

Acute HCV Infections and Re-infections in HIV+ MSM: Debunking the Myths.

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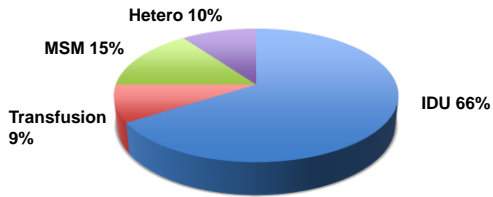
**“Sex without love is a
meaningless experience, but as
far as meaningless experiences
go it is pretty damn good!”**

Woody Allan

1. How important is per mucosal HCV transmission?
2. How has the epidemiology of acute HCV transmission in HIV changed?
3. What are the transmission factors?
4. Is this limited to HIV infected MSM?
5. What is the natural history of HCV in this population?
6. Is HCV reinfection a problem?
7. Treatment as prevention?

Epidemiology of HCV in HIV

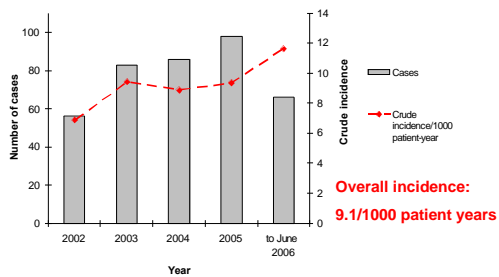
- 9-30% prevalence HCV/HIV co-infection.



Mohsen HIV Med 2005

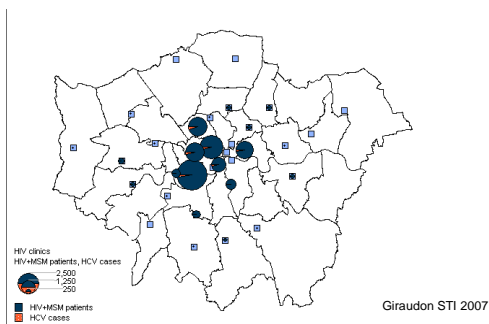
Is this changing?

UK temporal data of acute HCV in HIV + MSM

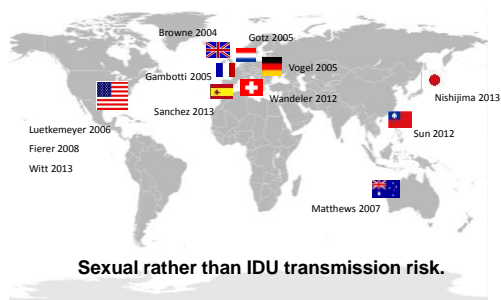


Giraudon STI 2007

UK temporal data of acute HCV in HIV+ MSM



Reports of acute HCV in HIV.



Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference

The European AIDS Treatment Network (NEAT) Acute Hepatitis C
Infection Consensus Panel

AIDS 2011, 25:399–409

Definition of acute HCV – NEAT consensus

1. Positive anti-HCV IgG in presence or absence of HCV RNA and a documented negative anti-HCV IgG in previous 12 months
2. Positive HCV RNA and a documented negative HCV RNA and a negative IgG in previous 12 months.
3. If absent past serology, positive HCV RNA in context of acute hepatitis (ALT >10x ULN)

NEAT AIDS 2011

How important is permucosal HCV transmission?

Transmission of HCV infection

Route of Exposure	HCV	HIV	HCV versus HIV transmission
Parenteral (needlestick)	1.5-3%	0.3%	> x10
Permucosal (sexual)	0.1-0.3%	1-5%	< x10
Vertical	2-5%	20-30%	< x6-10

HCV seroprevalence in high-risk STI groups

Risk group	Anti-HCV	Associated factors
FSWs	6%	Number of partners, other STIs, sex with trauma, non-use of condoms
STI clinic	4%	Risk for IDU > sexual factors. In non IDU : number of partners, high-risk sexual contacts, HIV+
MSM	4%	Risk for IDU > sexual factors. In non IDU : HIV+, number of partners, sexual practices

Terrault Hepatology 2002

Studies of HCV discordant heterosexual couples

Study	Type of study	Study population	N	Duration follow-up	Incidence /1000 PY (cases)
Kao 2000	Prospective	Taiwanese	112	46 m	0.23 (1)
Vandelli 2004	Prospective	Italian	776	120 m	0.37 (3)
Tahan 2005	Prospective	Turkish	216	36 m	None
Terrault 2013	Cross-sectional	USA	500	180m	0.72 (3)

Risk was 1 per 190,000 sexual exposures.

