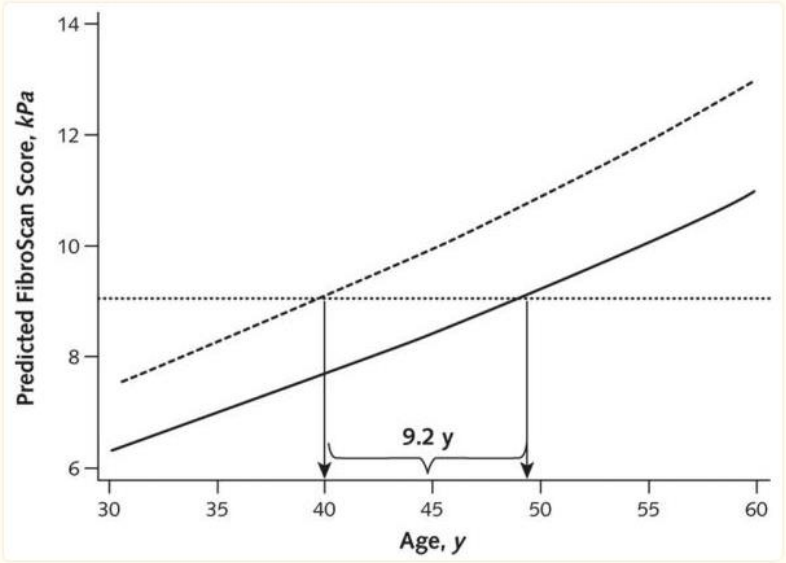
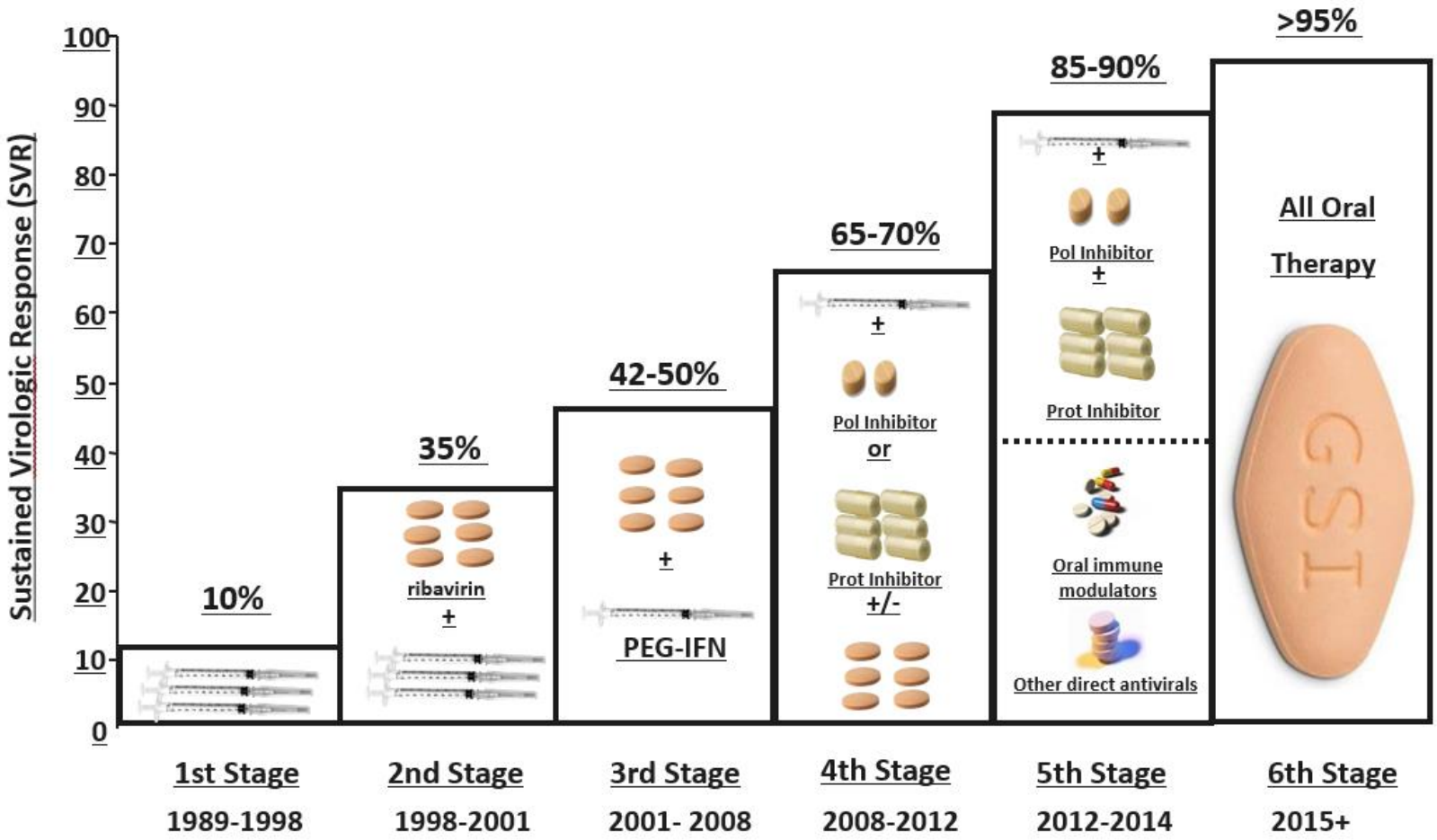


