



GGD Amsterdam

Molecular Epidemiology of HCV infections in the Netherlands.

Thijs van de Laar
GGD Amsterdam

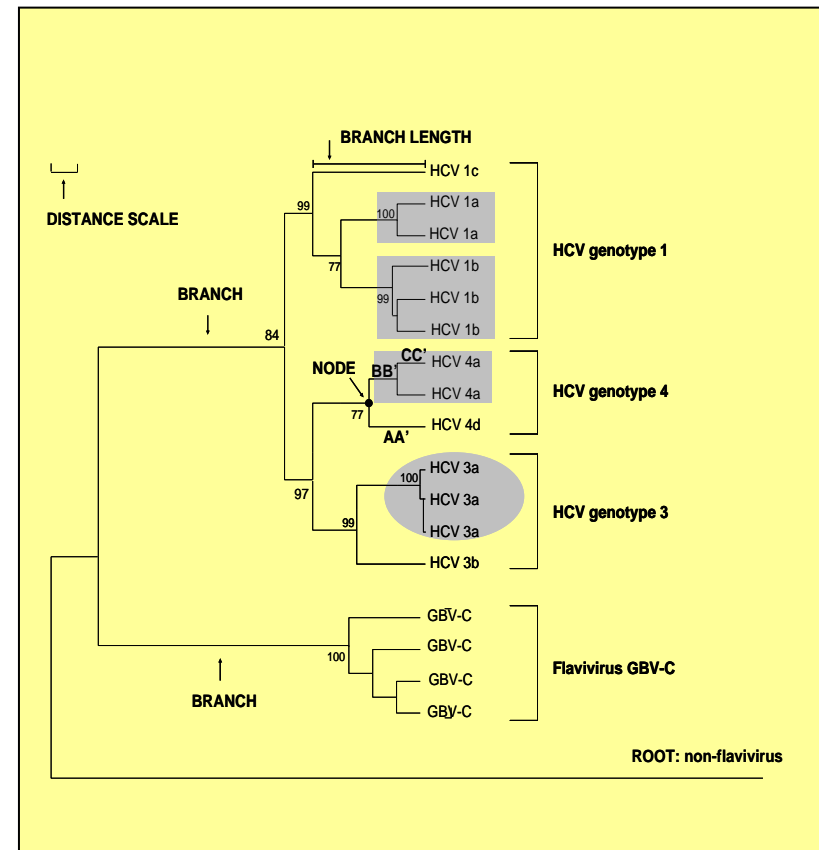


Molecular Epidemiology of HCV

- HCV - genetic variability:
 - 7 genotypes – 30-35%
 - 89 subtypes – 15-30%

- Genetic diversity:
 - Geographic origin
 - Mode of transmission
 - Timescale of spread

- To compare we need:
 - Consensus region (NS5B)
 - Unified classification system





Molecular Epidemiology

- General population
- Injecting drug users (IDU)
- Men who have sex with men (MSM)



General population – HCV prevalence

- Estimated HCV prevalence (0.1-0.4%)

Population	Year	Nr screened	Prevalence	Author
Dutch population	1995	7373	0.08%	<i>Veldhuijzen</i>
A'dam pregnant*	2003	5146	0.31%	<i>Urbanus</i>
A'dam population	2005	1355	0.66%	<i>Baaten</i>
Arhem/Nijmegen	2006	2200	0.18%	<i>Slavenburg</i>

* Testing still ongoing



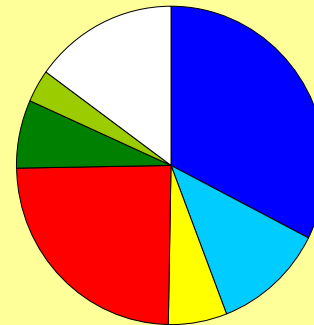
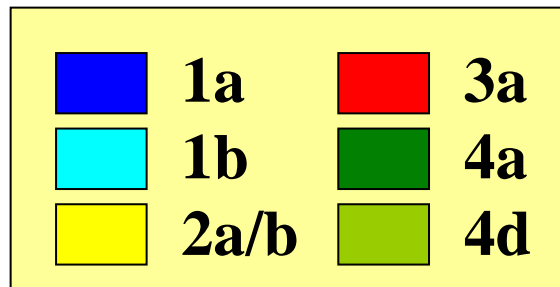
HCV genotype distribution the Netherlands:

- | | |
|----------------|---|
| •GT 1a/b : 50% | Treatment (SVR)
difficult (50%) |
| •GT 2a/b : 10% | good (90%) |
| •GT 3a : 30% | good (90%) |
| •GT 4a/d : 10% | intermediate (60%) |

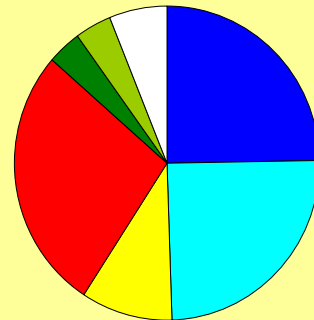
Prevalent HCV infections

BUT

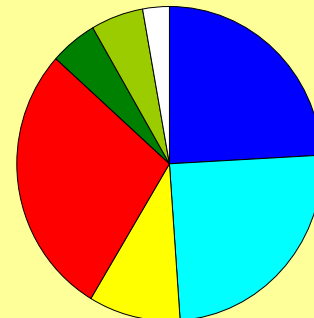
genotype distribution is dynamic



N=179
Lanl



N=81
Blood bank
Van de Laar et al, 2005



N=351
Hospital
De Vries et al., 2006



Prevalent HCV infection – general population

- **Epidemiological profiles** of HCV prevalent candidate donors

Transmission route	%	Genotype*
Blood products before 1991	30%	1b + 2a/b + (1a)*
IDU-related	21%	3a + 1a + 4d
Endemic countries	12%	4a + 'Other'
Other parenteral	19%	mix
No risk	18%	1b + 2a/b

*Incidental spillover from high risk groups to the general population



Incident HCV infection – general population

Transmission route	Patient	Genotype*
Occupational/Health care	F, 35 yrs	1b
Nosocomial/Hospitalisation (B)	M, 55 yrs	Untyped
Sexual/household	F, 42 yrs	3a (partner ex-IDU)
Sexual/household	F, 56 yrs	3a (partner ex-IDU)
Sexual/household	F, 40 yrs	RNA-negative

* Incidental spillover (from high risk groups) to the general population through mostly non-parenteral modes of transmission