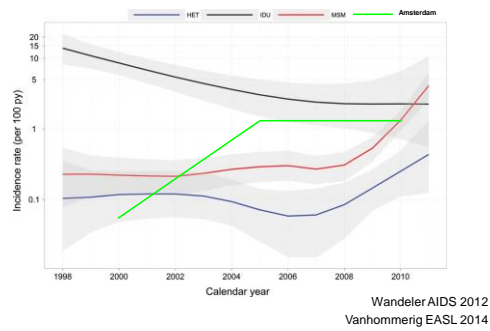
How has the epidemiology of acute HCV transmission in HIV changed?

Incidence of HCV in HIV cohorts

Study	Period	Numbers	Population	Acute HCV	Incidence/100 PY
Swiss HIV Cohort	1988-2004	N=3327	IDU	69	7.4
			Hetero; no IDU	11	0.18
			MSM; no IDU; unsafe sex	8	0.7
			MSM; no IDU; safe sex	6	0.2
PRIMO, France	1996-2005	1405 PY	MSM	4	0.35
			Female	2	0.78
PH cohort, Sydney	2005-2007	N=159	MSM	0	0
Twenty clinics Brighton & London, UK	2002	42,985 PY	MSM	56	0.69
	2006		MSM	84	1.16
Amsterdam cohort studies	1984-2003	4408 PY	MSM	8	0.18
	2000-2003	572 PY	MSM	5	0.87

NEAT AIDS 2011

Swiss Cohort HCV incidence rates



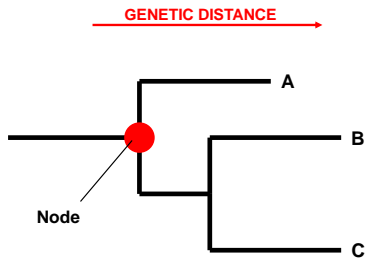
Multicenter AIDS Cohort USA HCV incidence

Participants	1980s and 1990s Recruits				2000-2003 Recruits			
	Incident Infections (no.)	PYs	IR/1000 PYs	95% CI	Incident Infections, No.	PYs	IR/1000 PYs	95% CI
HIV-negative men								
1984-1989	8	12 354	0.65	.28-1.28	NA	NA	NA	NA
1990-1994	0	6913	0	0-53	NA	NA	NA	NA
1995-1999	0	3064	0	0-1.20	NA	NA	NA	NA
2000-2004	1	3112	0.32	.01-1.79	1	835	1.20	.03-6.67
2005-2011	2	3787	0.53	.06-1.91	4	1715	2.33	.64-5.97
HIV-positive men								
1984-1989	41	7299	5.62	4.03-7.62	NA	NA	NA	NA
1990-1994	18	4779	3.77	2.23-5.95	NA	NA	NA	NA
1995-1999	11	3185	3.45	1.72-6.18	NA	NA	NA	NA
2000-2004	5	2648	1.89	.61-4.41	7	1038	6.74	2.71-10.88
2005-2011	6	2334	2.57	.94-5.60	11	2133	5.16	2.57-9.23

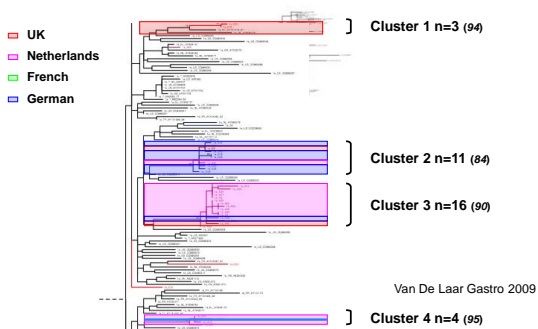
Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; IR, incidence rate; NA, not applicable; PYs, person-years.

