Epidemic of Sexually-transmitted Hepatitis C Infection among HIV-infected Men Who Have Sex with Men

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Sexually-transmitted HCV in HIV-infected MSM is an International Epidemic

- HCV is sexually-transmitted?
  - Illustrative patient case study
- Review of international epidemic
- Findings from New York City and the U.S.
- The U.S. and the international epidemic

Patient

- 46 y.o. HIV-infected man, lawyer, presented for initial medical care
  - HIV acquired via sex with men
- Initial medical evaluation:
  - CD4 count 427/26% cells/μL
  - HIV viral load 26,168 copies/mL
  - hepatitis A Ab+; hepatitis B sAb+ (vaccinated); hepatitis C antibody negative
  - LFTs with normal range
- Antiretroviral therapy was deferred

Patient

3 mo later returned for routine check-up

- felt well, no complaints, exam normal
- but new social history:
  - recent unprotected sex with many men, some anonymous, met via internet
  - using crystal methamphetamine, cocaine, "ecstasy," amyl nitrate, marijuana at "parties"
  - not injecting these or other drugs, no EtOH

Patient

Labs:

- CD4 458/26% cells/μL
- HIV VL 32,444 copies/mL

BUT:

- ALT 960 U/L
- AST 760 U/L
- Alk phos 211 U/L
- Total bili 1.0 mg/dL

Patient

Follow-up testing:

- HCV Ab: newly positive (negative 3 mo prior)
- HCV VL: 5.9 $\log_{10}$ IU/mL
- HCV genotype: 1a
- RPR: non-reactive

HCV Acquisition: our patient, what's new?

Men-who-have-sex-with-men (MSM) as risk group:

- no evidence in '70s and '80s of sexual transmission among MSM
- HCV in HIV *negative*, *non*-IDU MSM: 0.3 to 2% prevalence in U.S.
  - similar to U.S. general population

HCV Acquisition: our patient, what's new?

- injection drug use not mode of transmission
- sexual transmission likely (while it does not occur in discordant heterosexual couples)
- HIV was present before new HCV infection

HCV Acquisition–things we thought we knew

- HCV isn't sexually transmitted
  - Marincovich B, et al. **Absence of hepatitis C virus transmission in a prospective cohort of heterosexual serodiscordant couples**. *Sex Transm Infect*, 79:160-162; 2003
  - Tahan V, *et al.* **Sexual transmission of HCV between spouses**. *Am J Gastroenterol*, 100:821-824; 2005
  - Vandelli C, *et al.* **Lack of evidence of sexual transmission of hepatitis C among monogamous couples: results of a 10-year prospective follow-up study.** *Am J Gastroenterol*, 99:855-859; 2004
- ...in discordant *heterosexual* couples

HCV Acquisition–things we thought we knew

- MSM don't get HCV through sex
- Seroprevalence studies in '70s and '80s did not suggest sexual transmission among MSM
  - HCV in HIV *negative*, *non*-IDU MSM: 0.3 to 2% prevalence in U.S.

HCV Acquisition–things we thought we knew

- There are lots of kinds of sex
- Things change over time

Primary HCV in HIV+ MSM: Initial Epidemic Reports

Browne 2004
Gilleece 2005

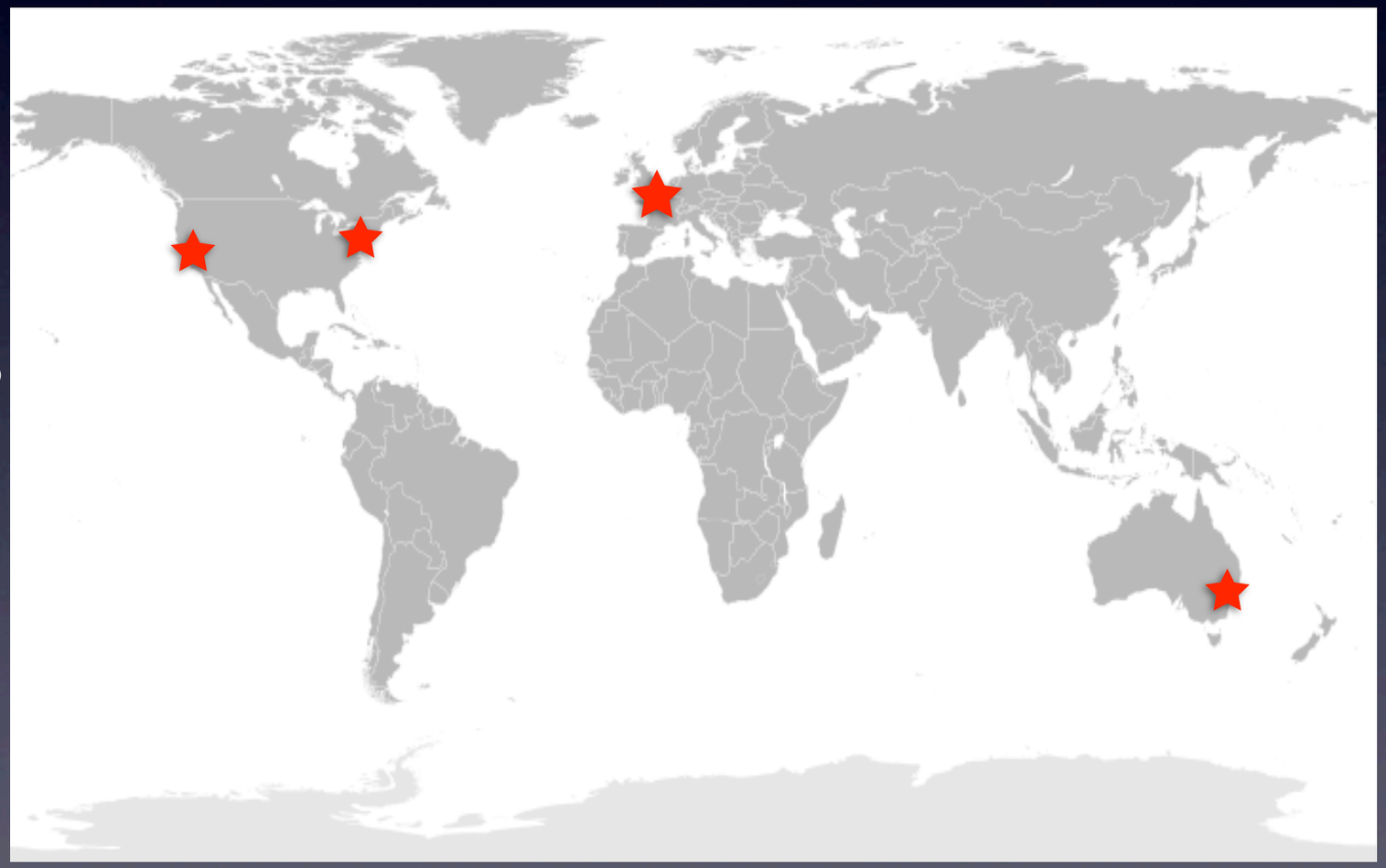
Ghosn 2004
Gambotti 2005

Götz 2005

Vogel 2005

Primary HCV in HIV+ MSM: Further Epidemic Reports

Luetkemeyer 2006
Fierer 2008



Matthews 2007

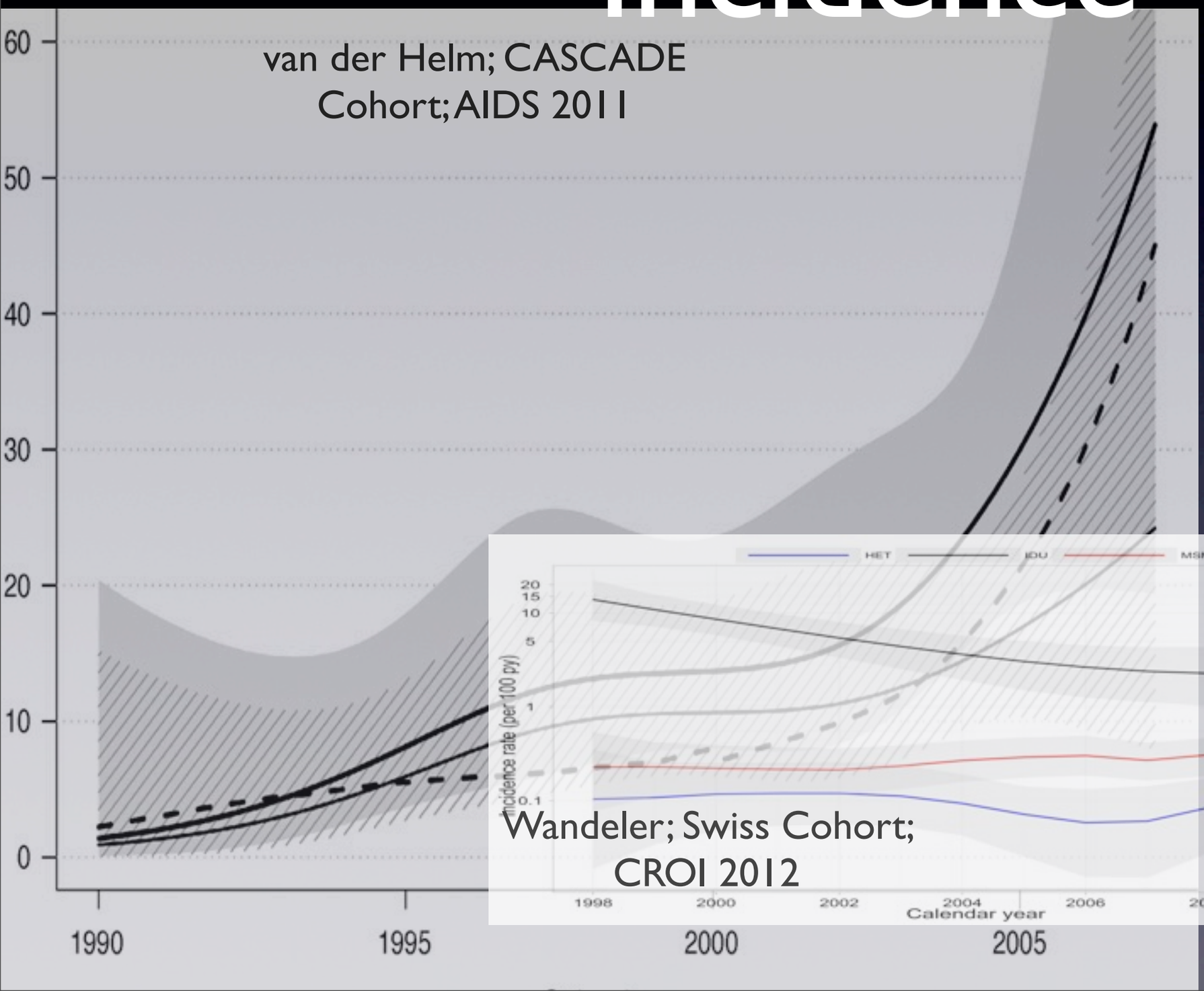
Primary HCV in HIV+ MSM: Further Epidemic Reports