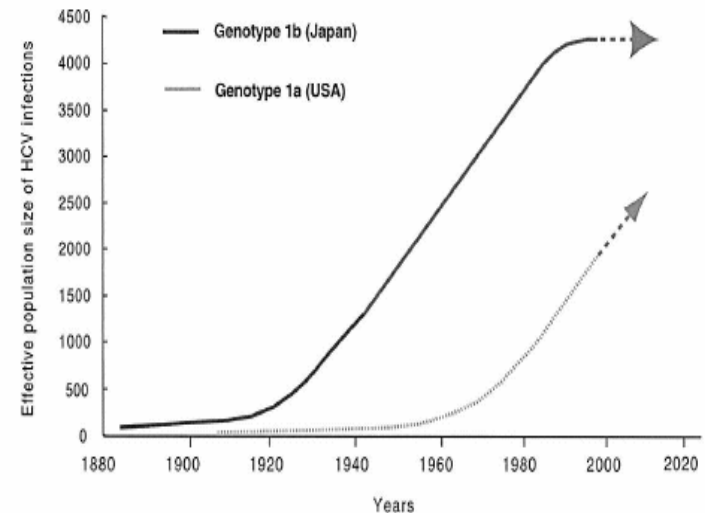


Spread general population

- Screening of donorblood (1992):
 - Donor selection
 - HCV serology and HCV-RNA

- Estimated residual risk in NL (2000-2002):
 - 1:31.500.000 donations (negligle)

- Incidental spillover high-risk populations
Ongoing spread in dialysis centres (1995-1997)

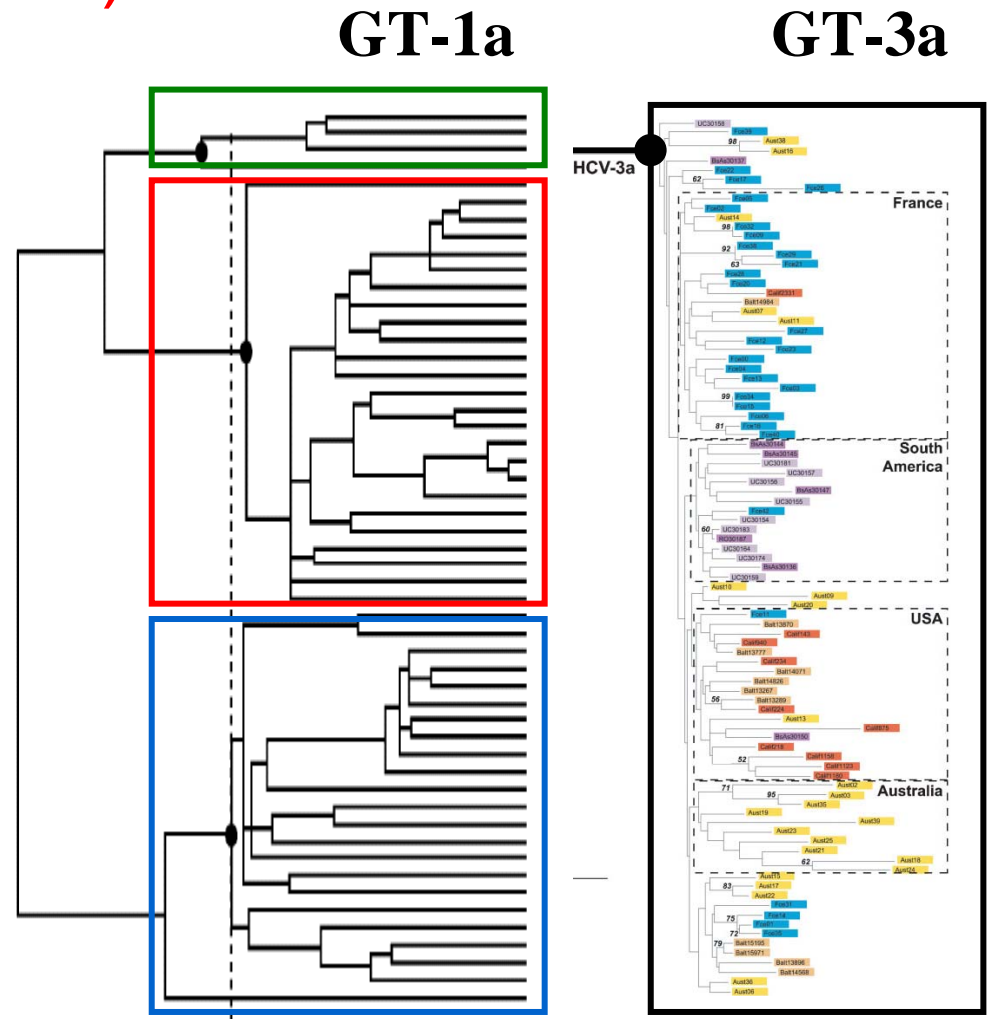


Consequence: Genotype shift towards less HCV GT 1b and 2a/b



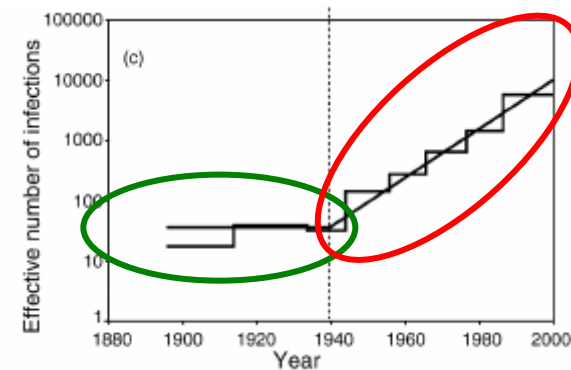
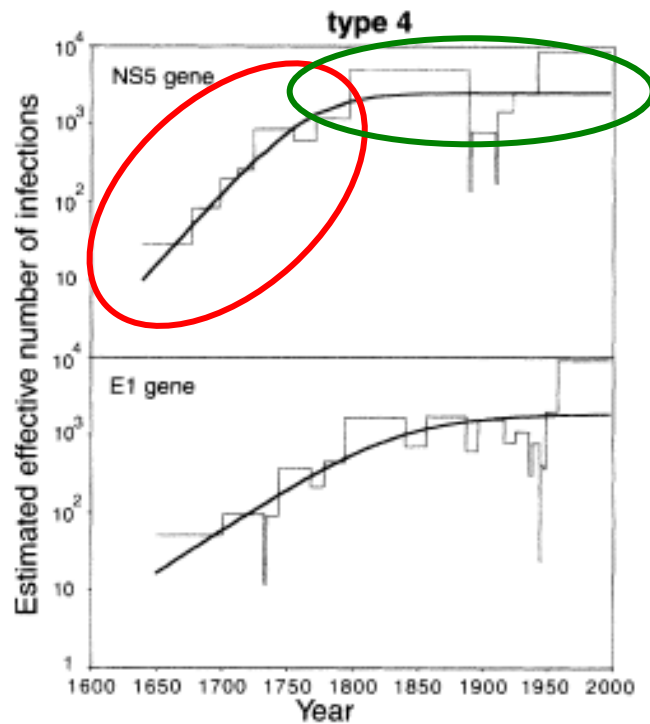
Injecting drug users (IDU)