Witt CID 2013

Molecular epidemiology

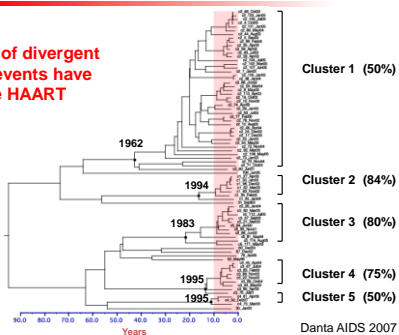


International incident HCV phylogeny



Molecular clock analysis of HCV clades

Majority (64%) of divergent (transmission) events have occurred since HAART introduction.



Molecular epidemiology

Two important points:

1. Temporally occurring simultaneously across countries and not from one city to another.
2. Transmission increased following HAART introduction.

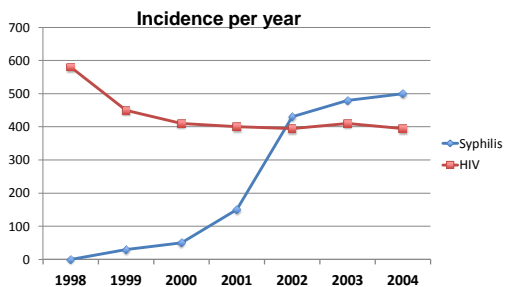
Molecular evidence argued against a virological change to explain HCV transmission.



“What I was wondering is, Doctor, can you make me straight during the week and gay on the weekends?”

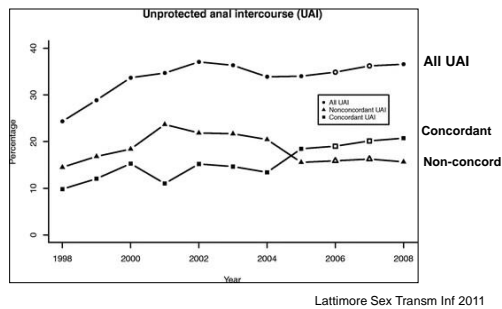
What are the behavioural transmission factors?

San Francisco HIV paradox.....



Adapted Truong, Sex Transm Inf 2006

Seroadaptive behaviours over time.



Mucosal trauma – sexual behaviours

	London (n=190)	Germany (n=101)	USA (n=75)
Univariate	UAI Fisting Rimming S&M practices Sex toys Group sex	Rectal trauma with bleeding Fisting (no gloves) Group sex	UAI (ejaculation) Fisting Sex toys STI
Multivariate	Group Sex OR 9.16	Rectal trauma with bleeding OR 6.19	UAI (ejaculation) OR 21

Danta AIDS 2007
Schmidt Plos One 2011
CDC MMWR 2011

Mucosal trauma – drugs

Non-injected recreational drug (nasal and rectal):

- Disinhibition of sexual risk behaviour
- Mucosal hyperaemia and trauma
- Shared paraphernalia

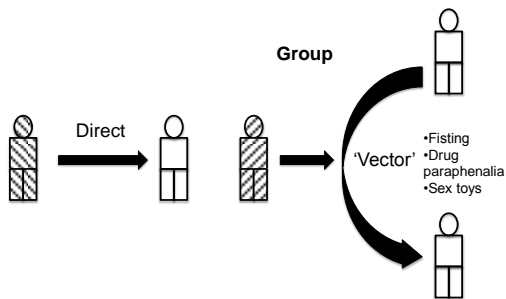
Drugs:

Metamphetamine – OR 28 in USA study

Others: Ketamine, gammahydroxybutyrate, amyl nitrate, cocaine, MDMA, LSD

Danta AIDS 2007
Schmidt Plos One 2011
CDC MMWR 2011

Transmission



What are biological transmission factors?