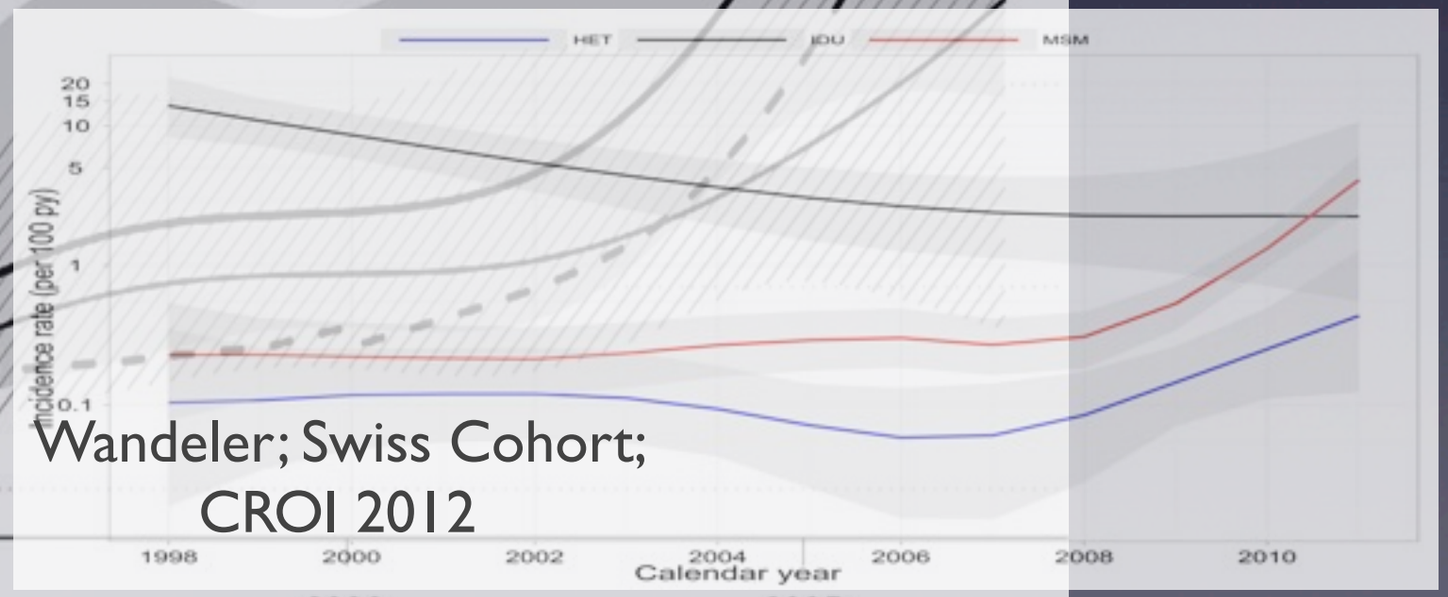
Bottieau 2010

Barfod 2011

Montoya 2011

Primary HCV in HIV+ MSM: Incidence





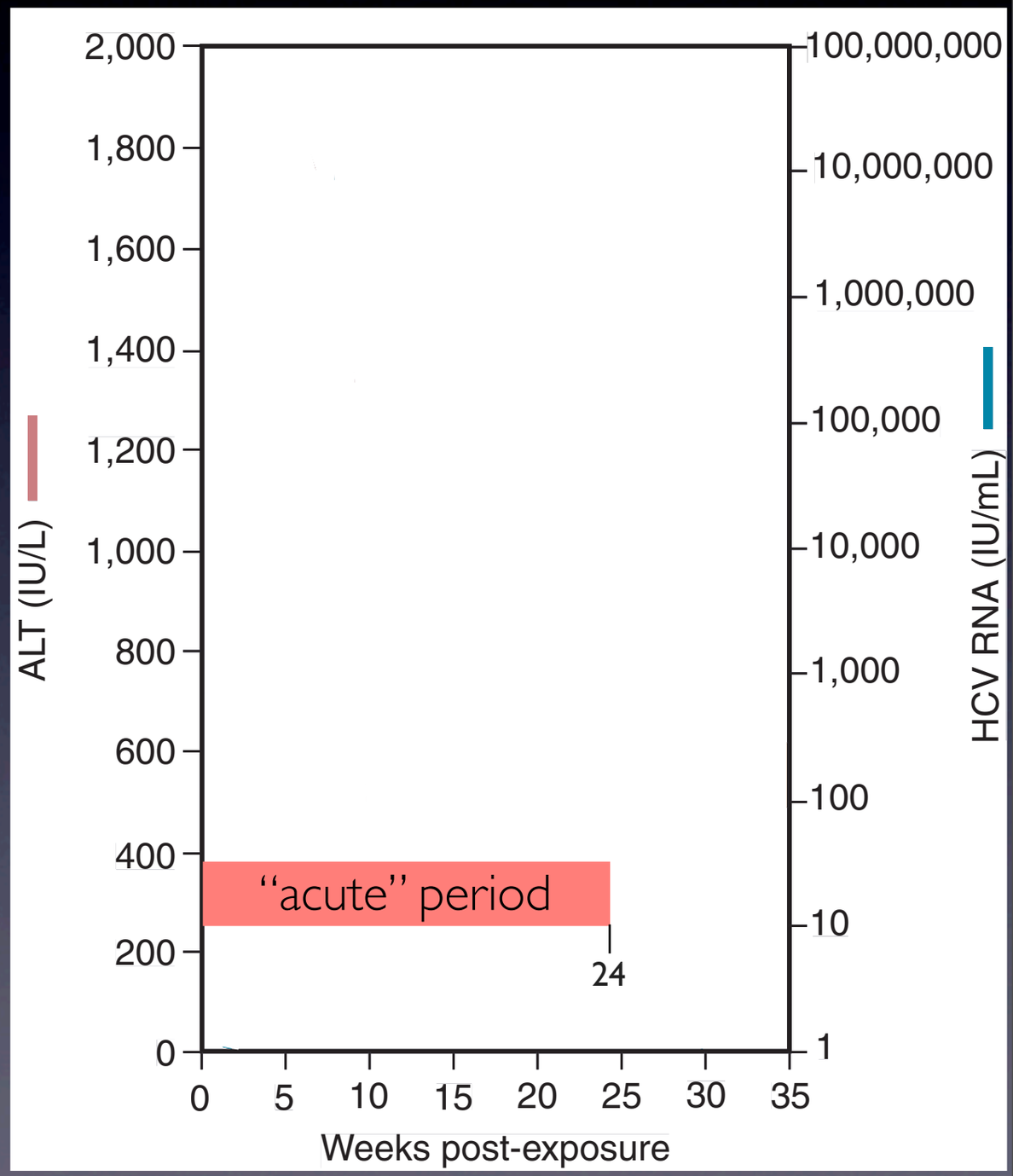
Demographics of International Epidemic

	N	Age (years)	MSM	CD4 count	ART (%)	IDU (%)	Main Geno
UK	107	36	all	550	67	17	1a
Holland	57	40	all	na	na	3	1a
France	10	40	all	625	75	0	4d
Germany	24	38	all	447	na	4	1a
Australia	24	41	all	596	63	50	1a
New York	78	40	all	477	74	13	1a

van de Laar Gastroenterology 2009
Fierer MMWR 2011

Early Course of HCV Infection

- viremia detectable within 7 to 10 days
- ALT elevation 2 to 8 wk
- Ab seroconversion ~6 wk (3rd gen) to ~9 wk (2nd gen)
- HCV VL fluctuates widely (> 1 log)
  - presumably due to "battle" with immune response

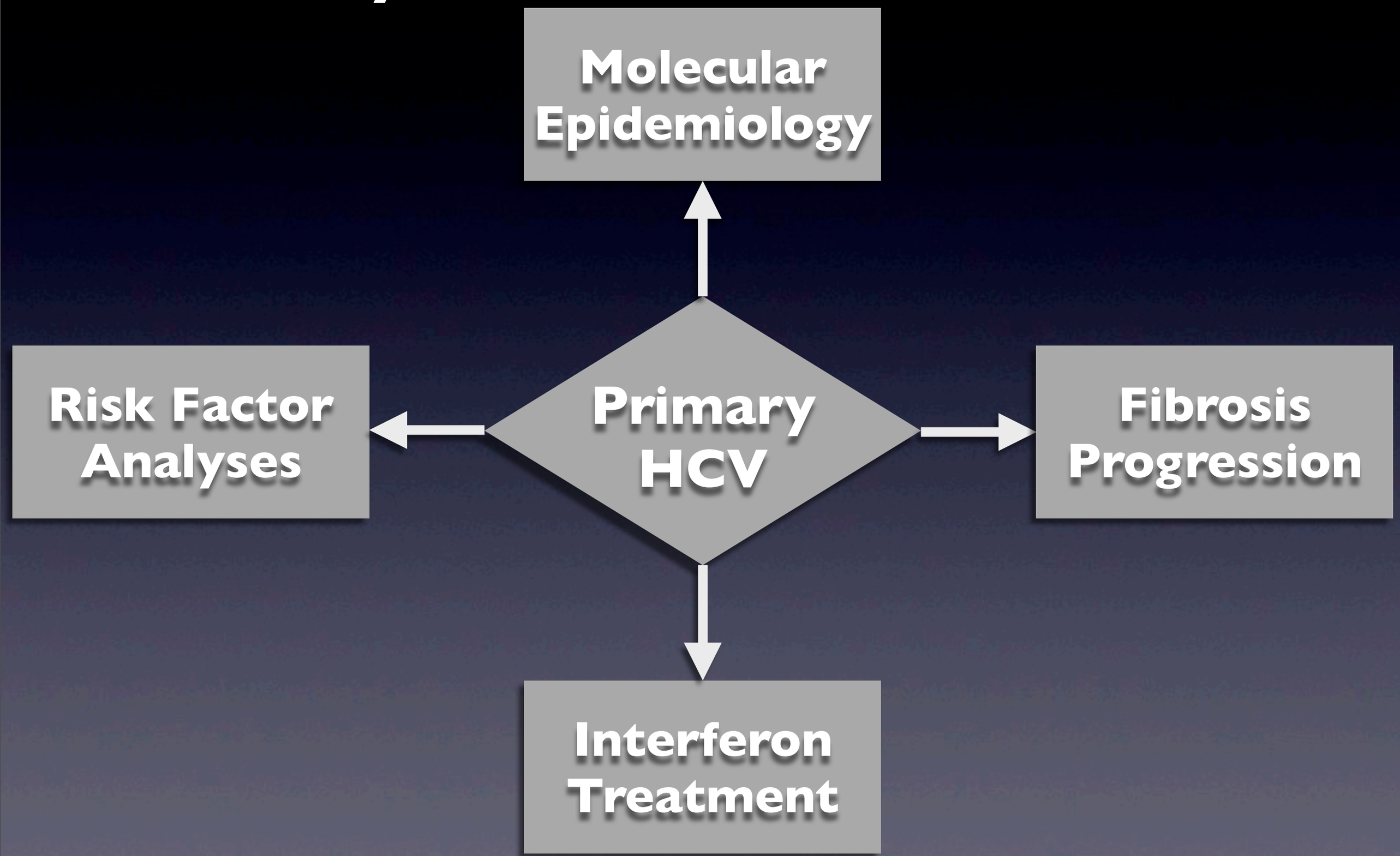


Sulkowski M, JAMA 2002

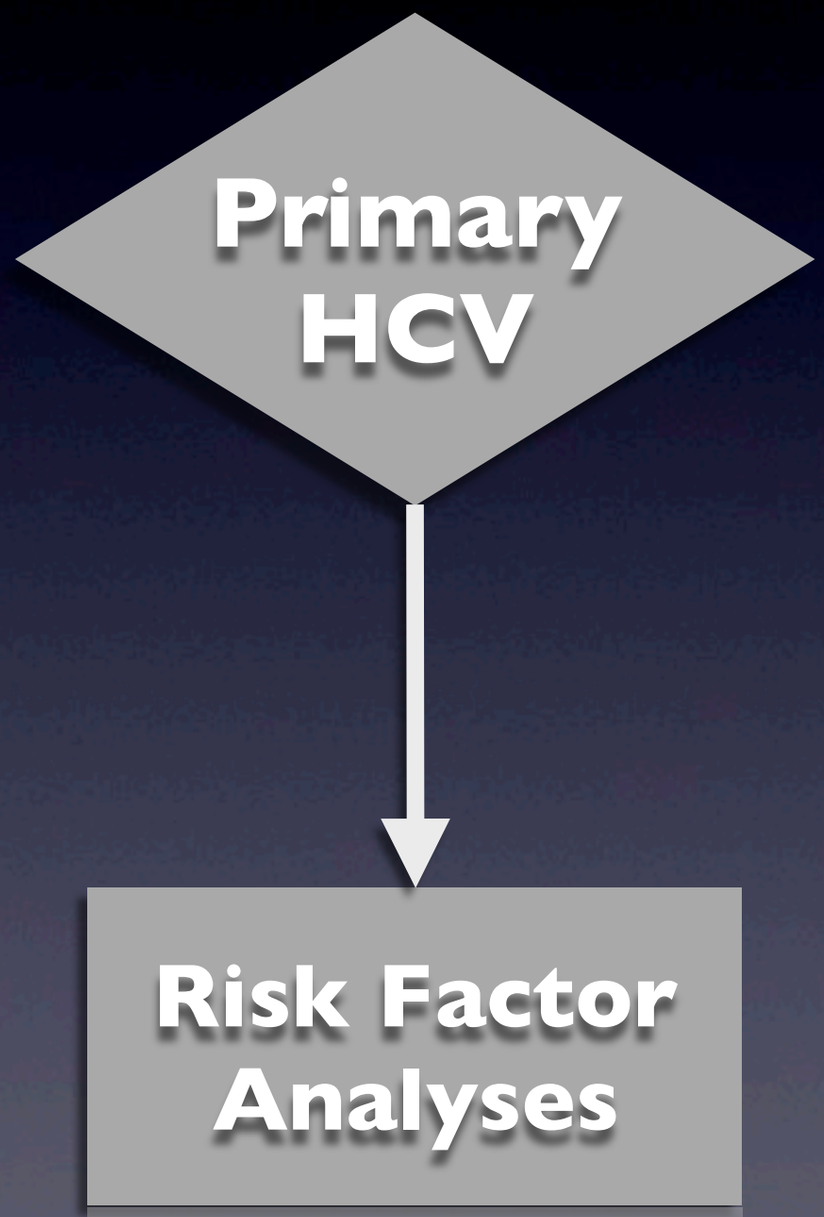
“Acute” HCV Infection

- “acute” defined as first 6 months of infection
  - 6 mo. period is not based on biological characteristics of new HCV infection
- “acute” does not denote severity, simply chronicity
  - in fact, ~80% of patients *asymptomatic* during “acute” HCV

Primary HCV in HIV+ MSM



Primary HCV in HIV+ MSM



New HCV in HIV+ MSM: Case Definition

- HIV-infected MSM examined at Mount Sinai during October 2005–December 2010 who had:

  1. a newly elevated alanine transferase (ALT) level
  2. a newly positive HCV-antibody test result, and
  3. no other evident cause of the newly elevated ALT level

- If no record of a previous negative HCV-antibody test:
  - jaundice or ALT elevation of more than 15-fold above the upper limit of normal (i.e., >450 U/L)

New HCV in HIV+ MSM: Baseline Demographics

Characteristic [N=74]	Result
Age, median (yrs)	39 (range 23-63)
Race/ethnicity	
White	41 (55%)
Black	14 (19%)
Hispanic	18 (24%)
Asian	1 (1%)
CD4 count, median (cells/μL)	483 (range 66-1,258)
Duration of HIV infection, median (yr)	8 (range 0-23)
Receipt of antiretroviral drug therapy	55 (74%)
HIV viral load < 400 copies/mL	50 (68%)
No prior HCV-positive serology	9 (12%)
Seroconversion interval median (mo) [N=65]	12 (range 0-110)
Presence of jaundice on presentation	14 (19%)
Peak ALT, median (U/L)	665 (range 72-5,291)
Peak HCV viral load (log_{10} IU/mL)	6.68 (range <0.7-8.0)
HCV genotype [N=72]	
1a	65 (90%)
1b	4 (6%)
2b	2 (3%)
3a	1 (1%)