- HCV prevalence (50-80%)
- IDU genotypes: 1a and 3a
 - 1a: 3 separate introductions
 - 3a: 1 single introduction





Timescale - spread of HCV in Europe



Two-phase epidemic:

- **Steady state:** west African origin
- **Exponential growth:** 1940 IDU



Injecting drug users (1985-2005)

- Less injection drug use: impopularity

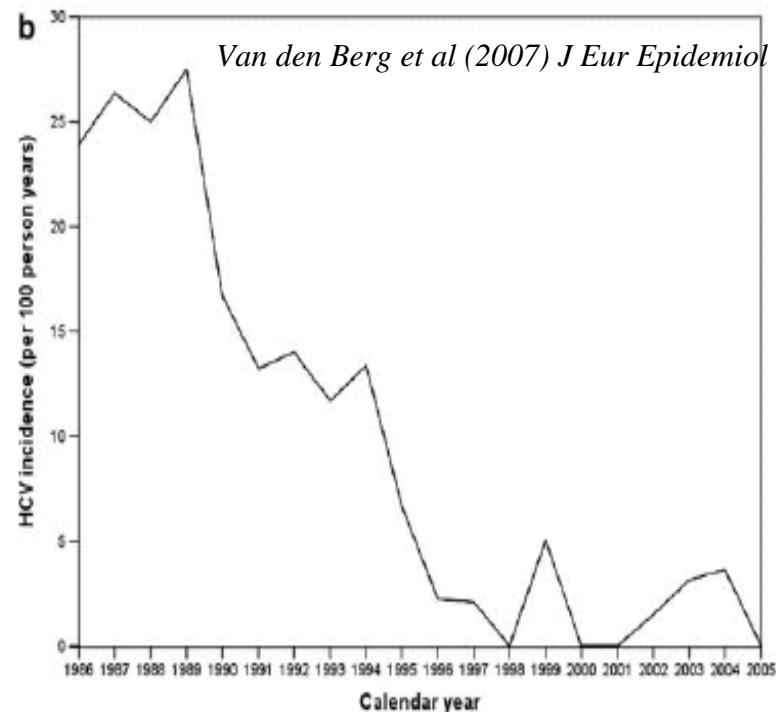
- 1985-1989: 90% DU < 30 yrs ever injected
- 2000-2004: 31% DU < 30 yrs ever injected

HCV prevalence young DU: 83% → 14%

- Safer injection: Harm reduction

- NEP combined with methadone treatment
- Larger window of intervention

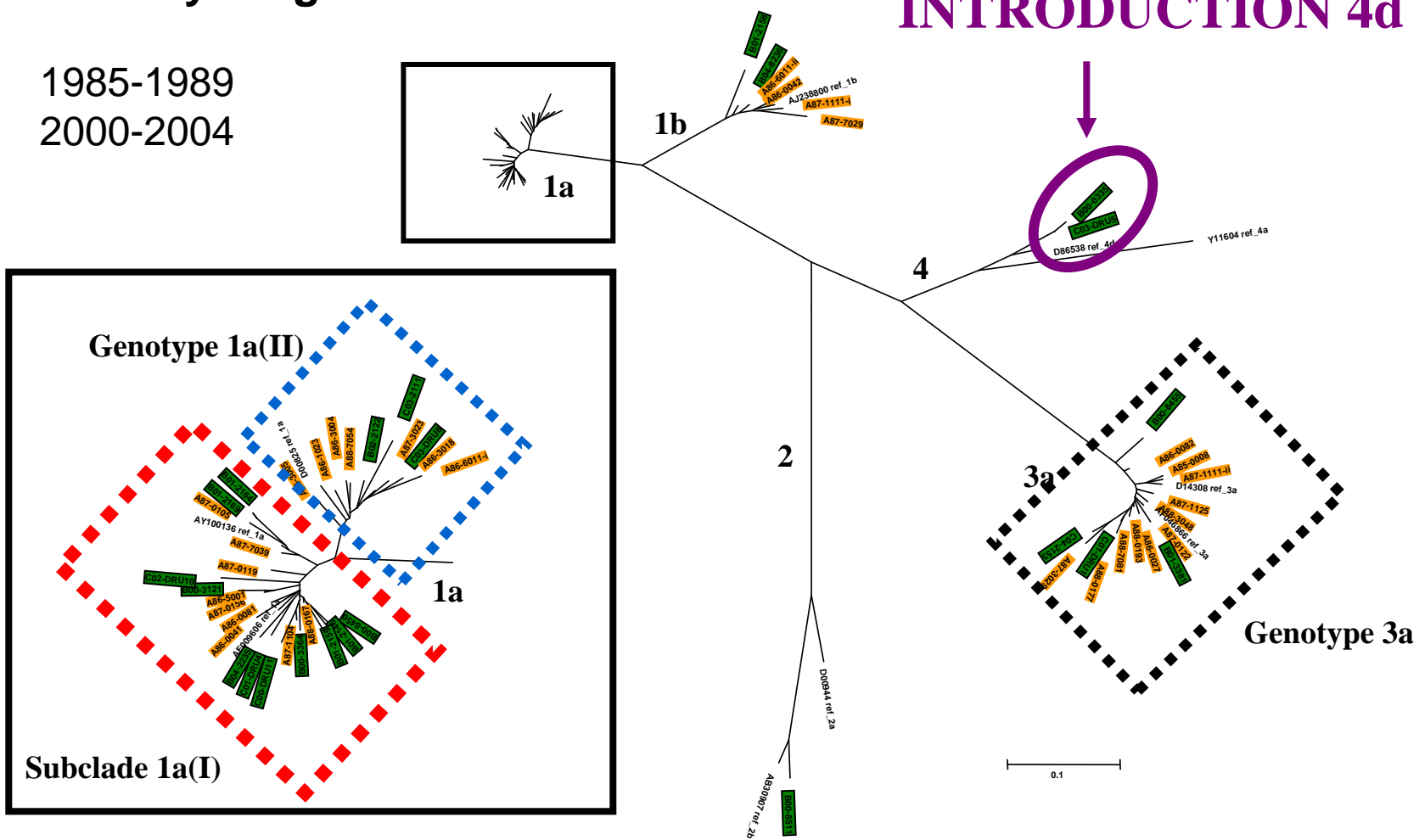
HCV prevalence young IDU: 91% → 44% (30%)





HCV strains young IDU Amsterdam

- 1985-1989
- 2000-2004





Injecting drug users (IDU)

- Diversification of HCV genotype 1a and 3a
- Introduction and spread of HCV genotype 4d
- Genotypic shift towards difficult-to treat genotypes (1 and 4)
- HCV incidence is low → TREATMENT to decrease HCV reservoir further



HCV treatment of IDU

Cost-effective?