Figure 3

Liver fibrosis and age among persons coinfected with HIV and HCV (dashed line) and those with only HCV (solid line)

Kirk et al. Ann Int Med 2013

Hepatitis C therapie



Hepatitis C therapie bij HIV

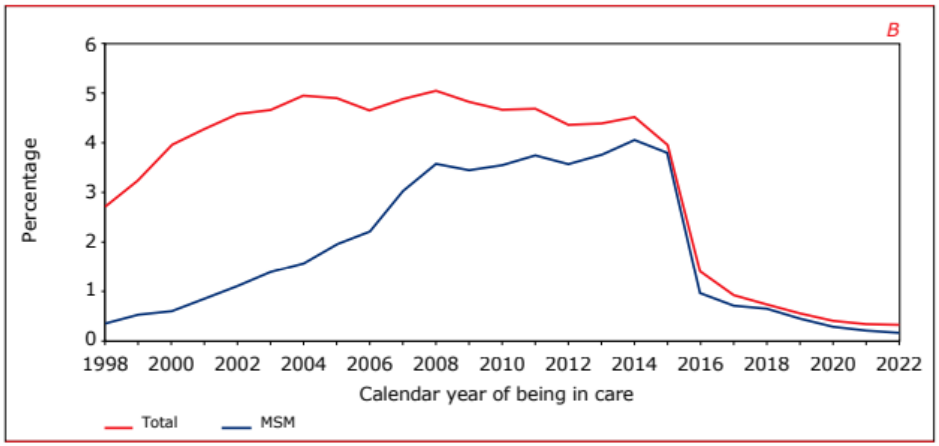
Drug-drug Interactions between Viral Hepatitis Drugs and ARVs