Risk Factors for New HCV: New York

- 22 cases were matched by age, race, and ethnicity with 1 to 10 HIV-infected MSM *without* HCV infection (N = 53)
- excluded all cases and controls reporting any prior injection of *any* drug
  - duration HIV infection, CD4 count, HIV VL not significantly different ($p > 0.05$)

Risk Factors for New HCV: New York

- Administered explicit questionnaire on sex, drugs, other behaviors over prior 12 months
- McNemar's test (matching analysis), univariable and multivariable analyses performed
  - Stephanie Factor

Risk Factors for New HCV: New York–Sex

Univariable analysis:

Significant Risks	p value
Receptive AI, no condom, +ejac	0.0022
Insertive AI, no condom, -ejac	0.0073
Insertive AI, no condom, +ejac	0.050
Performed rimming	0.010
Insertive fisting	0.0037
Receptive fisting	0.0047
Use of sex toys	0.014
Number of partners	0.038
Group sex	0.0045
Sex in public place	0.053
Had syphilis	0.0057
Had gonorrhea	0.013

Not Significant Risks	p value
Receptive AI, no condom, -ejac	1.00
Receptive AI with condoms	0.38
Insertive AI with condoms	0.58
Oral sex (all permutations)	0.06-1.00
Been rimmed	0.12

Risk Factors for New HCV: New York–Drugs

Univariable analysis:

Significant Risks	p value
Sex while high	0.0016
Marijuana	0.020
Cocaine	0.013
Ketamine	0.022
GHB	0.0025
Ecstasy	0.018

Not Significant Risks	p value
Sex drunk	0.19
Methamphetamine	1.00
Heroin	1.00
Poppers	1.00

Risk Factors for New HCV: New York

- Multivariable conditional logistic regression (forward, backward, and stepwise)
- Interaction terms built for all exposures with $p \leq 0.05$
- Final model included only exposures associated with new HCV infection at $p \leq 0.05$

Risk Factors for New HCV: New York

Multivariable analysis:

1. Receptive, unprotected anal intercourse without condoms, *with ejaculation (of partner)*:
   Odds Ratio 23.00 (2.17, 243.84) p = .009

2. Sex while high *on crystal methamphetamine*:
   Odds Ratio 28.56 (1.84, 443.03) p = .02

Risk Factors for Sexually-acquired HCV: London

Multivariable analysis (60 cases, 130 controls, Fisher's exact test):

1. Group sex with receptive or insertive UAI, or receptive or insertive fisting:

   Any 2: Odds Ratio 9.16 (3.51, 23.90)

   ≥ 3: Odds Ratio 23.50 (9.47, 58.33)

Danta, AIDS 2007

Risk Factors for Sexually-acquired HCV: Germany

Multivariable analysis (34 cases, 67 controls, Fisher's exact test):

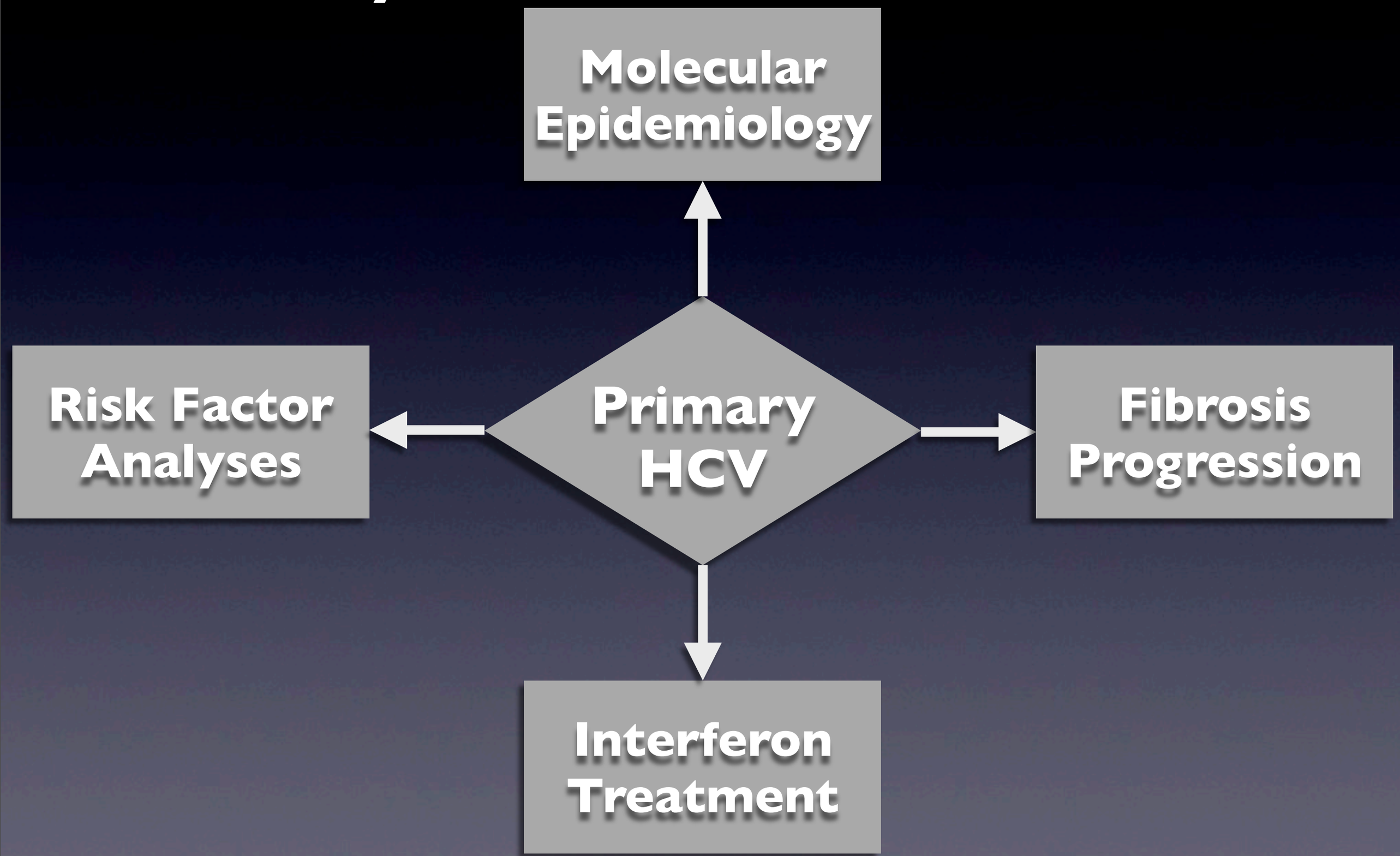
1. Rectal trauma with bleeding, frequently or always: OR 6.19 (1.17, 32.81) $p = 0.032$
2. Frequent receptive fisting without gloves: OR 5.71 (1.50–21.68) $p = 0.011$
3. Nasal drug use: OR 3.25 (1.06– 9.96) $p = 0.040$

Schmidt, PLoS One 2011

Risk Factors for Sexually-acquired HCV

London	Germany	New York
Group sex with ≥2 of:	Rectal trauma with bleeding, frequently or always	Receptive unprotected anal intercourse with ejaculation
receptive or insertive unprotected anal intercourse	Nasal drug use	Sex while high on crystal methamphetamine
or receptive or insertive fisting	Frequent receptive fisting without gloves	

Primary HCV in HIV+ MSM



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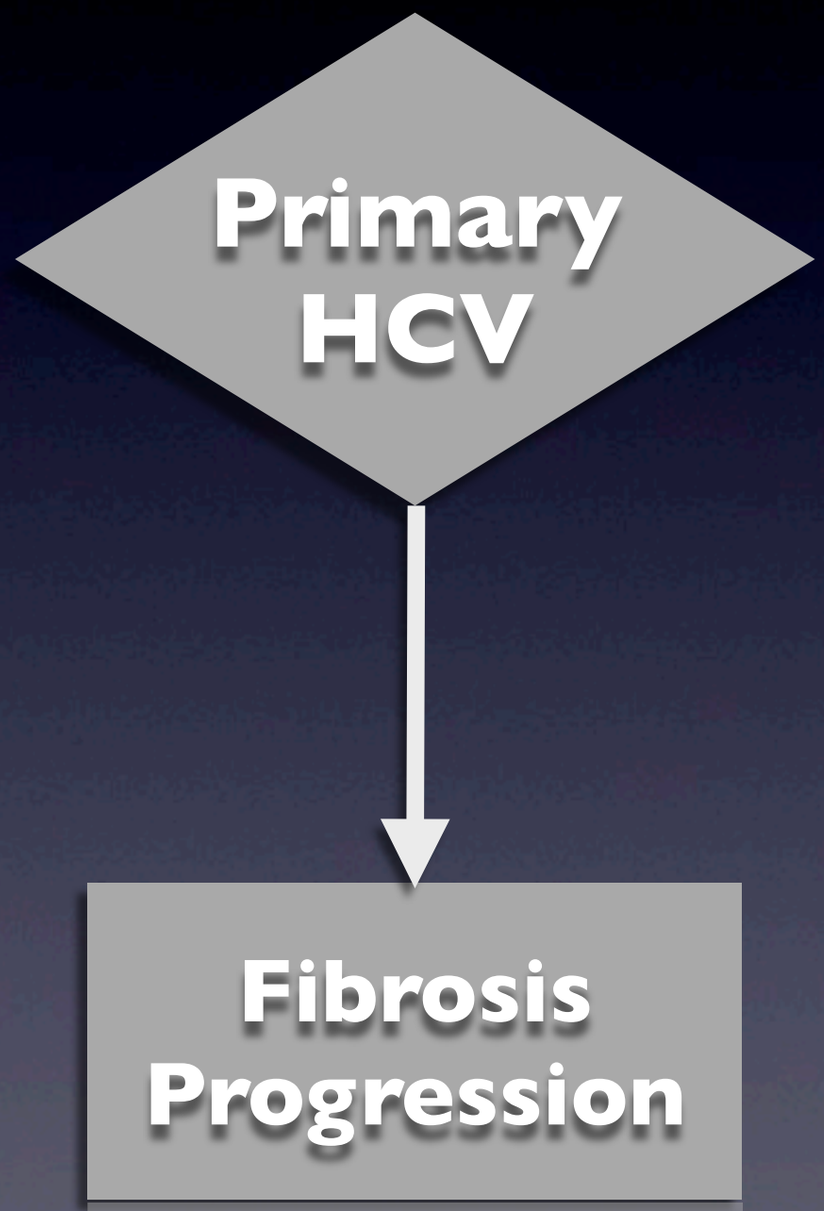


Fibrosis During Primary HCV Infection in HIV+ Men

BRIEF REPORT

JID 2008:198 (1 September)

Liver Fibrosis during an Outbreak of Acute Hepatitis C Virus Infection in HIV-Infected Men: A Prospective Cohort Study

Daniel S. Fierer,[1] Alison J. Uriel,[2] Damaris C. Carriero,[2] Arielle Klepper,[2] Douglas T. Dieterich,[2] Michael P. Mullen,[1] Swan N. Thung,[3] M. Isabel Fiel,[3] and Andrea D. Branch[2]

Divisions of [1]Infectious Diseases and [2]Liver Diseases, Department of Medicine, and [3]Department of Pathology, Mount Sinai School of Medicine, New York, New York

plantation and begin receiving immunosuppressive drugs, the FPR increases to ~0.14 U per year [1]. Injection drug users (IDUs), who typically acquire HCV infection before HIV infection [2], provide another example. Classic studies [3] indicate that the FPR of patients with chronic HCV monoinfection is ~0.11 U per year and that the FPR of patients with chronic HIV/HCV-coinfection is <2-fold greater, ~0.15 U per year. The majority of HIV/HCV-coinfected IDUs are not expected to develop cirrhosis (stage 4 fibrosis) for 20 years or more.