What about HCV reinfection and superinfection?



HCV reinfection and superinfection

- Reinfection – protective immunity
 - **YES:** Incidence of HCV reinfection < Incidence initial infection
 - **NO:** Incidence HCV reinfection = incidence initial infection

- Amsterdam HCV seroconverter (SC) study
 - 59 HCV seroconverters (1985-2005)
 - 5 time points per SC (RNA + viral typing)
 - Frequency HCV reinfection and superinfection



Results: SC without viral clearance

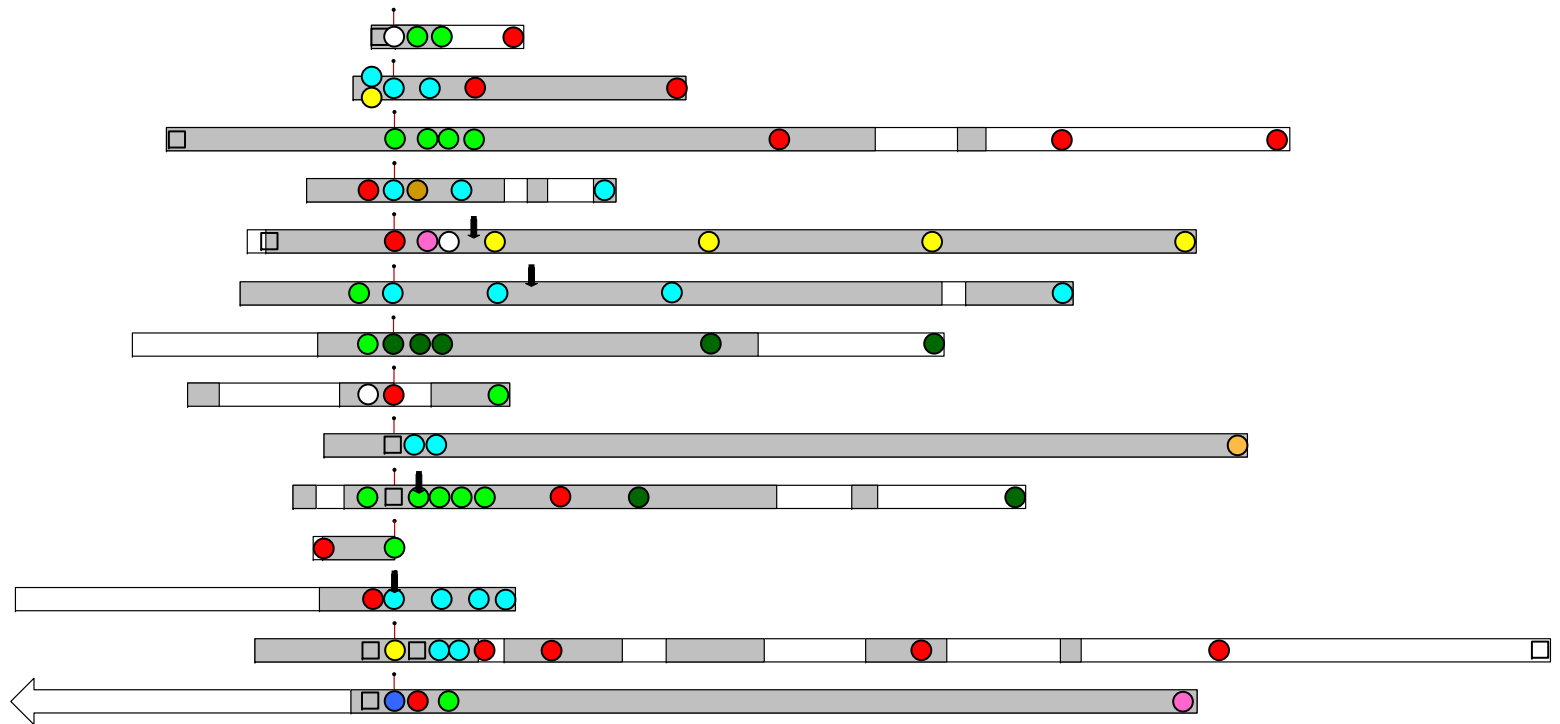


Figure 2

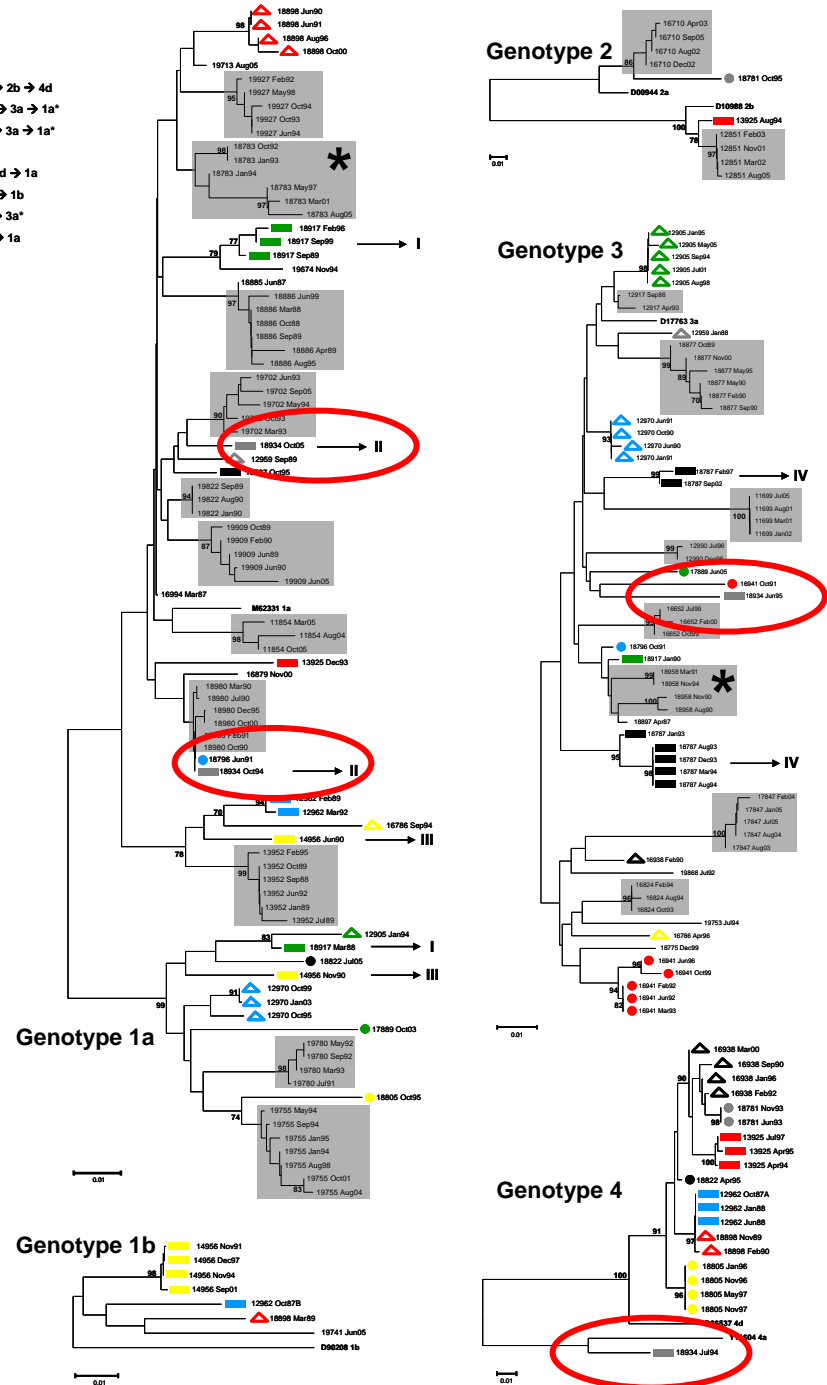
- IDU 13925: 1a → 4d → 2b → 4d
- IDU 18917: 1a → 1a* → 3a → 1a*
- IDU 18934: 4a → 1a → 3a → 1a*