Viral hepatitis drugs		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/ RPV	DTG	EVG/c	RAL	TAF	TDF
HCV DAAs	elbasvir/ grazoprevir	↑	↑376% ↑958%	↑	↑66% ↑650%	↑271% ↑1186%	↓4% ↑7%	↓54% ↓83%	↓	↓	↑7% ↓2%	↔ ↑	↔	↔	↔	↔	↓2% ↓19%	↑118% ↑436%	↓19% ↓11%	↔	↓7% ↓14%
	glecaprevir/ pibrentasvir	↑	↑553% ↑64%	↑	↑397%	↑338% ↑146%	↔	↓	↓	↓	E 84%	↑	E	E	↔	↔	↔	↑205% ↑57% E47%	E47%	↔	E29%
	sofosbuvir	↔	↔	↑	↑34%	↔	↔	↓6%	↔	↔	↑9%	↑	↔	↔	↔	↔	↔	↔	↓5% D27%	↔	↓6%
	sofosbuvir/ ledipasvir	↑a	↑8% ↑113%a	↑a	↑34% ↑39%a	↔a	↑4% ↓8%	↓6% ↓34%a	↔	↔	↑10% ↑8%a	↑	E	↑7% ↓13%	↔	↔	↔	↑36% ↑78%a	↓5% ↓9% D~20%	E32%	E a
	sofosbuvir/ velpatasvir	↔a	↑22% ↑142%a	↔a	↓28% ↓16%a	↓29% ↑2%a	↔	↓3% ↓53%	↓	↓	↑16% ↓1%	↑	E	↔	↔	↔	↓8% ↓9%	↑a	↑24% ↓2%	↔	E a
	sofosbuvir/ velpatasvir/ voxilaprevir	↑	↑40% ↑93% ↑331%	↑a	↓28% ↓5% ↑143%b	↑	↔	↓	↓	↓	↔	↑	E	↑9% ↓4% ↓9%	↔	↔	↔	↑22% ↑16% ↑171%a	↔	E	E a
HDV	Bulevirtide	↑	↑	↑	↑	↑	E	↑	↑	↔	E	↔	E	↔	↔	E	↔	↑	↔	↔	↔

Colour legend

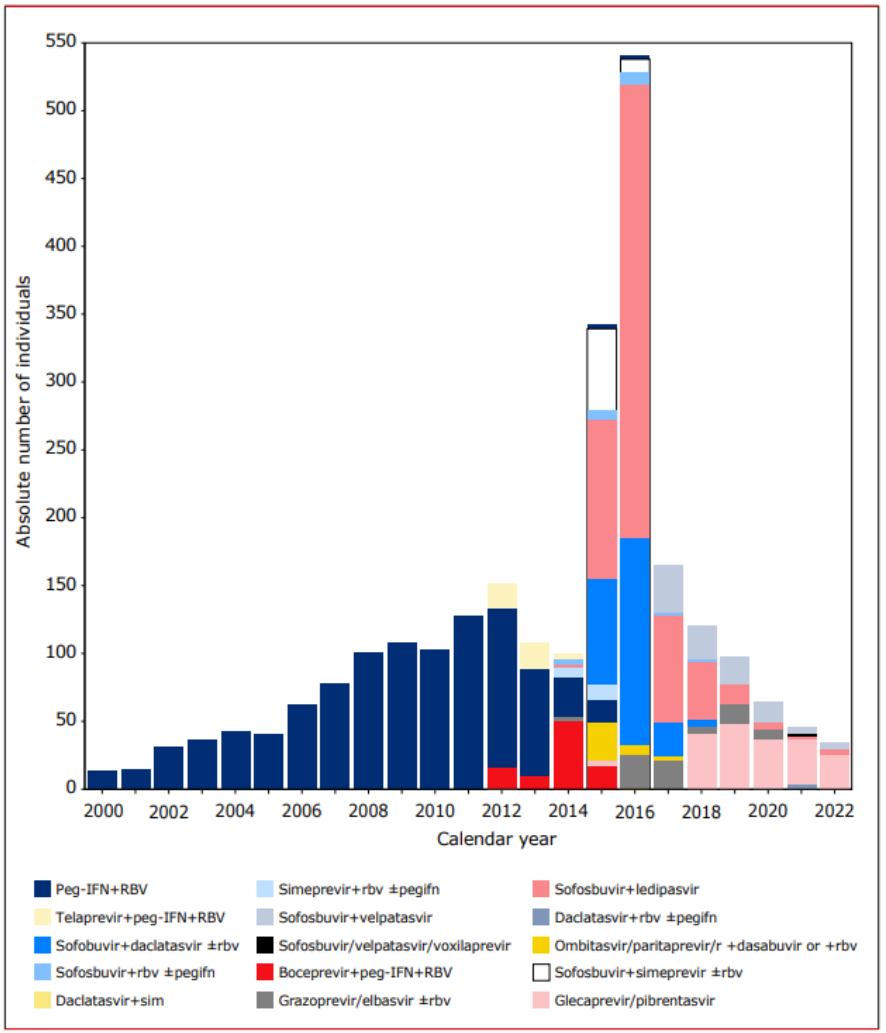
- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/ monitoring or dosage adjustment is unlikely to be required