In contrast, patients who acquire HCV infection when they already have defects in cellular immunity are reported to progress to cirrhosis, end-stage liver disease, and death in as few

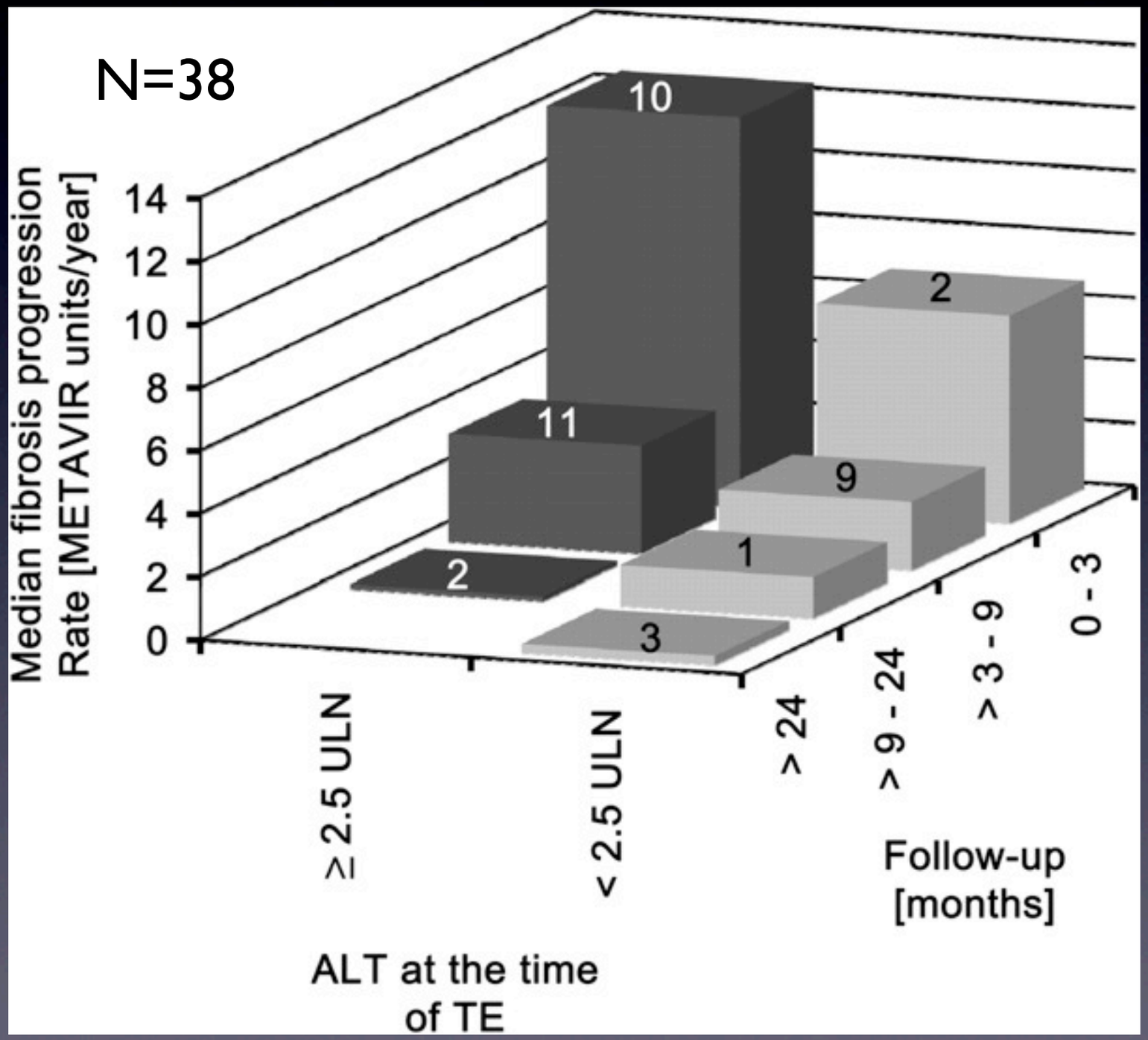
Liver biopsy showed moderately advanced fibrosis (Scheuer stage 2) in 9 (82%) of 11 patients. No other cause of liver damage other than acute HCV infection was identified.

Fibrosis During Primary HCV Infection in HIV+ Men

- Antwerp, Belgium 2001 through April 2010
- 37 patients had liver biopsy, median 7 months (range: 3–36 months) after diagnosis of HCV infection:
- 22/37 (59%) had stage 2 or 3 fibrosis