- IDU 12962: 1b/4d → 4d → 1a
- IDU 14956: 1a → 1a* → 1b
- IDU 18787: 3a → 1a → 3a*
- ▲ IDU 18898: 1b → 4d → 1a

- ▲ IDU 12905: 1a → 3a
- ▲ IDU 12959: 3a → 1a
- ▲ IDU 12970: 3a → 1a
- ▲ IDU 16786: 1a → 3a
- ▲ IDU 16938: 3a → 4d
- IDU 16941: 3a → 3a*
- IDU 17889: 1a → 2a
- IDU 18781: 4d → 2a
- IDU 18796: 1a → 3a
- IDU 18805: 1a → 4d
- IDU 18822: 4d → 1a

Reinfection / Superinfection

- **MULTIPLE** HCV infections (41%)
- 1-4 HCV strains per IDU
- Reinfection with same HCV subtype
- Lack of immunological protection

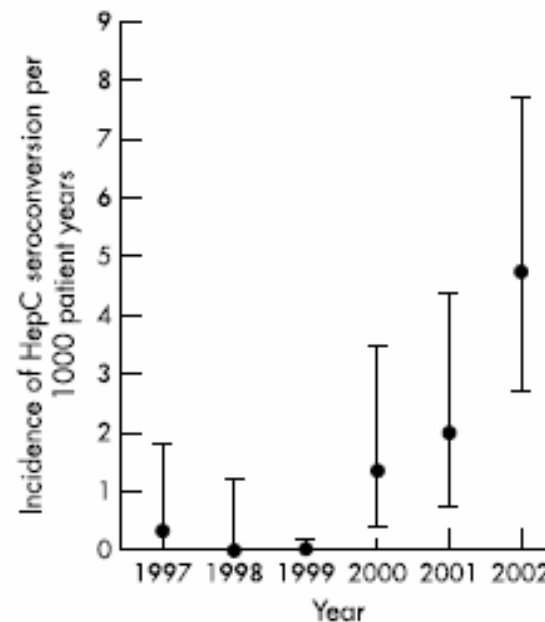




New risk groups: MSM

- Since 2000: Increased HCV-incidence among MSM in the UK.

- More case reports:
 - **The Netherlands (Ruijs 2004; Agtmael 2004; Götz 2005)**
 - France (Ghosn 2004; Gambotti 2005)
 - Switzerland (Rauch 2005)
 - Germany (Vogel 2005)
 - England (Gilleece 2005)
 - Australia (Matthews, 2006)
 - United States (Bateman, 2006)



Figuur uit: Browne et al (2004) STI



HCV incidentie MSM in NL

Screening Amsterdam Cohort Studies

- 1985-1999: 0.8/1000 PY
- 2000-2002: 8.7/1000 PY

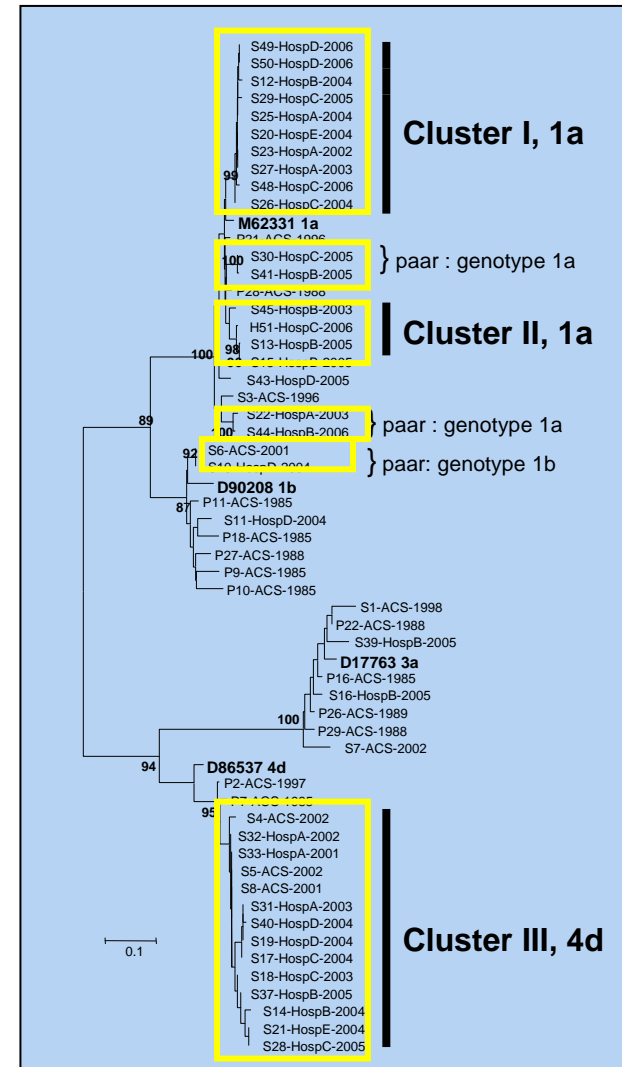
↑ 10x

Hospital notifications: 2002-2005 (n=34)

- High risk sexual behavior
- HIV-positive (97%)
- Genotypes 1 en 4 (92%)