Sexually transmitted infections

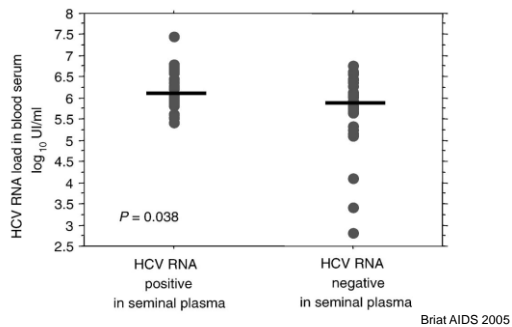
	London (n=190)	Germany (n=101)	USA (n=75)
Syphilis rate	41% versus 18%	56% versus 31%	50% versus 17%
Type	Syphilis Chlamydia Gonorrhoea	Syphilis Chlamydia Gonorrhoea	Syphilis Gonorrhoea

Mucosally ulcerative STIs (Syphilis and LGV):

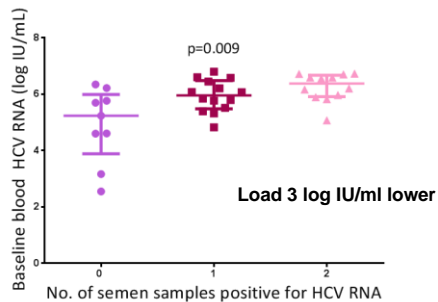
- Mucosal integrity disrupted
- Increased inflammatory cells

Danta AIDS 2007
Schmidt Plos One 2011
CDC MMWR 2011

Semen concentration in HIV/HCV co-infection



Semen concentration in HIV/HCV co-infection



Immunology of acute HCV in HIV infection.

HIV is associated with:

- Higher HCV load – 1 log IU/ml
- Lower HCV spontaneous clearance

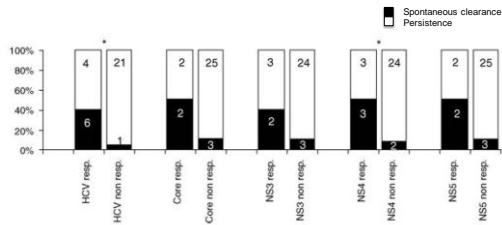
Innate immunity:

- Relationship with IL28b
- NK cells

Adaptive immunity

- Delayed anti-HCV IgG responses
- Impaired T-cell mediated immunity

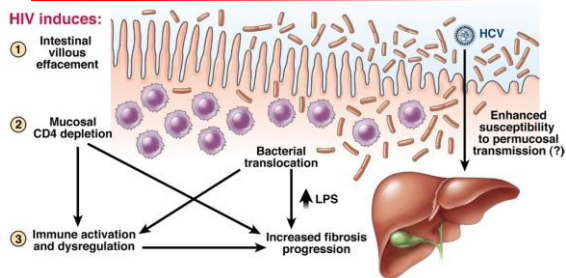
Cell mediated immune responses to HCV



HIV associated with reduce breadth and magnitude of cell mediated responses

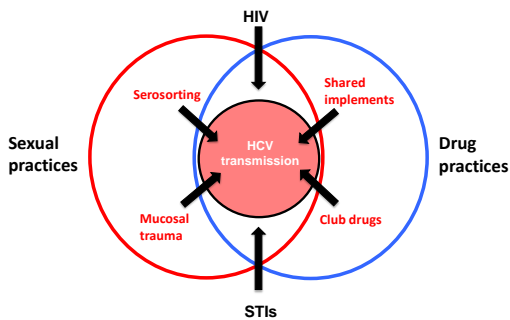
Schnuriger AIDS 2009

Role for mucosal immunology defect in HIV?



Kim Gastroenterology 2009

Summary of transmission



Is this limited to HIV infected MSM?

HCV transmission in HIV negative MSM

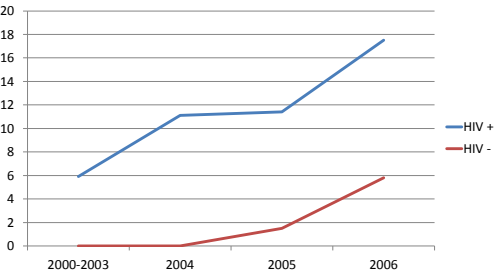
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2005-2011	6	2334	2.57	.94-5.60	11	2133	5.16	2.57-9.23

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; IR, incidence rate; NA, not applicable; PYs, person-years.