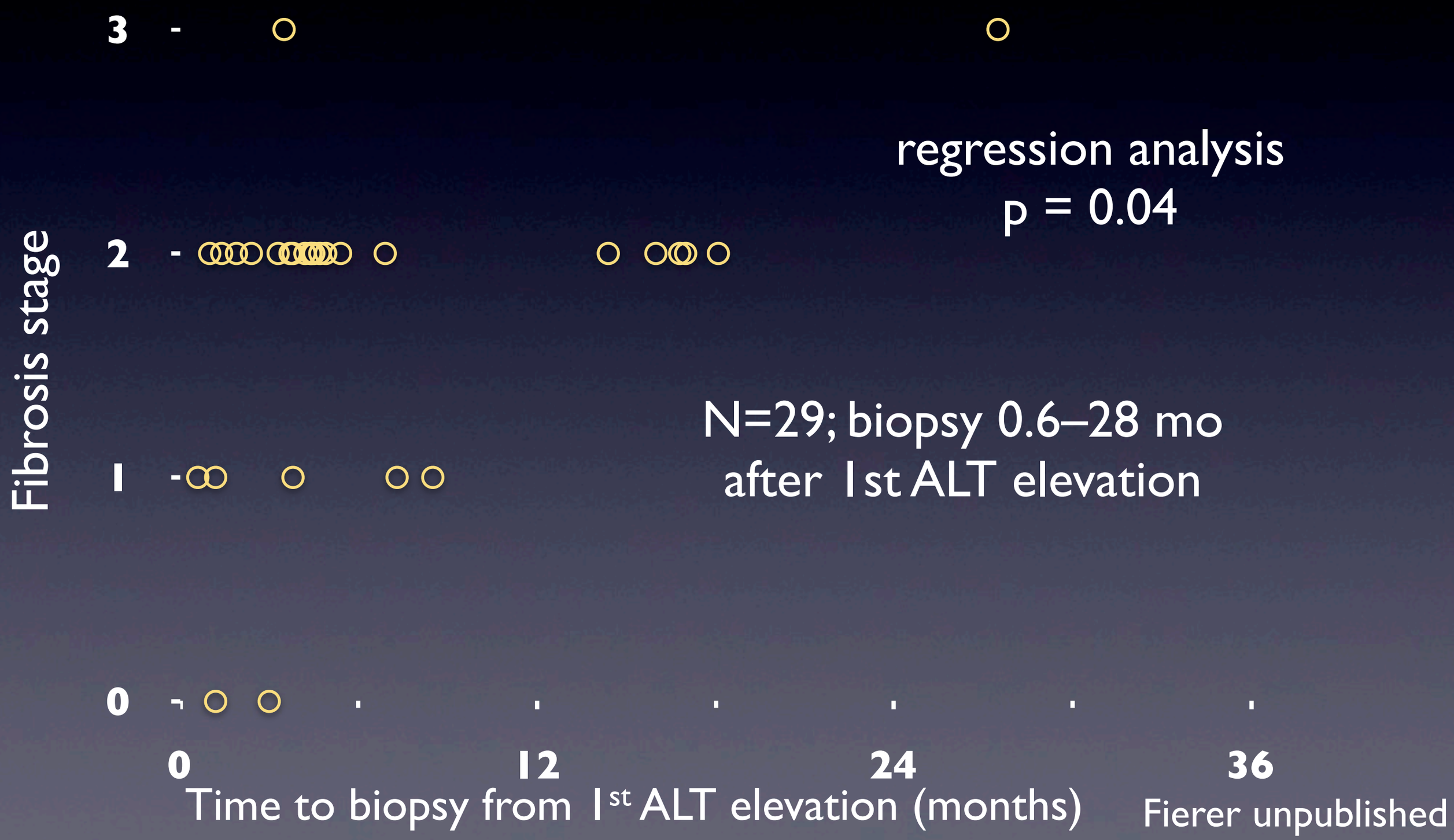
Bottieau Eurosurv 2010

Fibrosis During Primary HCV Infection in HIV+ Men

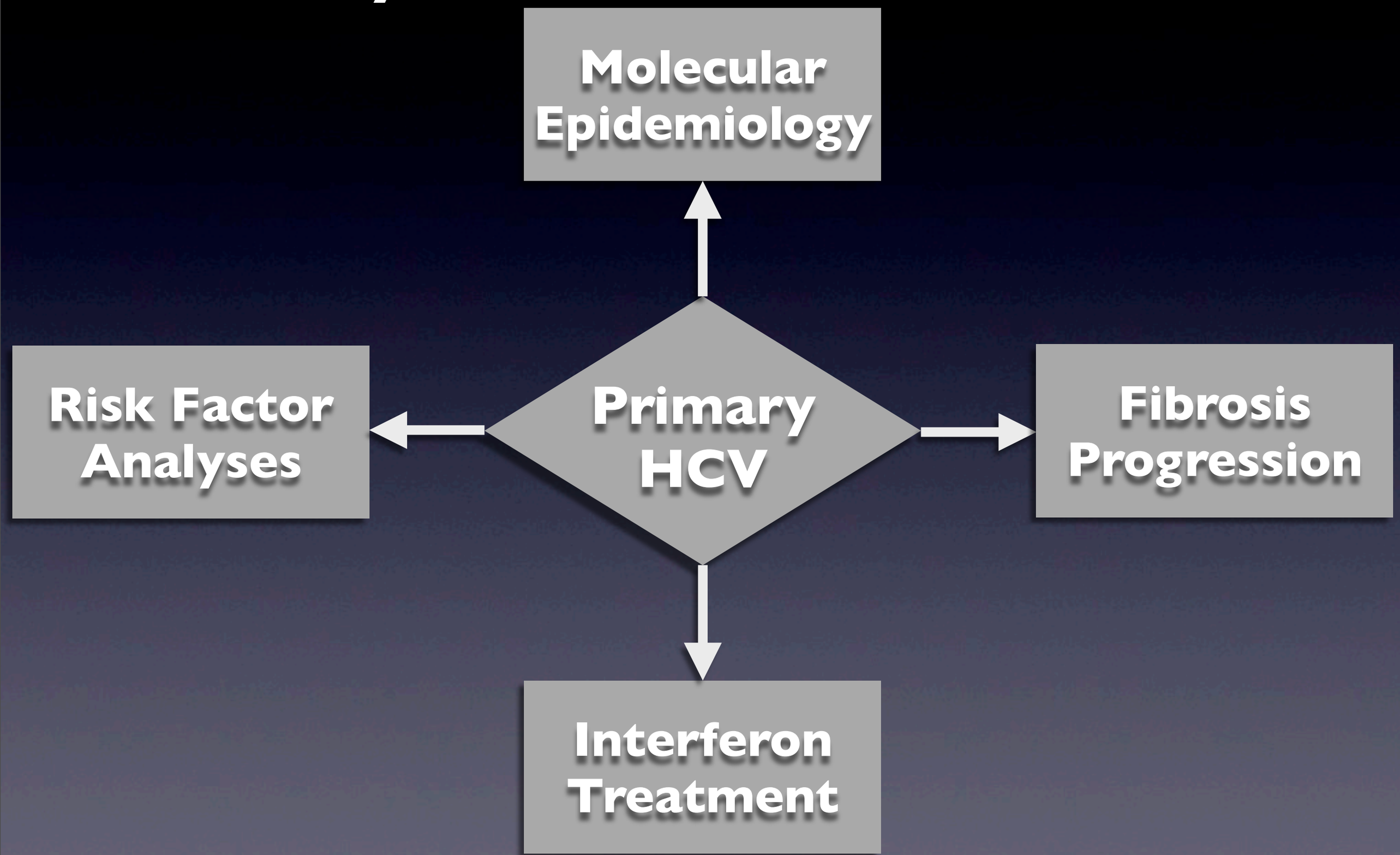


Vogel Clin Infect Dis 2012

Fibrosis During Primary HCV Infection in HIV+ Men



Primary HCV in HIV+ MSM



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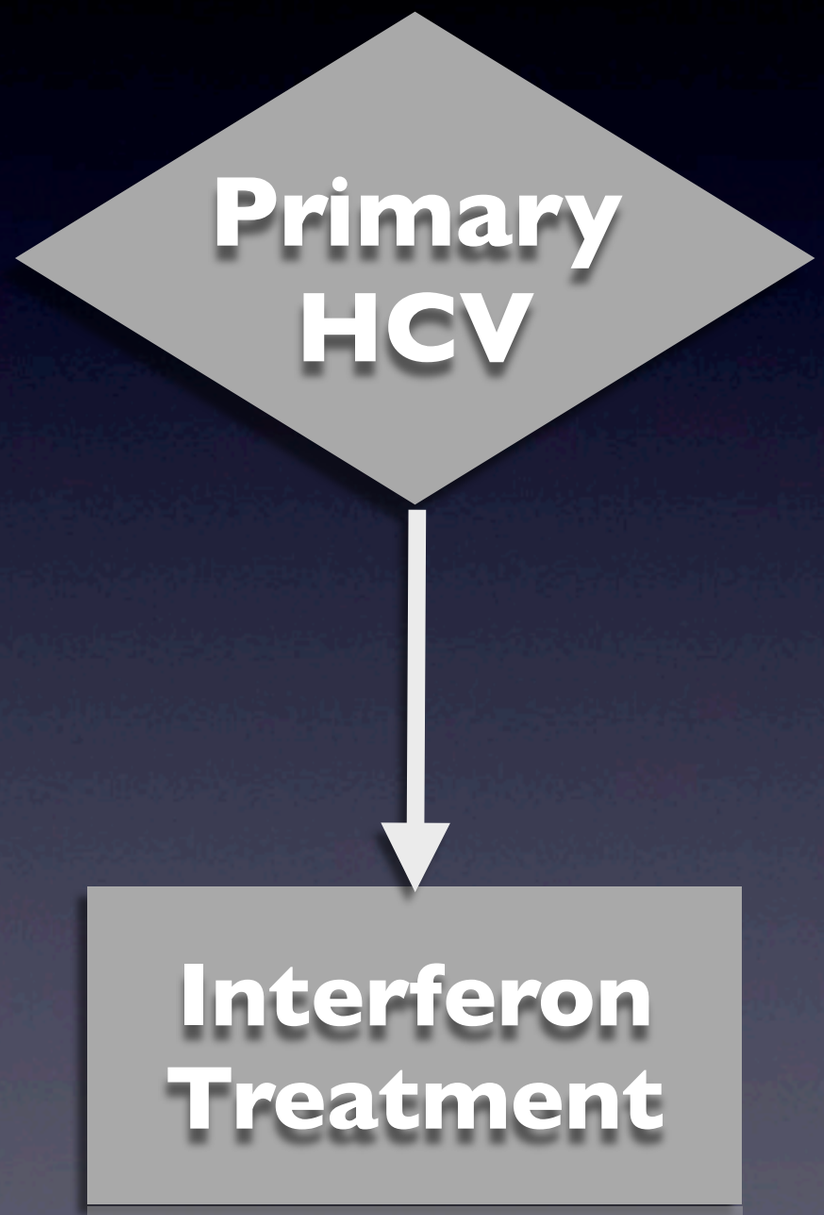
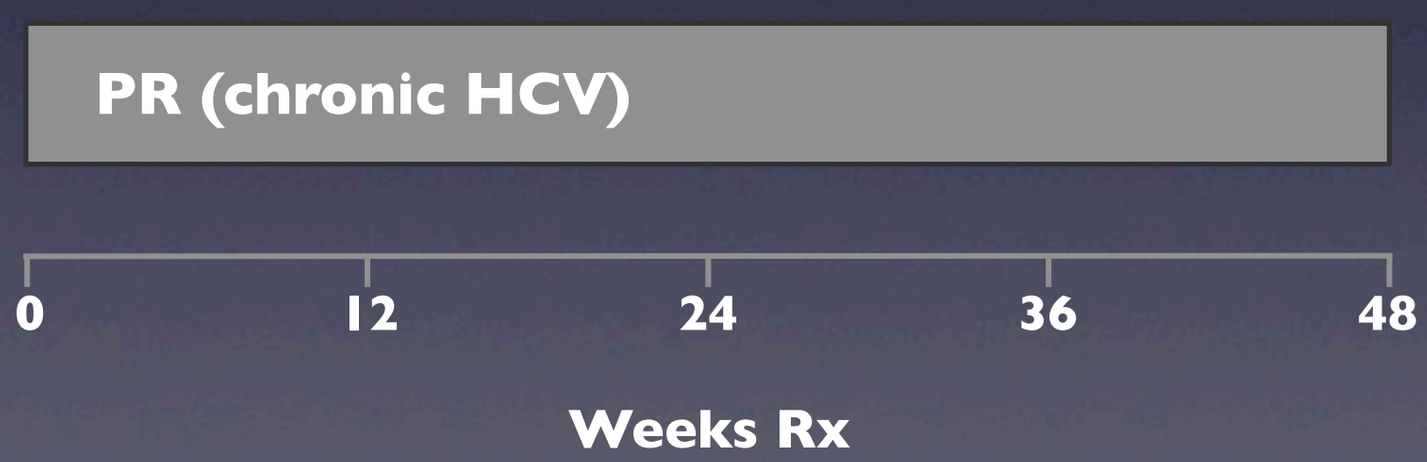
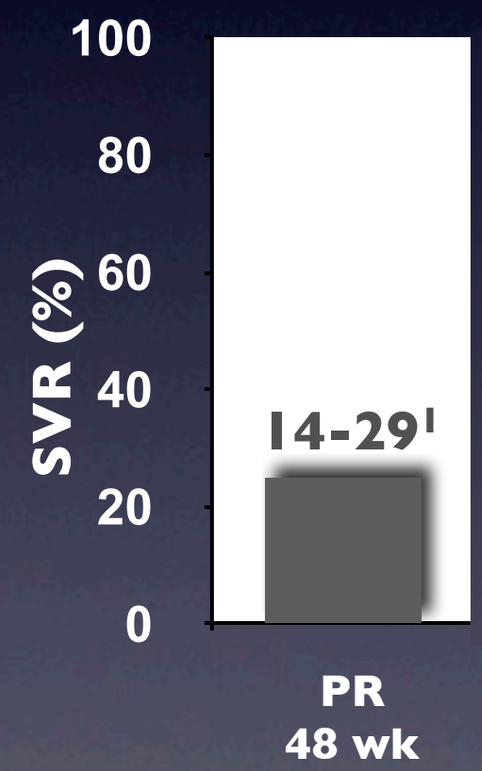