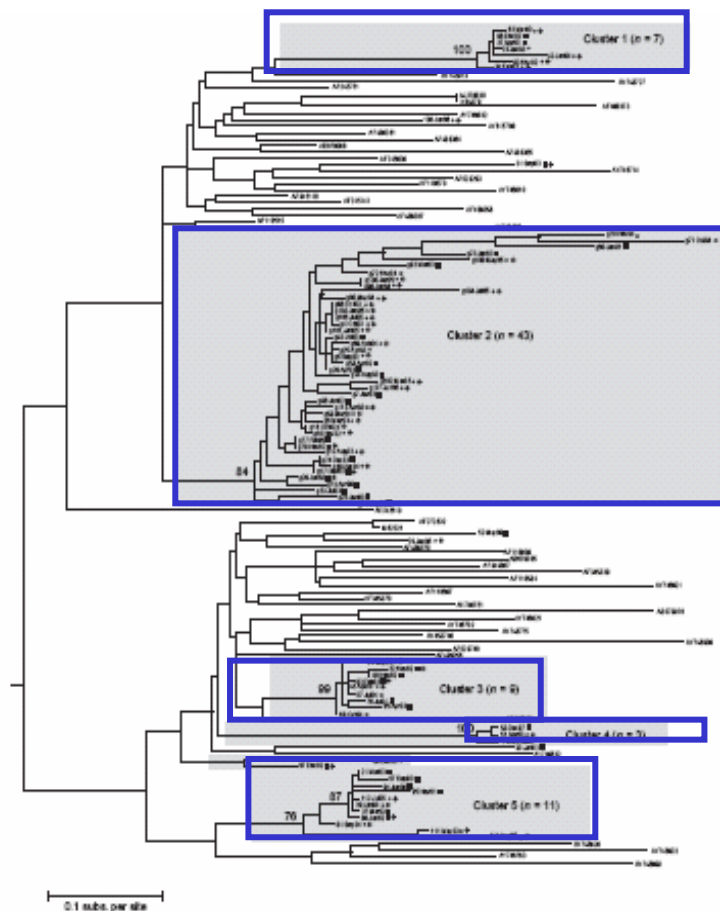
Outbreak:

MSM-specific HCV strains



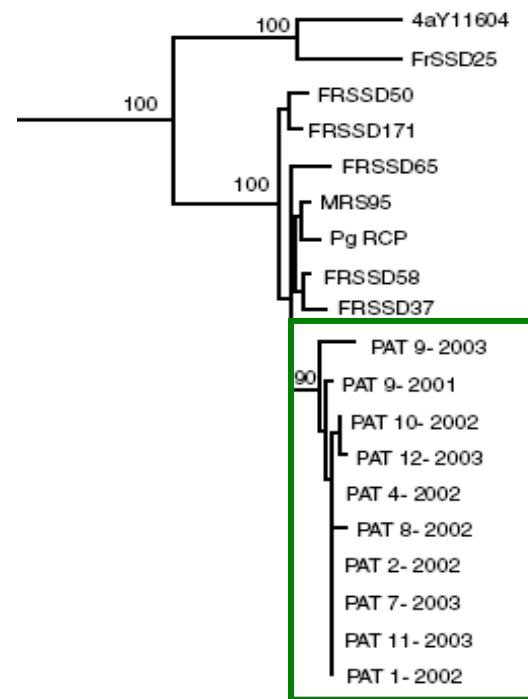


England: genotype 1a



Danta et al (2001) AIDS

France: genotype 4d



Serpaggi et al (2006) AIDS,



Sexual HCV transmission

Incidental national outbreaks

or

large international transmission network?



Clustering (85% of MSM)

Clusters en Paren	Genotype	Country mixing	Countries
Cluster 1 n = 37	1a	yes	UK, NL
Cluster 2 n = 34	4d	yes	UK, NL, D, F
Cluster 3 n = 19	1a	yes	UK, NL, D
Cluster 4 n = 17	1a	yes	UK, D
Cluster 5 n = 12	1a	yes	UK, NL, D, AUS
Cluster 6 n = 12	1a	no	UK
Cluster 7 n = 6	1a	yes	NL, D
Cluster 8 n = 6	1a	no	AUS
Cluster 9 n = 6	3a	yes	UK, F
Cluster 10 n = 4	1a	no	AUS
Cluster 11 n = 4	1b	no	UK
Paar A,B,C n = 6	1a	no	
Paar D,E n = 4	1b	no	
Paar F n = 2	3a	no	



- Engeland
- Nederland
- Duitsland
- Frankrijk
- Australië

Genotype 1a

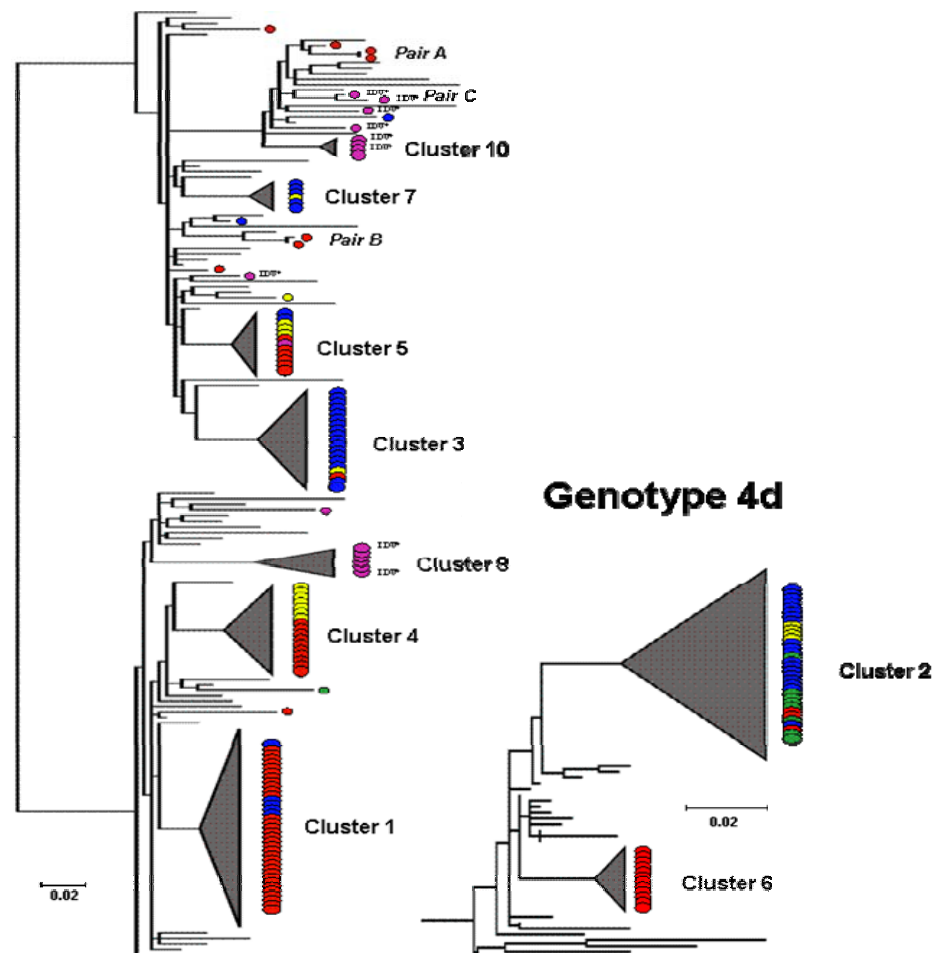


Figure 1: NS5B phylogenetic tree of HCV subtypes 1a (left) and 4d (right)
 Monophyletic clusters are shaded, country of origin: (●) England, (●) The Netherlands
 (●) Germany, (●) France, (●) Australia. Australian MSM with reported IDU are marked IDU*
 BOOTSTRAPS WEERGEVEN