Impact van DAA's op epidemiologie HCV bij HIV



- Overall seroprevalentie 11.2% -> 4.2%
- PWID 60 -70%
- HCV viremie bij MSM 4% -> 0.16%

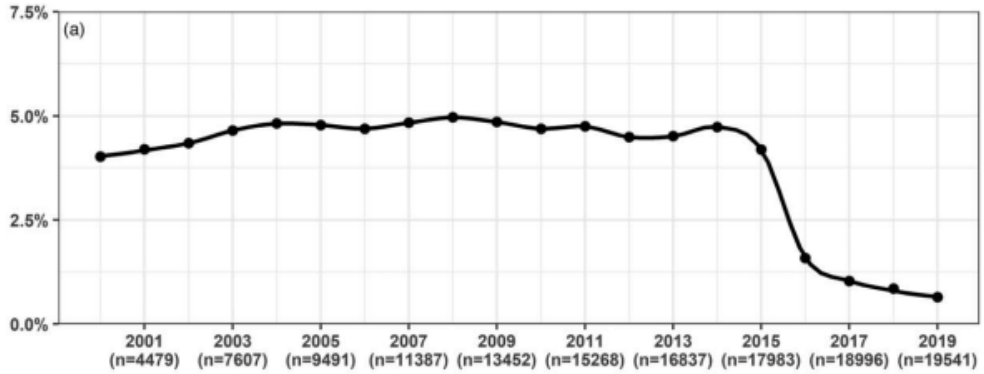
Figure 4.5: Number of individuals with HIV/HCV starting hepatitis C treatment per calendar year.



Legend: HCV=hepatitis C virus; RBV=ribavirin; PEG-IFN=pegylated interferon

Epidemiologie HCV bij HIV

Low hepatitis C virus-viremia prevalence yet continued barriers to direct-acting antiviral treatment in people living with HIV in the Netherlands