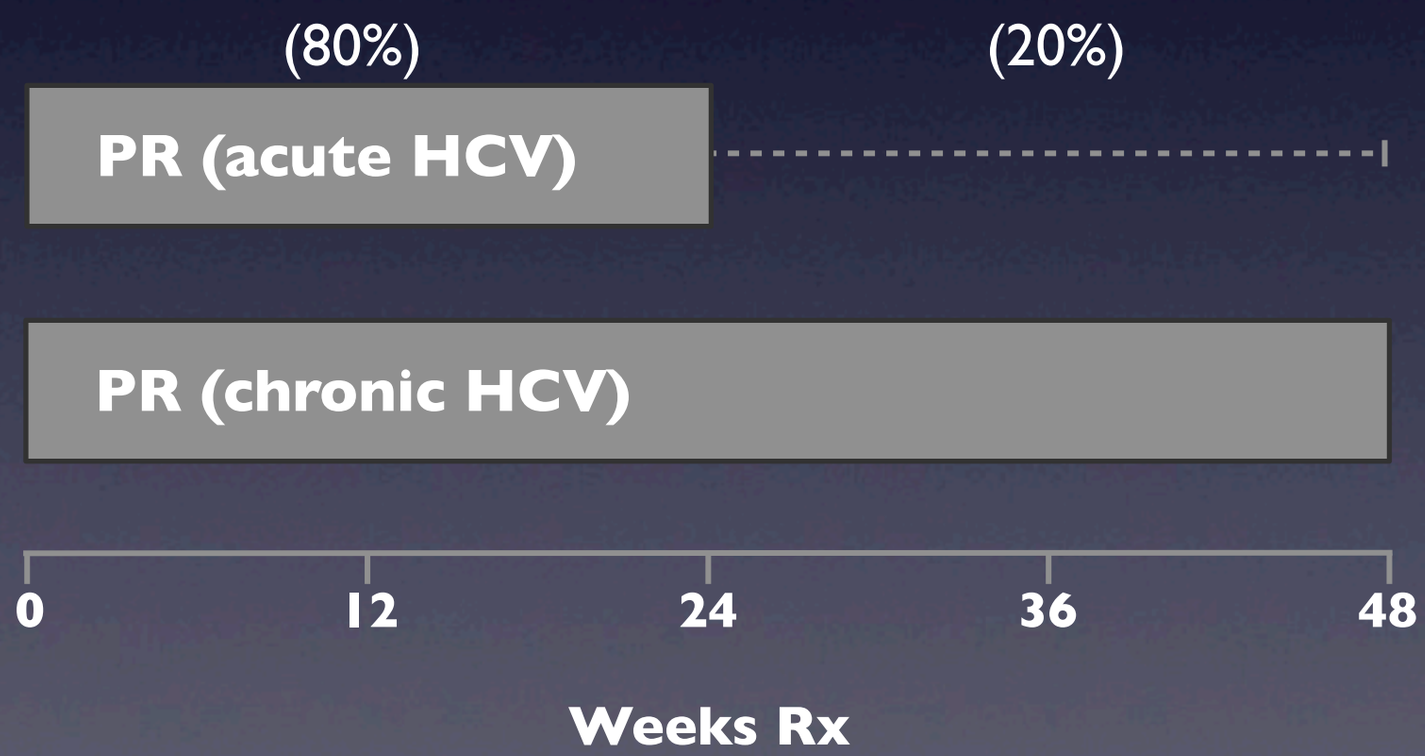
Treatment of Acute Geno 1 HCV in HIV

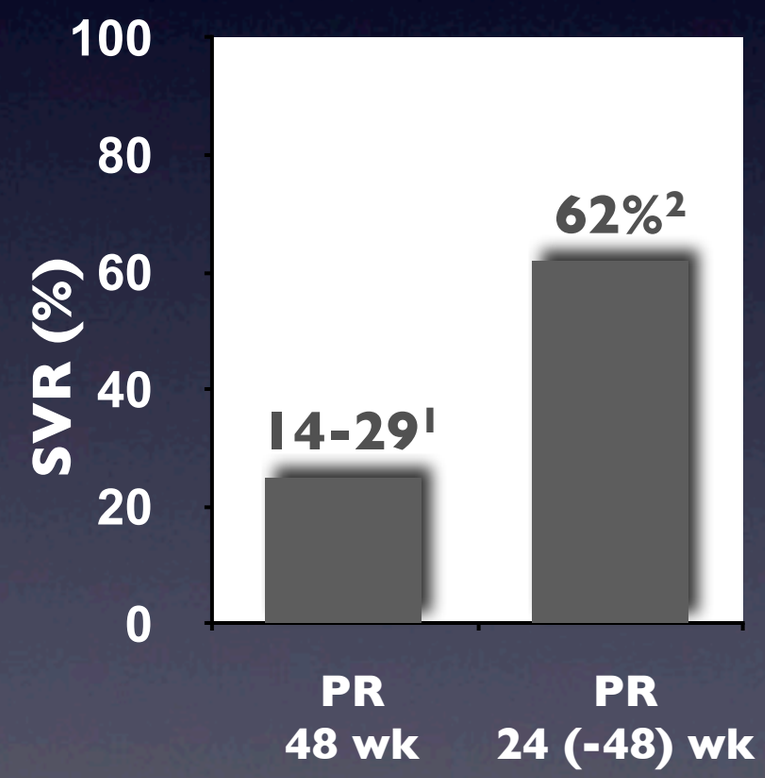




[1]ACTG, APRICOT

Treatment of Acute Geno 1 HCV in HIV

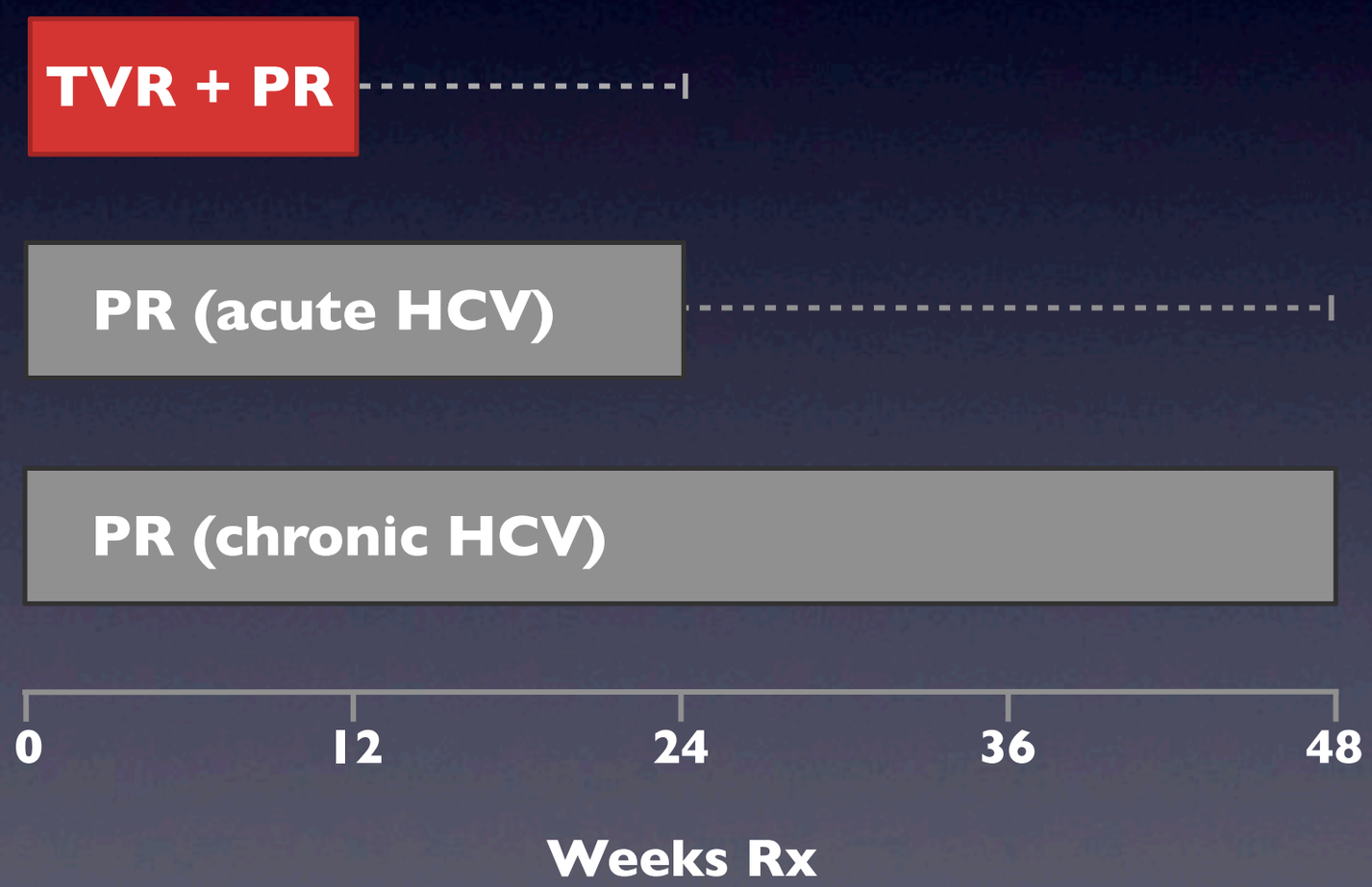


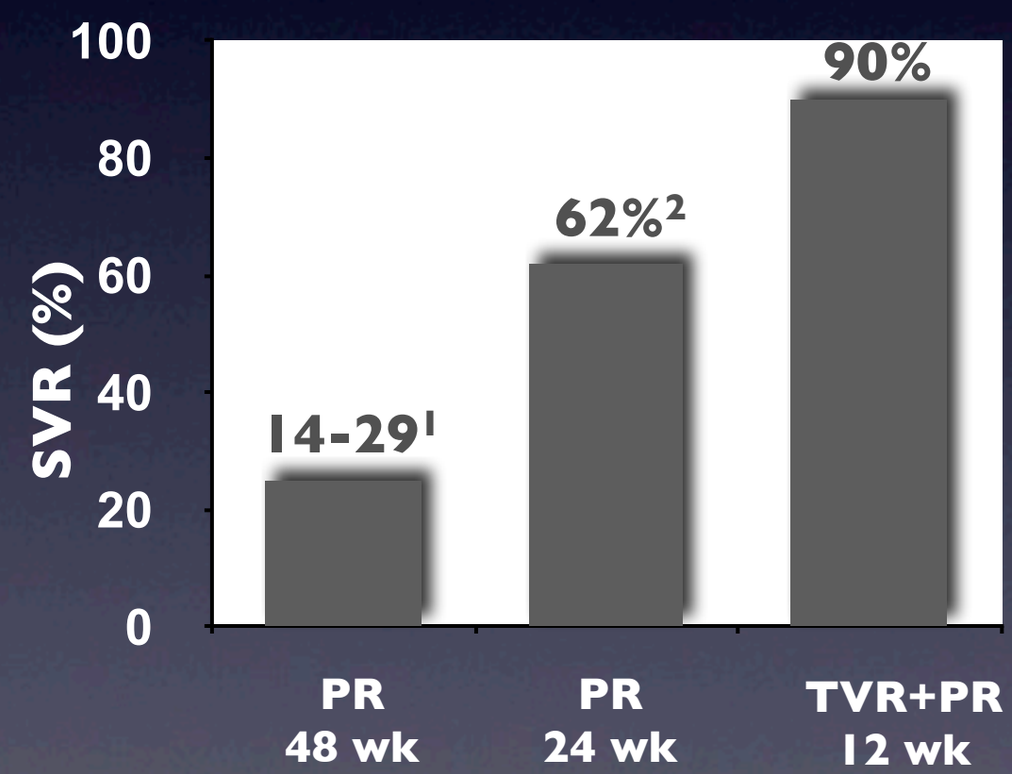


"Twice as good in half as long"

[1]ACTG, APRICOT; [2]Fierer unpublished

Treatment of Acute Geno 1 HCV in HIV





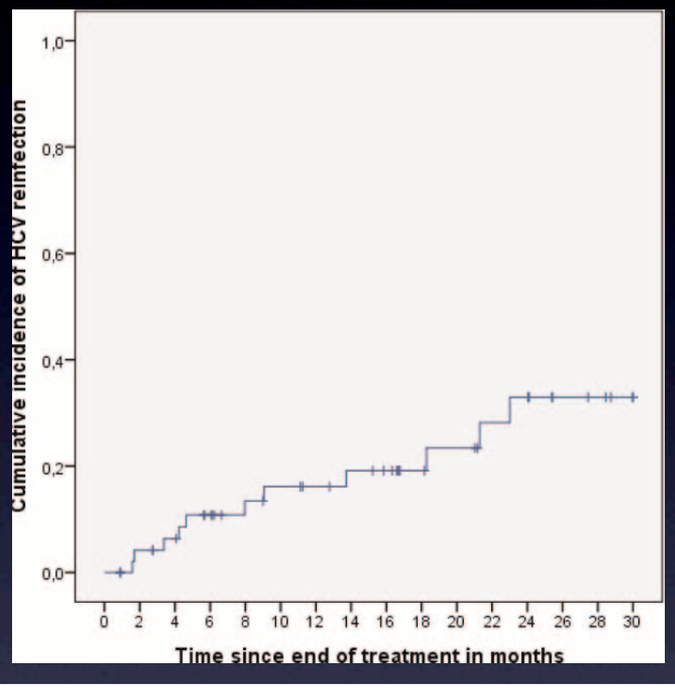
"Twice again as good in half again as long"

[1]ACTG, APRICOT; [2]Fierer, unpublished

Treated, cured, but… Re-infected

Lambers; Amsterdam; AIDS 2011:

- Reinfection: 11/51 (22%), median of 8.4 months after SVR
- Incidence: 15.2/100 PR
  - compared to ~13/100 PY for initial infections

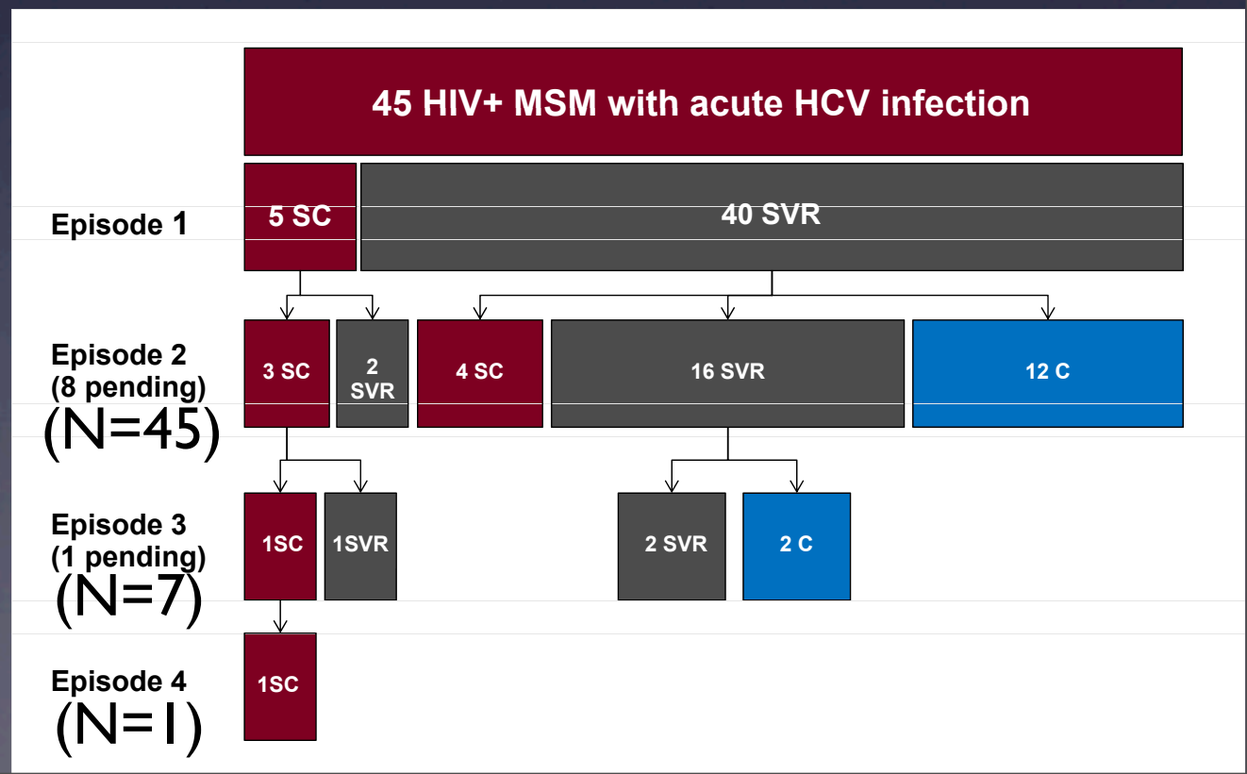


Jones; London; JAIDS 2010:

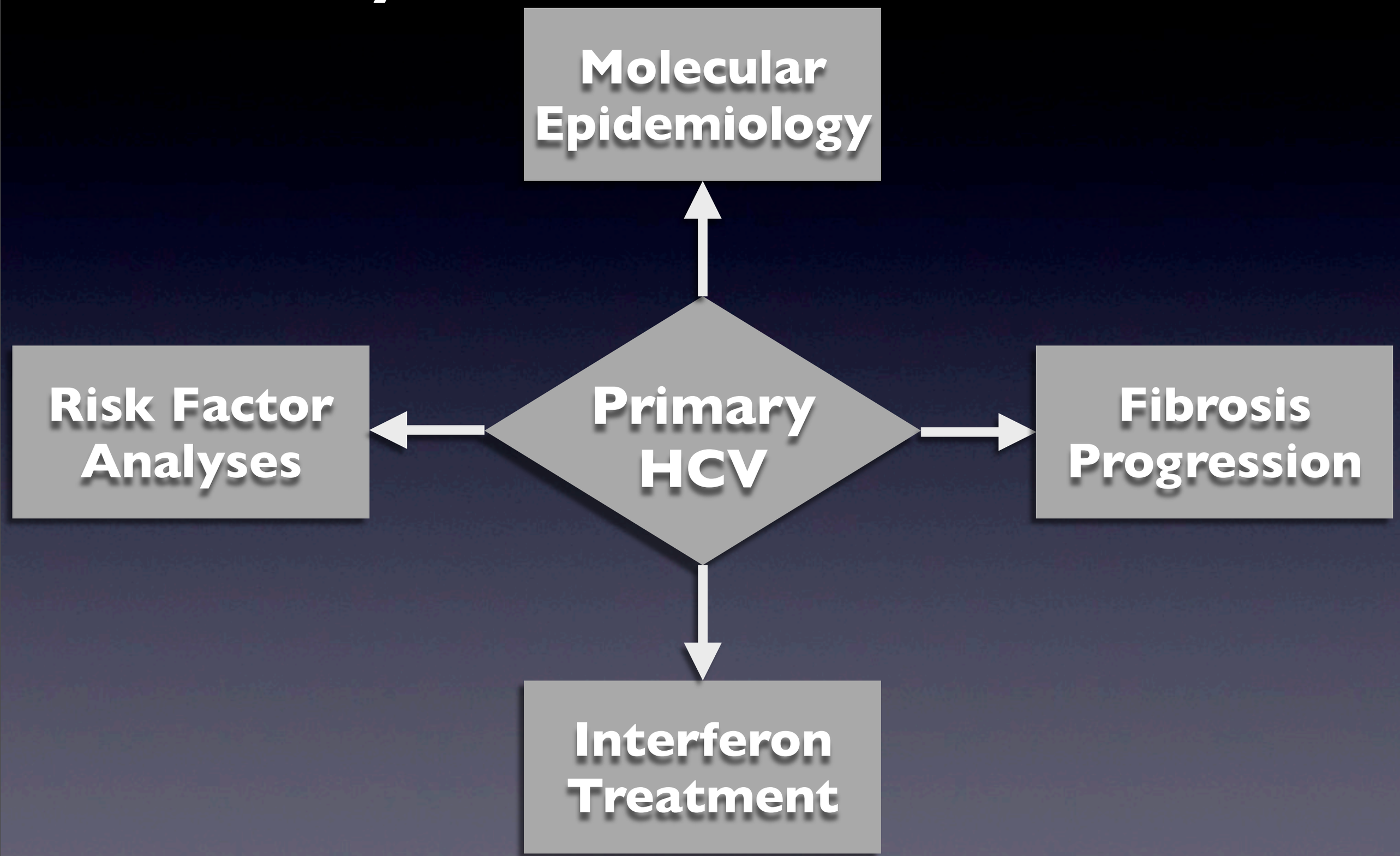
- Reinfection: N=22 [denominator unclear (?~110)]

Ingiliz #752 (Germany) CROI 2012

- Reinfection: N=53 [denominator unknown]



Primary HCV in HIV+ MSM



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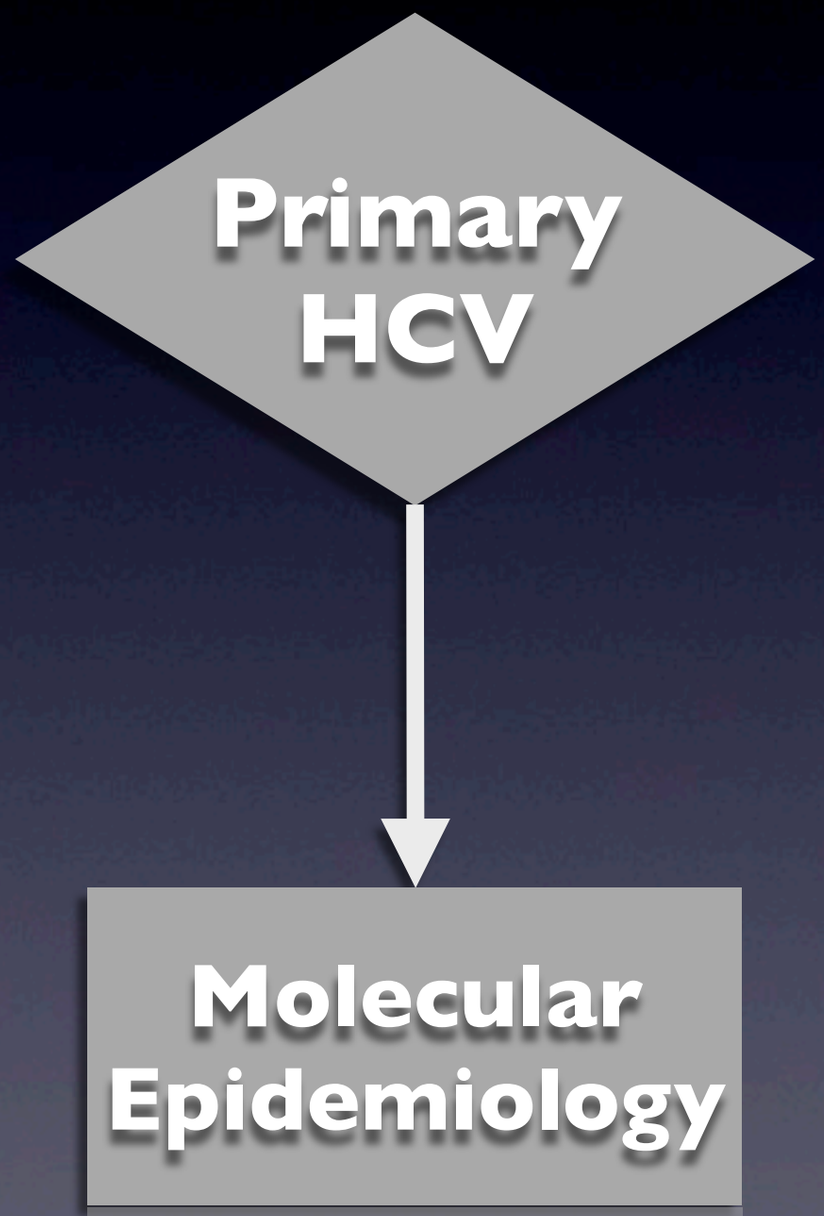


Molecular Epidemiology of Primary HCV: U.S.