Introduction and spread of HCV

Cluster	Genotype	Nr. of sequences	Year of origin (CI)	Number (%) of divergence events since		
				1996	1998	2000
1	1a	37	1984 (1974-1992)	31(86)	29(81)	20(56)
2	4d	34	1975 (1961-1988)	28(85)	26(78)	21(64)
3	1a	19	1993 (1985-1999)	17(94)	16(89)	13(72)
4	1a	17	1988 (1977-1997)	15(94)	14(88)	11(69)
5	1a	12	1996 (1989-2001)	11(100)	10(91)	9(82)
6	4d	12	1995 (1989-1999)	10(91)	8(73)	7(64)
7	1a	6	1998 (1990-2003)	5(100)	5(100)	4(80)
8	1a	6	1983 (1970-1993)	1(20)	1(20)	1(20)
9	3a	6	1984 (1974-1993)	0(0)	0(0)	0(0)
10	1a	4	2001 (1996-2004)	3(100)	3(100)	3(100)



What causes this unexpected and rapid spread of HCV among HIV+ MSM?

 **Virus** versus behaviour



HCV geïnfecteerde MSM

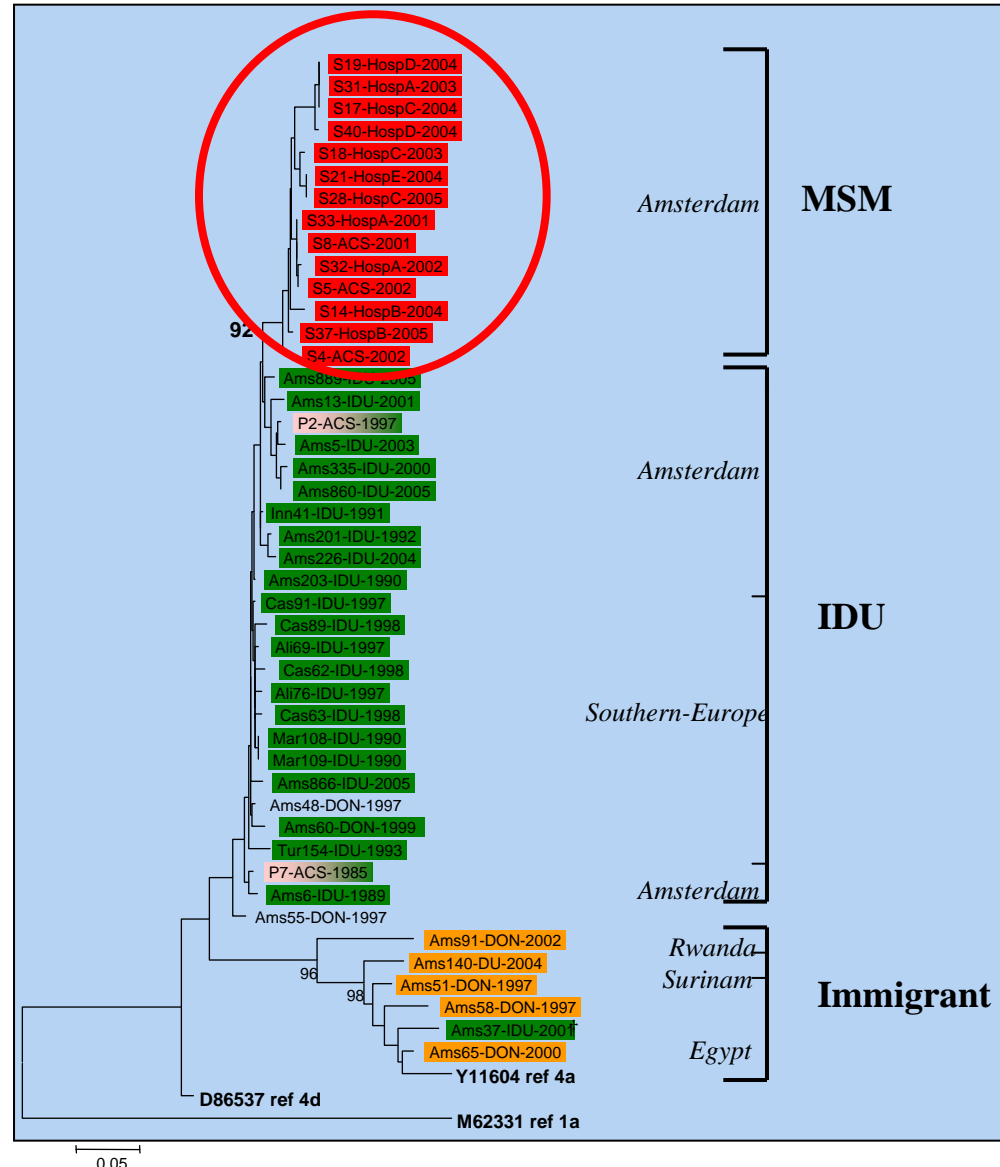
	Age	CD4-count	HAART	IDU
UK (n=107)	35	510	60%	17%
NL (n=58)	40	-	-	3%
D (n=24)	38	429	60%	4%
F (n=12)	40	604	75%	0%
AUS (n=24)	40	596	75%	50%
Total	38	518	62%	14%



Transmission Genotype 4

- = MSM (SC after 2000)
- = MSM (SC before 2000)
- = Injecting drug users (IDU)
- = Immigrants