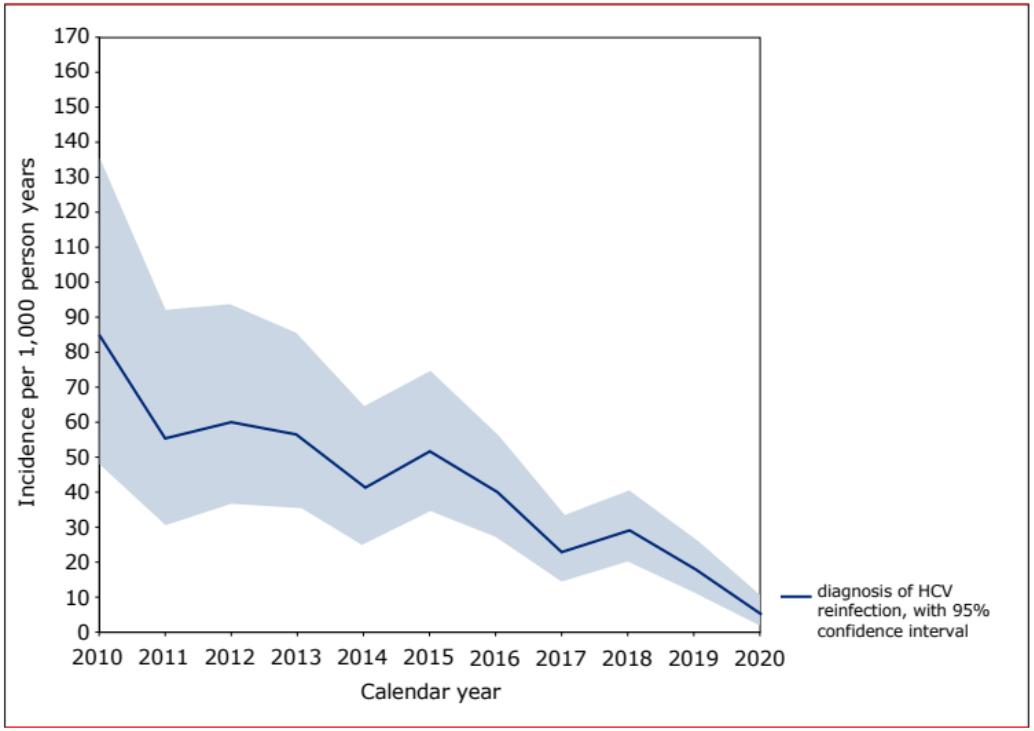


- Viremie bij 27 personen die nog in zorg waren
- Op verzoek van patiënt, ernstige comorbiditeit en non-compliance
- Hogere leeftijd en detecteerbaar HIV RNA geassocieerd met viremie

Isfordink et al. AIDS 2022

Re-infecties

Figure 4.6: Incidence of hepatitis C reinfection after earlier treatment-induced clearance among men who have sex with men, per calendar year.



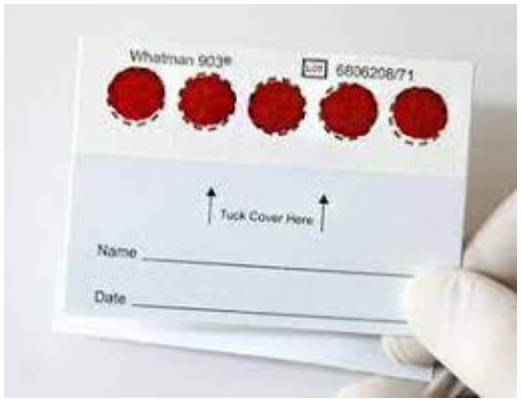
- Re-infectie is relevant fenomeen
- Hoger risico bij PWID en HIV coinfectie

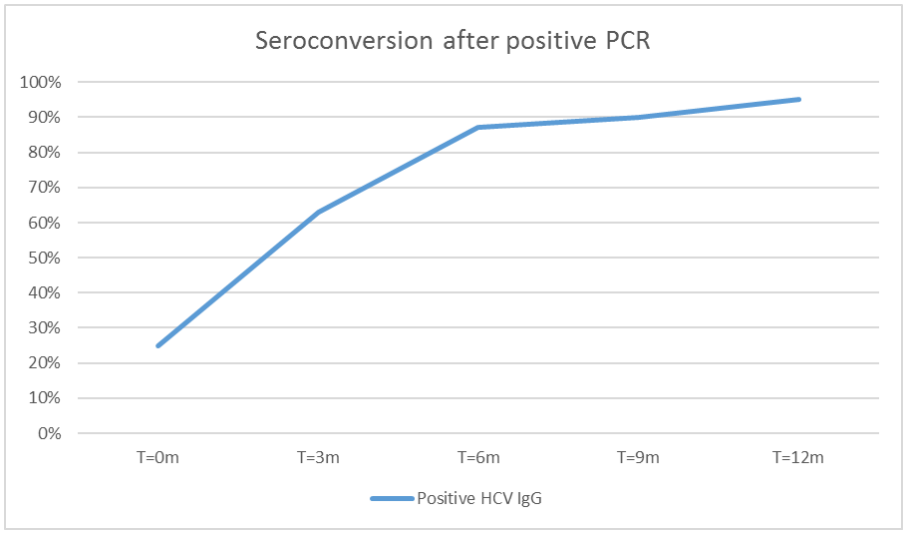
UMC Utrecht

SHM monitoring report 2021; Islam et al. Lancet Gastroent Hep 2017

Diagnostiek

1. PLWH should be screened for HCV at time of HIV diagnosis and annually thereafter[i]. Screening should use an anti-HCV antibody test[ii]
A positive result should be followed by HCV-RNA[iii] and genotype determination which is not mandatory if pangenotypic drugs are to be used. Alternatively, HCV core-antigen testing can be performed to establish chronic HCV infection. PLWH engaging in activities associated with increased risk of HCV transmission[iv] should be tested for HCV infection every 3 to 6 months. PLWH suspected of recently acquired primary HCV infection with a negative anti-HCV antibody test should be tested for HCV-RNA. HCV-RNA or HCV core-antigen testing is also recommended in PLWH with ongoing risk behavior for HCV re-infection after successful treatment or spontaneous clearance at 3 to 6-monthly intervals