- 102 genotype 1 isolates (Mt Sinai=69; Cornell=8; UCSF=12; Philly=2, MGH Boston=9; LA=1, and UCSD=1)

Kristen Marks, Andy Talal, Cornell; Brad Hare, UCSF; Kyong-Mi Chang, U Penn; Arthur Kim, MGH

Molecular Epidemiology of Primary HCV: U.S.

- 102 genotype 1 isolates (Mt Sinai=69; Cornell=8; UCSF=12; Philly=2, MGH Boston=9; LA=1, and UCSD=1)

- Yury Khudyakov, CDC Viral Hepatitis Branch
  - sequenced 436 bp region of HCV NS5B
    - MGH samples sequencing by Todd Allen, Allyson Bloom

- Thijs van de Laar, Amsterdam Health Services
  - Maximum likelihood phylogenetic trees constructed with bootstrapping (n=1000)
    - Bootstrap values > 70 represent robust monophyletic clusters

Kristen Marks, Andy Talal, Cornell; Brad Hare, UCSF; Kyong-Mi Chang, U Penn; Arthur Kim, MGH

Molecular Epidemiology of Primary HCV: U.S.

East coast

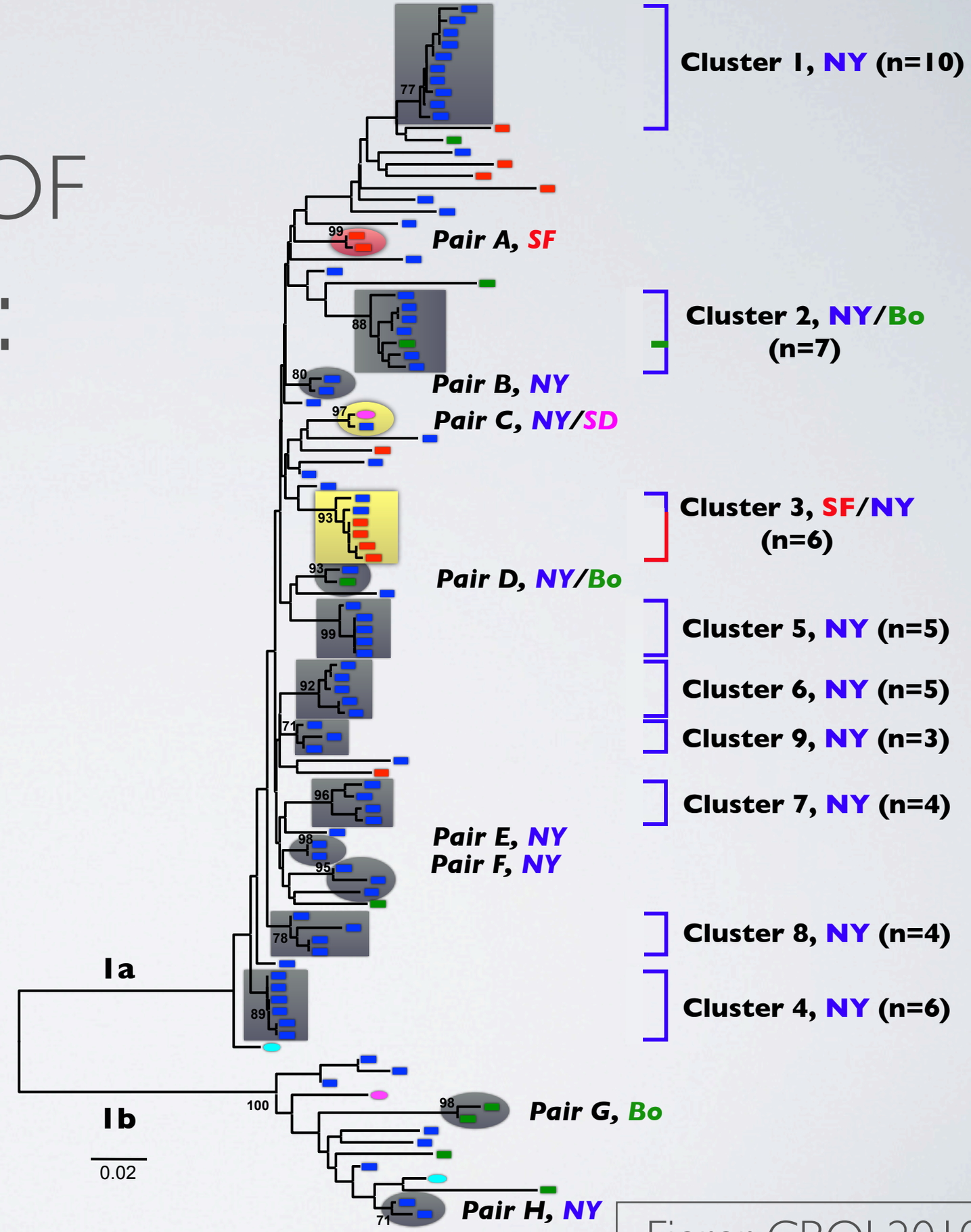
- New York (NY) N=77
- Philadelphia N=2
- Boston (Bo) N=9

West coast

- San Francisco (SF) N=12
- San Diego (SD), Los Angeles N=2

Clusters (n>2) and Pairs (n=2)

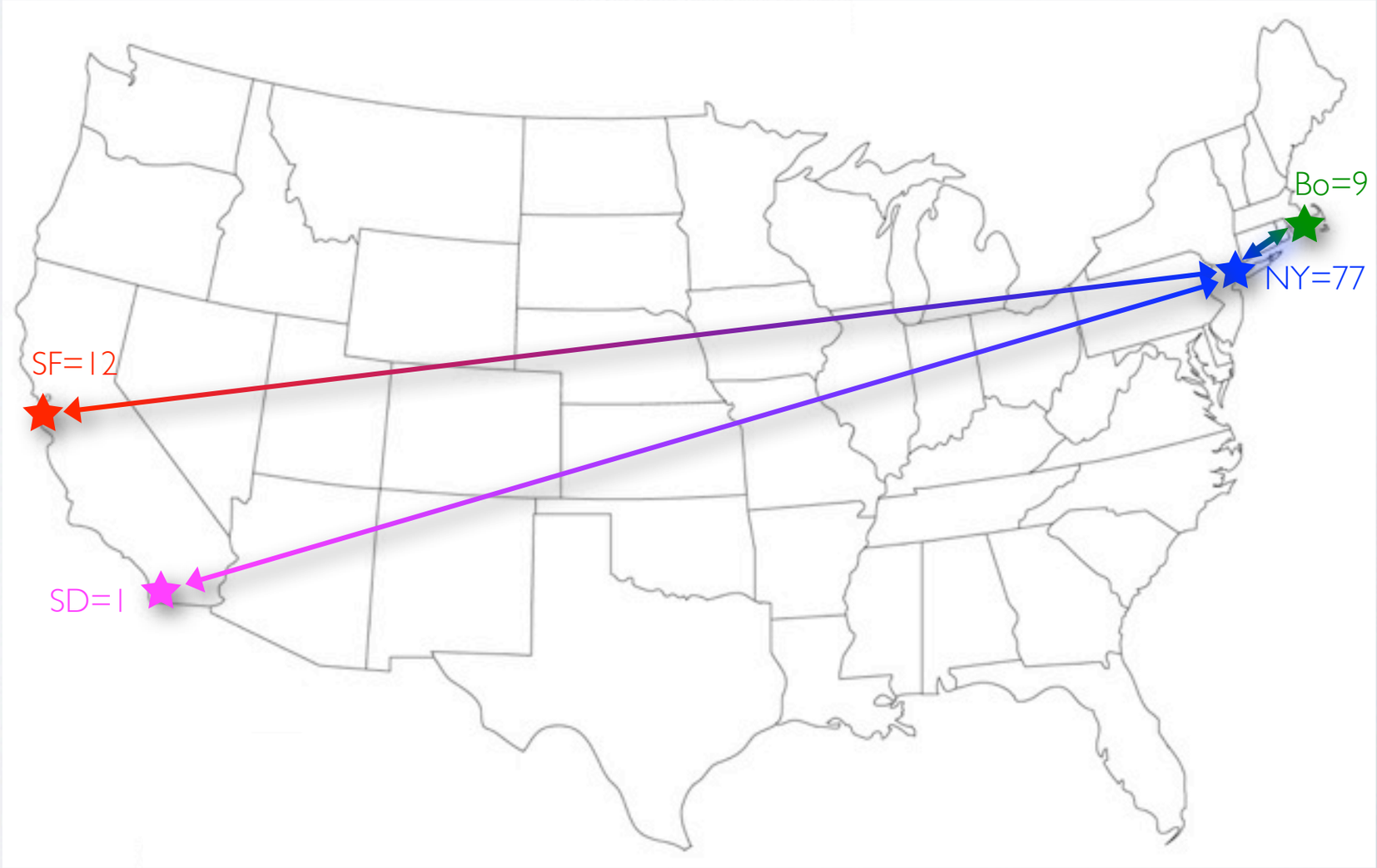
- **East coast**
- **West coast**
- **Mixed coasts**



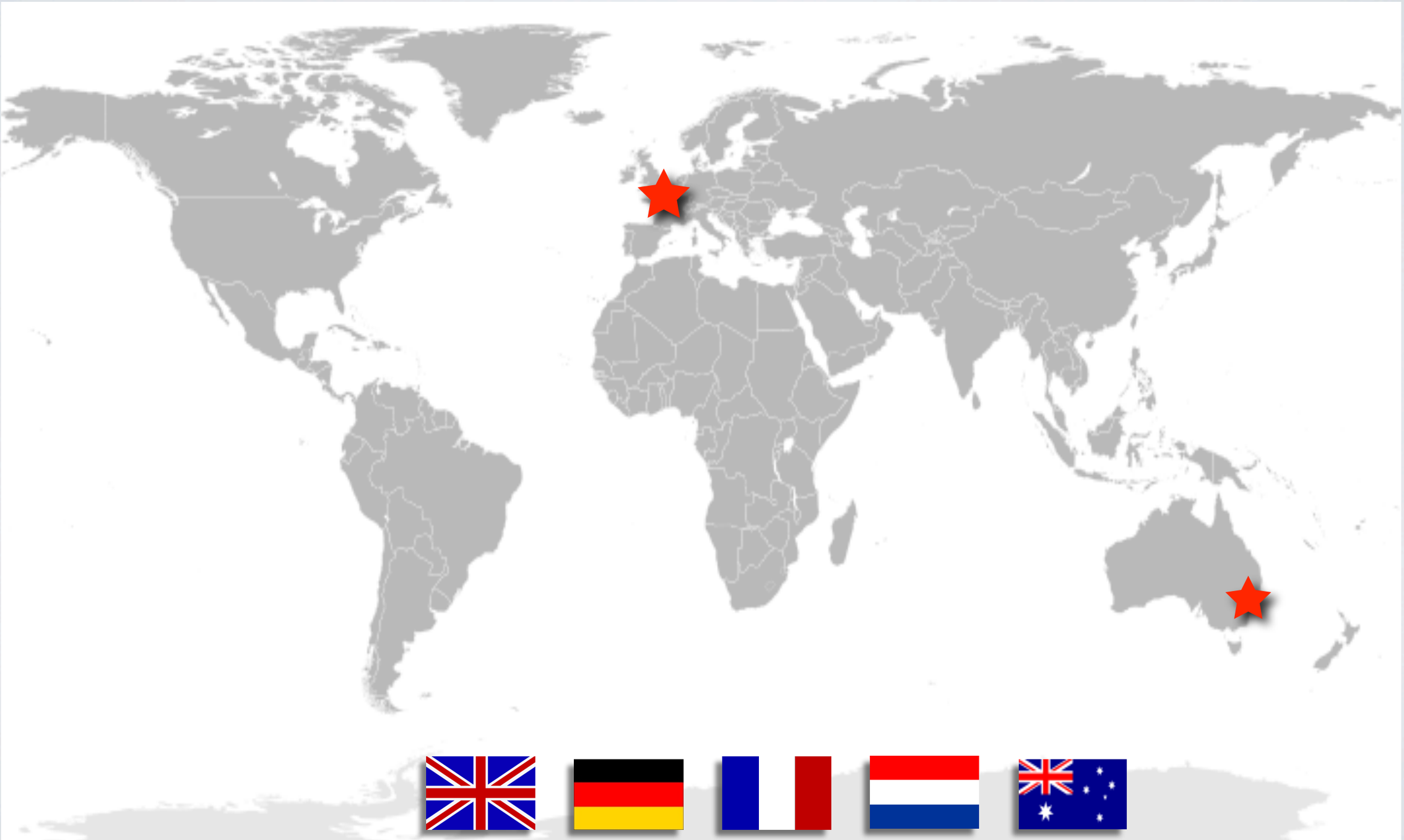
Fierer CROI 2010

Molecular Epidemiology of Primary HCV: U.S.