- Canadian crosssectional study; HIV negative MSM (n=1081)
- Prevalence 2.9%; related to IDU (37% v 0.3%).
- Incidence: 1 case associated with IDU
- No sexual transmission of HCV

Witt CID 2013
Alary Am J Pub Health 2005

Acute HCV in HIV negative MSM (UK; n=3536)



Richardson JID 2008

Acute HCV in HIV negative MSM

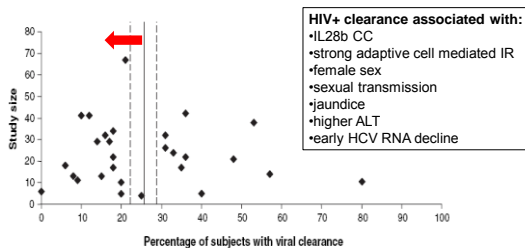
- Retrospective cohort London:
- N=36 of HIV negative MSM with acute HCV (10 spont cleared)
- Risk factors very similar to HIV+ MSM:
 - HCV positive partner (27%)
 - multiple sexual partners
 - group sex (35%)
 - fisting (35%)
 - recreational drug use (58%)
 - intravenous use (27%)
 - UAI (85%)
 - 30% had an additional STI.

McFaul BHIVA Liverpool 2014

What is the natural history?

Acute HCV infection

Meta-analysis of spontaneous viral clearance



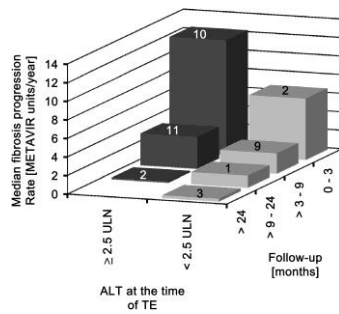
Micallef J Viral Hep 2006
NEAT AIDS 2011

Comparison of acute HCV in HIV+ and HIV-

	ATAHC (Aus)		Hep-Net (Ger)	
	HIV + (n=27)	HIV - (n=76)	HIV + (n=157)	HIV - (n=259)
Age years	40	30	39	37
Male sex %	100	62	99	58
HCV G1 %	60	42	71	68
HCV non-G1	40	68	29	32
Transmission				
IDU	44	81	1	17
Heterosexual	0	7	1	20
MSM	49	1	97	2
HIV				
CD4	614	NA	473	NA
CDC class 1	93	NA	29	NA
HAART	59	NA	59	NA
HCV				
Symptomatic	48	46	32	59
Peak ALT	981	937	261	660
Jaundice			10	58
Duration	22	39	8	7
HCV RNA	4.8	4.5	5.8	5

Matthews CID 2009
Vogel CID 2009

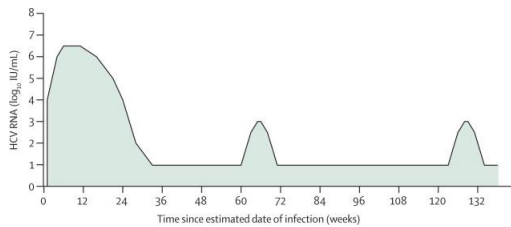
Fibrosis progression following acute HCV



Vogel CID 2009

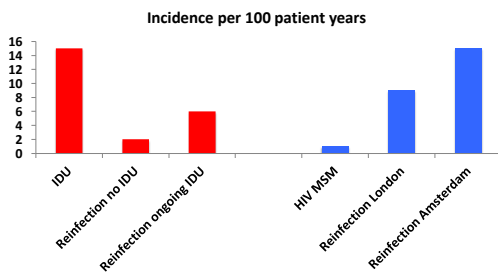
Is HCV reinfection a problem?

HCV reinfection – natural history



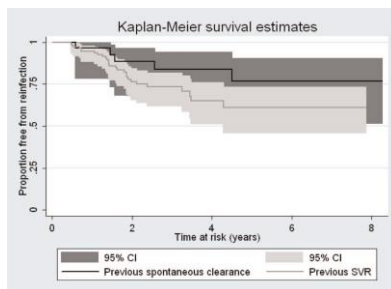
Grebely Lancet Inf Dis 2012

HCV reinfection in IDU and MSM



Martin AIDS 2013
Aspinall CID 2013

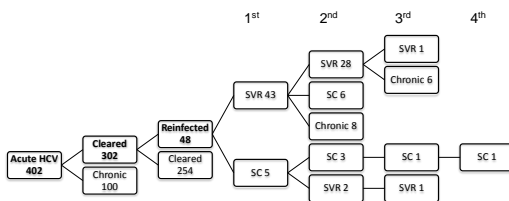
HCV reinfection in HIV+ MSM in London



25% were reinfected within 2 years

Martin AIDS 2013

Reinfection in Hep-Net cohort (German)