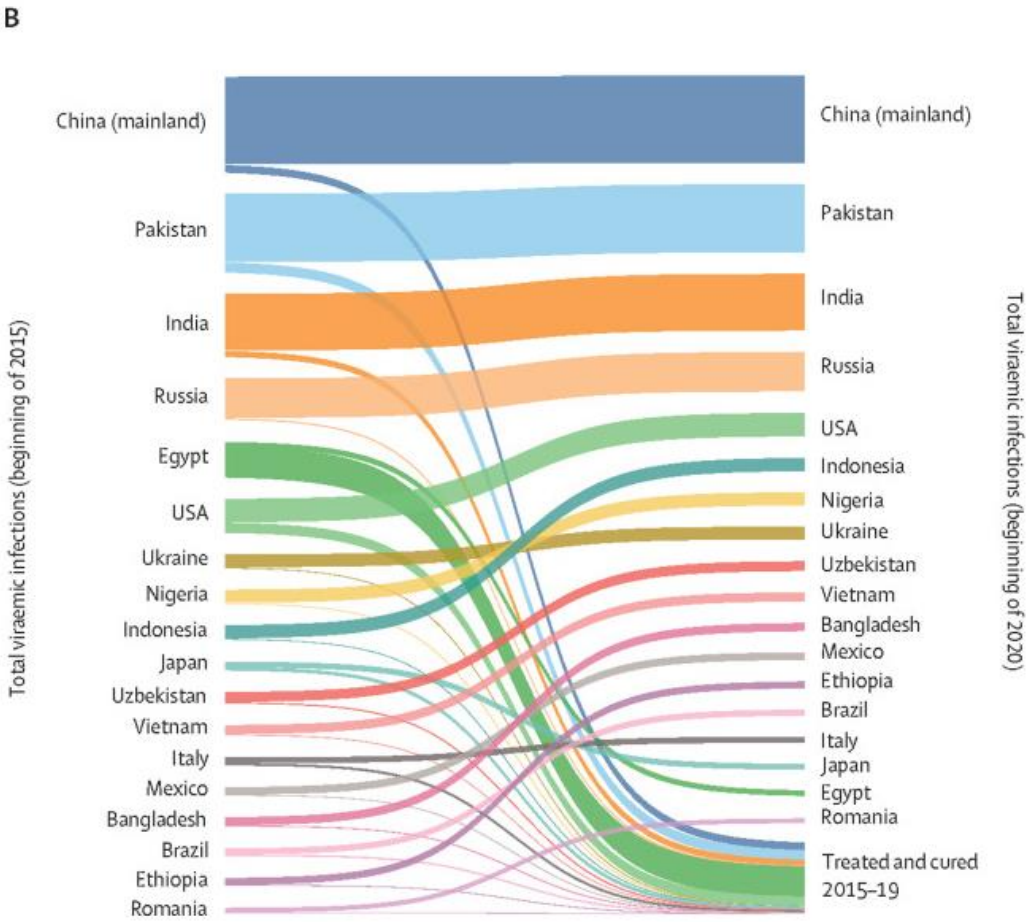




Thomsen et al. AIDS 2009 (edited figure)

Hepatitis C preventie

- Safe seks (m.n. hoog risico handelingen)
- ‘Treatment as prevention’
- Geen vaccin beschikbaar
- Pre-expositie profylaxe?



Polaris consortium Lancet Gastroent Hep 2022

Take home messages

- Co-infecties met virale hepatitis komen frequent voor bij HIV
- Het natuurlijk beloop is verschillend en heeft therapeutische consequenties
- Verlies de relevantie van hepatitis B niet uit het oog zelfs in het ‘tenofovir era’
- Draag je steentje bij aan HCV eliminatie

Vragen?