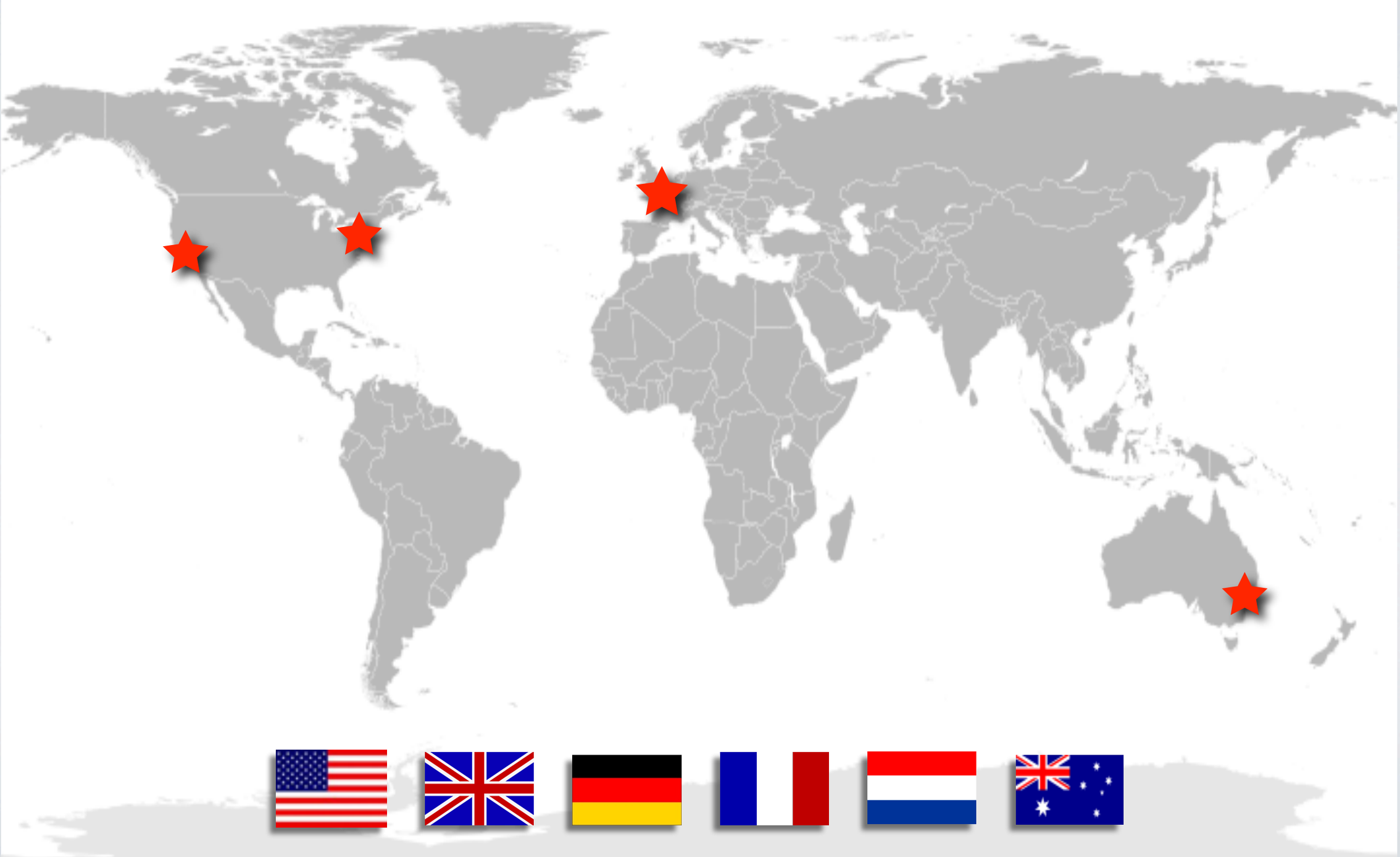
- 67% of MSM harbored an HCV sequence very similar to one found in at least one other MSM, with clustering in cities, but:
- Limited clustering between East and West coasts: 1 pair (1NY↔1Bo)
  - 6-patient cluster (4 SF↔2 NY)
  - 1 pair (1SD↔1 NY)



Molecular Epidemiology of Primary HCV



Molecular Epidemiology of Primary HCV: Adding the U.S.



Molecular Epidemiology of Primary HCV: International

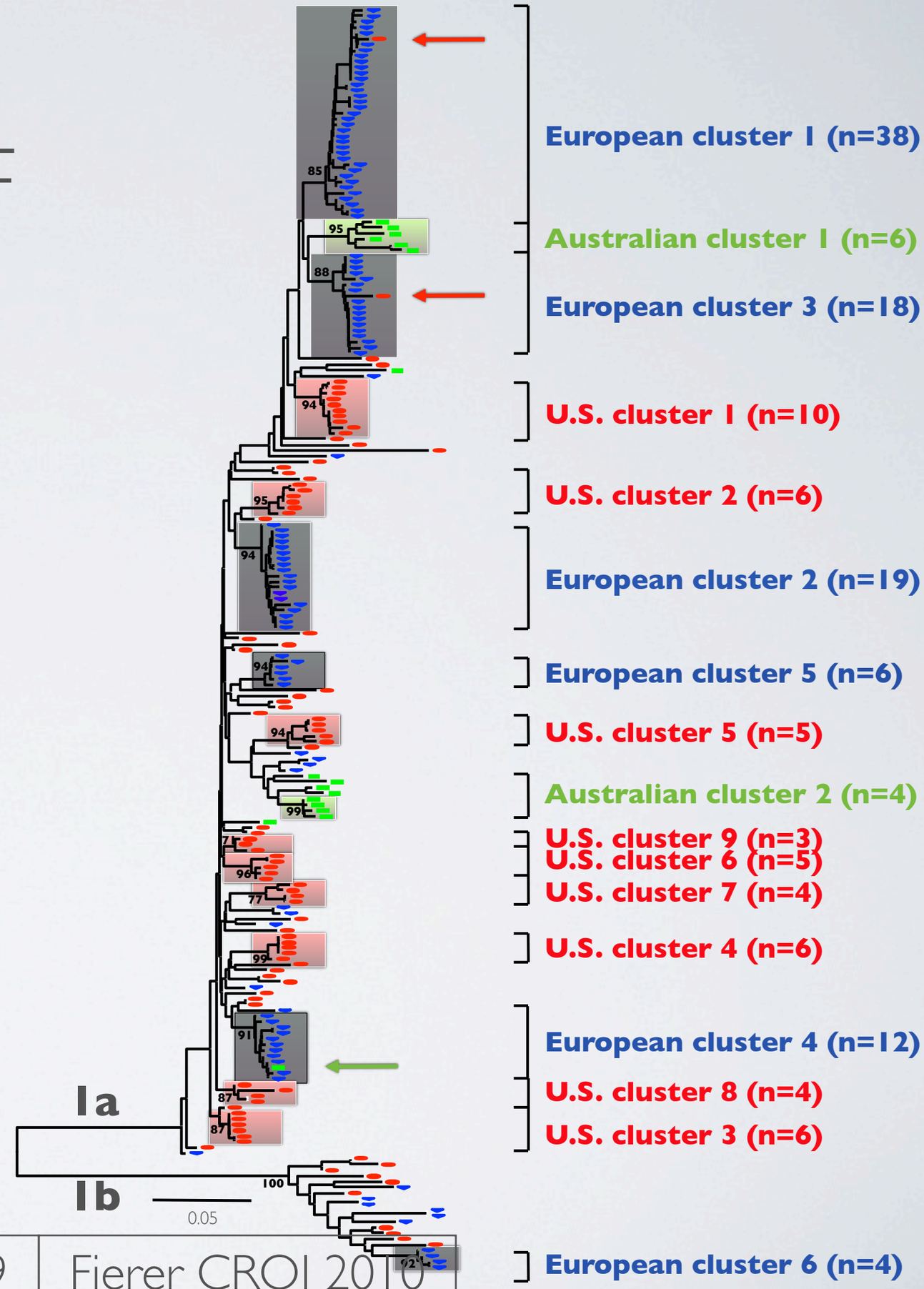
- Europe (Eng, Neth, Ger, Fr) N=112
- Australia (Syd, Melb, Brisb) N=16
- U.S. (NY, Phil, Bo, SF, LA, SD) N=102

Clusters (n>2)

- **European**
- **Australian**
- **U.S.**

European + Australian cluster

European + U.S. cluster

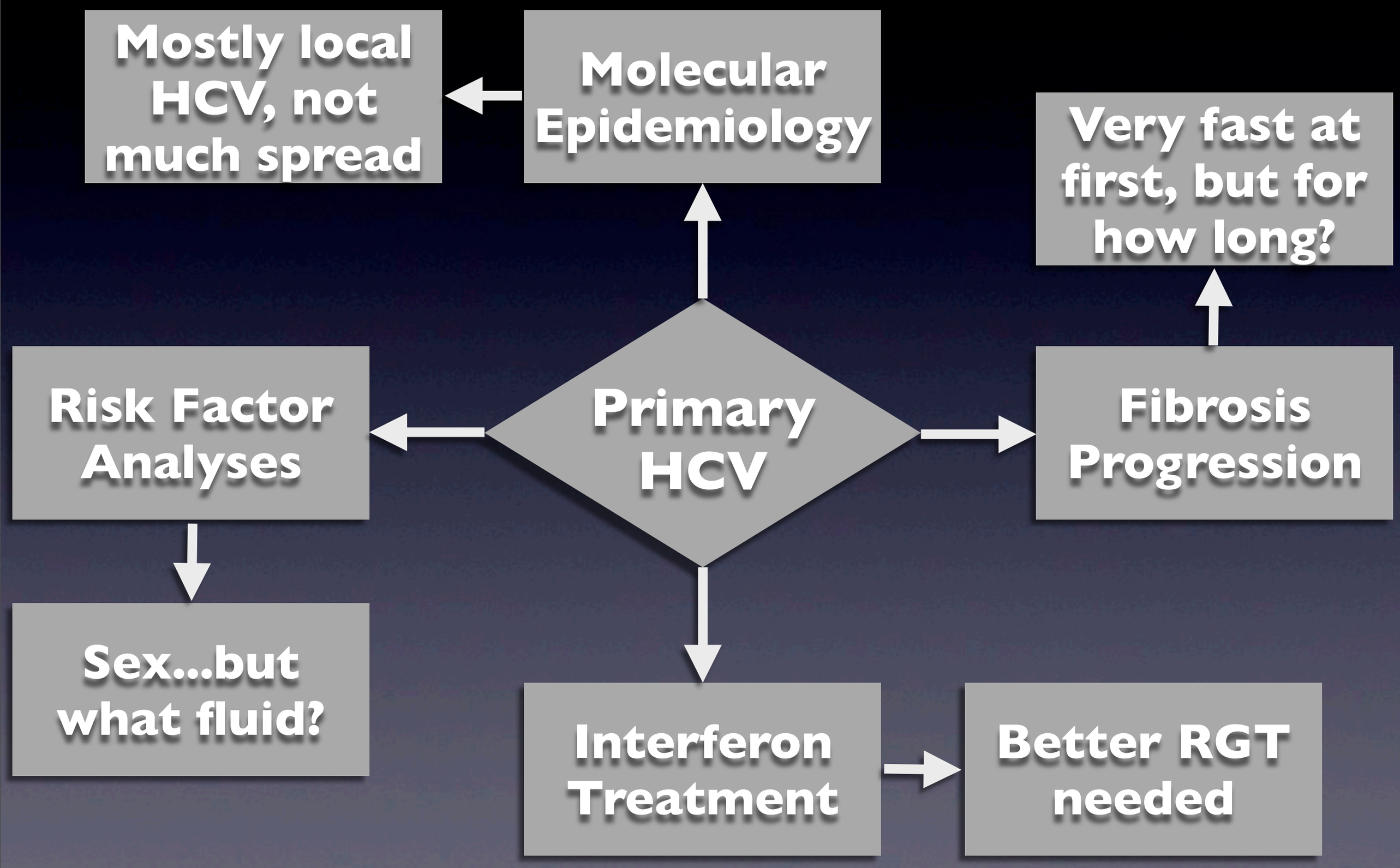


Thijs van de Laar...Mark Danta Gastro 2009 | Fierer CROI 2010

Molecular Epidemiology Primary HCV

- Epidemic of new HCV in HIV+ MSM in U.S. is demographically similar to Europe and Australia
- Molecular epidemiology shows little overlap between U.S., European, and Australian cities, suggesting largely independent evolution of epidemics, not a network of transmission
- Similar transmission practices are occurring across continents and hemispheres: larger prevention interventions are needed

Conclusions



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- Douglas Dieterich
- Michael Mullen
- Arielle Klepper
- Wouter van Seggelen
- Kathryn Childs
- Andrea Branch
- 35 NYC referring providers

CDC team (Viral Hepatitis Branch):

- Deborah Holtzman
- John Ward
- Yury Kudhyakov
- Scott Holmberg

International team:

- Thijs van de Laar (Amsterdam)
- Mark Danta (London, Australia)