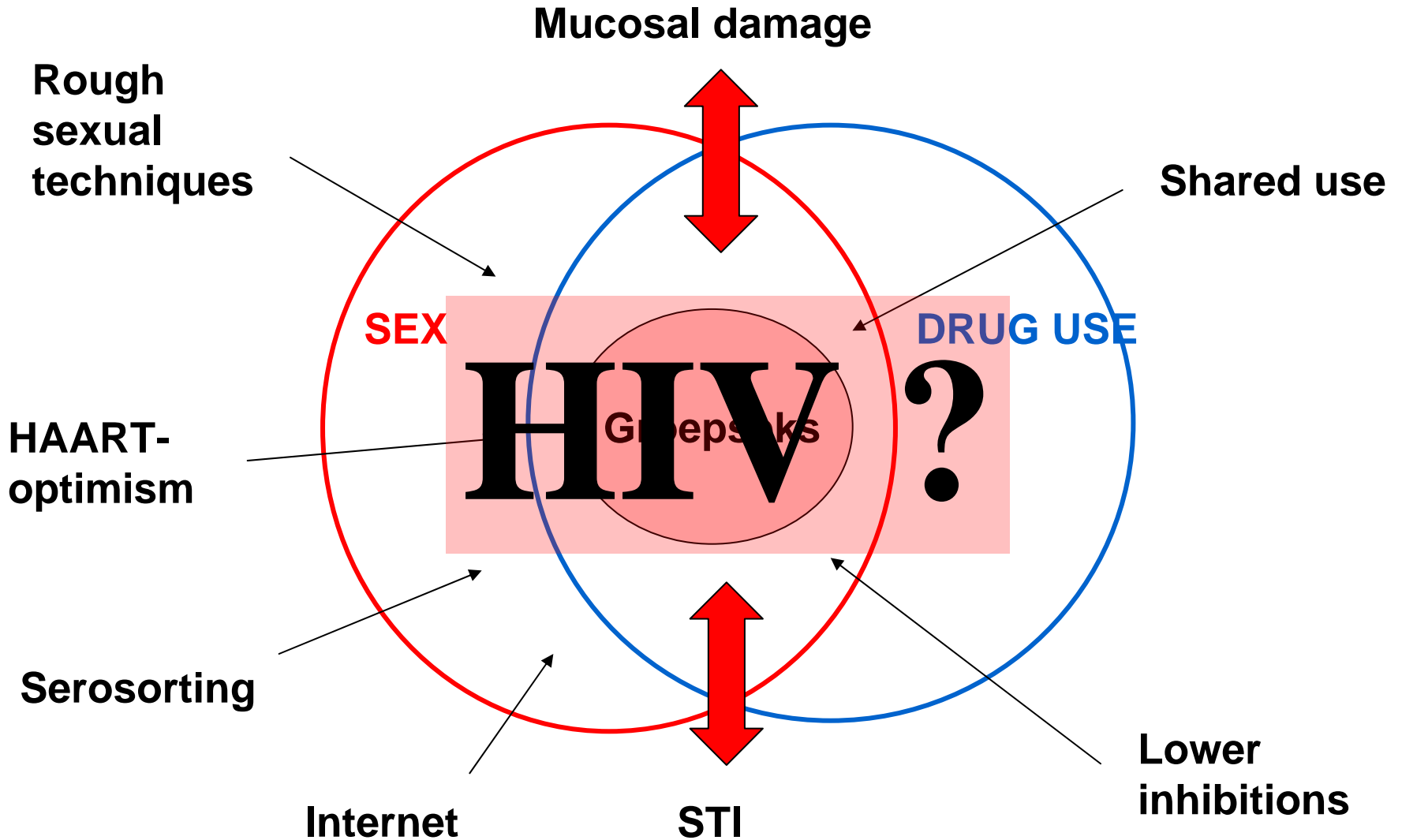
UNique MSM-specific HCV strain of HCV genotype 4 distinct from the strain circulating among IDU





Case control studie: UK (Danta *et al*, AIDS 2007)

	control	case	P-waarde
UAI (- ejaculation)	50% (p)	90% (p)	0.0001
	48% (a)	83% (a)	0.0001
UAI (+ejaculation)	35% (p)	83% (p)	0.0001
	33% (a)	58% (a)	0.003
Rimming	77% (p)	98% (p)	0.0007
	77% (a)	92% (a)	0.03
Fisting	26% (p)	75% (p)	0.0001
	13% (a)	58% (a)	0.0001
Toys	43%	78%	0.0001
Group sex (>2pers)	53%	88%	0.0001
Partydrugs	71%	97%	0.0001





The role of HIV?

Spread:

- 1) Increased susceptibility
- 2) Increased infectivity
- 3) HIV sersorting
- 4) Infectivity and background levels HIV vs HCV

Clinical progression:

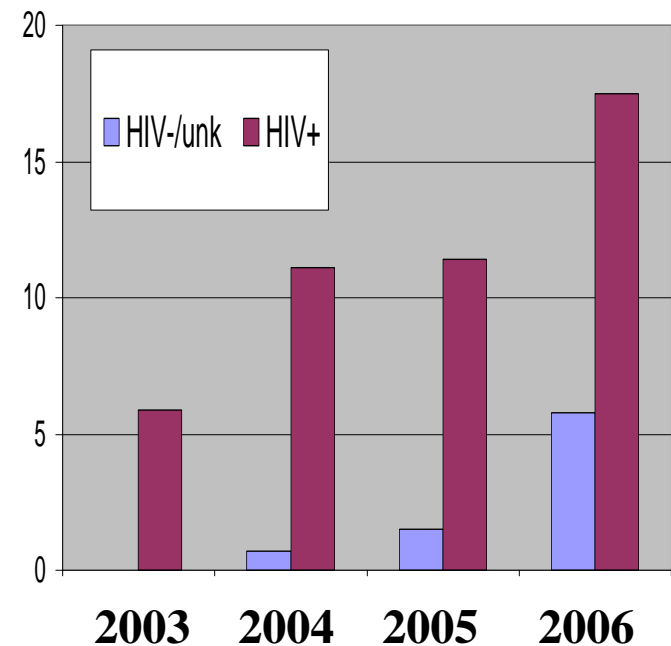
- 1) Higher rate of chronicity (> 90%)
- 3) Faster progression to liver disease
- 4) Less favourable treatment outcome
- 5) Hepatotoxicity caused by HAART



Update spread HCV among HIV+ MSM

- UK: HCV incidence among HIV+ increases 20% each year.
- HCV rare among HIV- MSM
- Increase HCV incidence **NOT** caused by intensified HCV screening
- HCV prevalence STI-clinic A'dam
 - May 2007: 15%
 - Nov 2007: 18%
 - April 2008: 21%

HCV incidence: HIV+ MSM GUM clinic Brighton





HCV among HIV+ MSM – current focus!

- Implement **routine HCV screening** in HIV positive MSM
- **Early diagnostics**: Early treatment and prevention of new cases
- **Targeted education and prevention** strategies to raise awareness of risks HCV among HIV+ MSM
- Monitor **HIV-negative MSM!** Are they at risk?



Thanks

Colleagues of Cluster Infectious Diseases **GGD Amsterdam**

Colleagues of Medical Microbiology **AMC Amsterdam**

HIV departments: **OLVG, AMC, Slotervaart Hosp, VUMC**

International Collaboration on acute HCV in HIV+ MSM

Erasmus MC and **GGD Rotterdam**

Roel Coutinho **RIVM**

Oliver Pybus **University of Oxford**

VHPB Organising committee