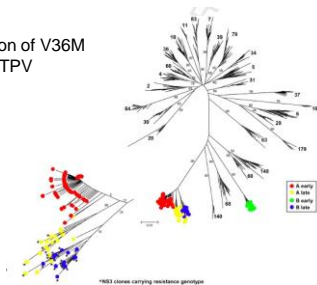
In 48 individuals there were 108 HCV infections.

No predictors of clearance in reinfection.

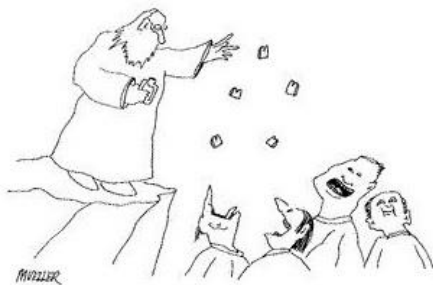
Ingiliz HIV Med 2014

Reinfection – transmission of DAA resistance

Transmission of V36M mutation – TPV resistance



Franco Gastro 2014



Moses hands down easy to swallow tablets.

What is effect of postexposure prophylaxis (PEP) and preexposure prophylaxis (PrEP) ?

Impact of PrEP and PEP....

Postexposure prophylaxis (PEP) and Preexposure prophylaxis (PrEP) have clear benefits reducing HIV transmission.

Unclear impact on sexual risk behaviour:

- Behavioural disinhibition or risk compensation

But,

- Increased engagement with health services

Liu JAMA 2006

HCV infection in UK PrEP study

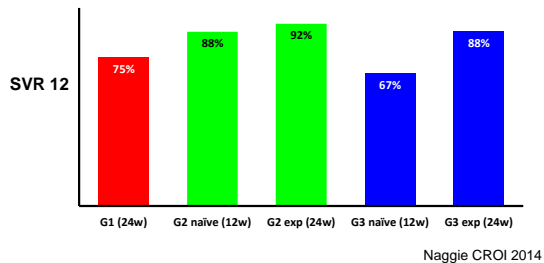
- **PROUD study (n=500):**
- Immediate versus deferred PrEP.
- Tested 160 and found 5 acute HCV cases with incidence rate 1.3%; 3 in PrEP arm; 2 deferred arm.
- Risk: 1 IDU and 4 permucosal.
- Recommend testing HCV in PrEP individuals.

Tiraboschi BHIVA Liverpool 2014

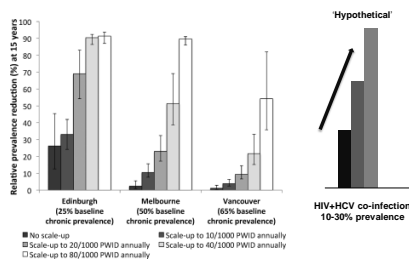
Treatment as prevention?

Will HIV impact HCV cure rates with DAAs?

PHOTON 1 – G1,2,3 experienced and naïve HCV/HIV n=182
Sofosbuvir + RBV weight based.



Treatment as prevention in HCV





Conclusions

- Ongoing HCV infections in HIV+ MSM.
- Per mucosal rather than parenteral transmission of HCV in HIV+ MSM, but parenteral transmission may be under reported.
- Identified transmission risk factors should form the basis of education interventions.

Conclusions

- Need regular surveillance/screening of at risk individuals; includes at risk HIV negative MSM; at least annual testing.
- Reinfection rates are very high and unclear what the impact of PrEp will be. As a result, this would be an ideal group for treatment as prevention.
- Changing times from Interferon to DAA has significant cost and treatment implications in this population.

World Cup 2014

Bosnia & Herzegovina



Russia



Versus



Chile



Germany

Mexico



No sex bans in successful winning team!
