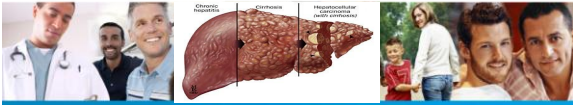


The Evolving Spectrum of Acute Hepatitis C



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Hepatitis C Symposium



HCV: Then and Now

- Currently: 3.2 Million Americans are HCV-Infected
- Greatest incidence was in the 1970s and 80s
- Decreased incidence because of harm reduction for IDU, and blood screening
- Incidence in the past year probably 17,000
 - But, only 849 cases reported to CDC because it is usually asymptomatic
- Incidence has increased in recent years in MSM as a new STD

AHCV disease course

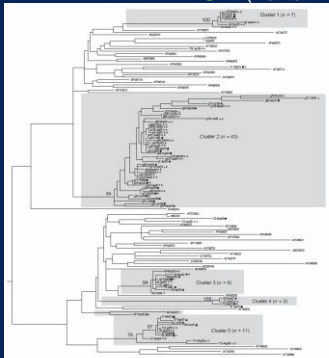
- Typically subclinical and anicteric
 - Up to 95% without classic symptoms
 - Non-specific symptoms (fatigue, nausea) *may* develop within 12 wks of exposure
- Most (85% in HIV(-), 95% in HIV+) new infections progress to CHCV
 - defined by HCV RNA persistence for 6 mos
- HCV Ab may remain negative up to 6 mos, sometimes longer
- Pathogenic mechanisms leading to chronicity ill-defined

The New AHCV Epidemic

- Starting in 2000, clinicians Europe and Australia reported AHCV outbreaks among HIV+ MSM associated with
 - traumatic sexual practices (i.e. multiple partners, S and M, “fisting”)
 - STIs, especially syphilis
 - Club drugs/stimulants, but not IDU
- HCV acquired via sexual transmission due to bleeding during unprotected anal intercourse?
 - facilitated by HIV, mucosal STI lesions?

Dominguez AIDS 2006 Vogel Viral Hepat 2005 Ghosh HIV Med 2004 Luetkemeyer AIDS 2006 Gileecee JAIDS 2005 Serpagni AIDS 2006 Filippini STD 2001 Marx CID 2003 Browne Sex Transm Infect 2004 Colfax AIDS 2002 Rauch CID 2005 Gileecee JAIDS 2005

Epidemic of Sexually Transmitted AHCV in HIV+ MSM (Danta. AIDS, 2007)



- Mapped HCV genomes
- Found uncommon HCV types virologically distinct from other strains, in clusters of cases among HIV+ MSM suggesting common infection source
- Clustering typical with multiple, independent parallel chains of transmission, each seeded by single source infection

Ongoing Epidemic of Sexually Transmitted HCV among HIV+ MSM -- France

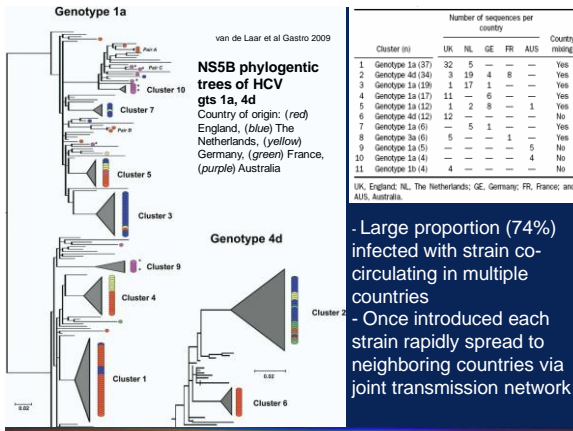
- Clinical, biological and NS5b genetic sequencing data 32/94 AHCV cases
- Median age at AHCV diagnosis: 40 yrs
 - median time between HIV and HCV diagnosis 10 yrs
- 2/3 patients: other STIs present at time AHCV diagnosis
- Majority reported unprotected anal intercourse
- Half had genotype 4d, rare in France
 - Among 16 with genotype 4d, 15 were in one cluster
 - 2006-7 cluster closely related to 4d viruses isolated in Paris 2001-3, suggesting ongoing epidemic sexual transmission

Ghosh 16th CROI 2009, Abstract 800

Evidence of a Large, International Network of HCV Transmission in HIV+ MSM

van de Laar et al GASTROENTEROLOGY 2009

- International phylogenetic study investigated existence of HCV transmission network
- 226 HIV+ MSM diagnosed with recent HCV in England, The Netherlands, France, Germany, Australia 2000-2006 enrolled into molecular phylogenetic study
- NS5B region of HCV genome amplified, sequenced
- Phylogenetic analysis revealed 11 clusters



Evidence of a Large, International Network of HCV Transmission in HIV+ MSM

- Evolutionary analysis of HCV lineages indicates that 85% of transmissions occurred since 1996 – 63% after 2000
- Changing pattern HCV transmission since 1990s given rise to spread HCV in HIV+ MSM all over Europe. Some subjects traveled to US and had unprotected sex during AHCv period
- Prospective studies suggesting true increase in HCV incidence among European MSM

Van der Laar JID 2007; Giraudon STI 2007; Fox AIDS 2008
 Van Der Laar Gastroenterology 2009

How common is HCV in MSM?

Netherlands

- HCV seroprevalence among HIV+ MSM rose from 1%-4% before 2000 to 21% in 2008
- 2/532 (0.4%) HIV-negative MSM HCV-infected

Urbanis IAS 2008, Urbanis AIDS 2009

Why is HCV more common among HIV+ MSM now?

Behavioral/Epidemiological Factors

- The onset of HAART meant that patients could live longer and healthier lives
 - Therapeutic optimism: belief HAART reduces infectiousness, loss of collective memory
 - Prevention fatigue, increases in sexual risk
 - Serosorting/adaptation: clustering STI/HCV
- MSM with HIV/HCV co-infection may be riskier
 - Case-control study, co-infected MSM more likely to report unprotected anal sex, traumatic sex, group sex, party drugs than mono-infected MSM
- Changes in ways to meet partners
 - Internet; International travel; Circuit parties

Fishman CROI 2009

Why is HCV more common among HIV+ MSM now?

Biologic factors

- No super bug
- Co-infection facilitates HCV spread
 - HCV plasma RNA levels tend to be higher in co-infected pts, correlating with increased HCV transmission
 - HCV RNA more often detected in semen of coinfectd vs. mono-infected men
- Erectile enhancing meds, party drugs increase "staying power," more opportunities for mucosal abrasion, bleeding

Enhanced surveillance

An Emerging Syndrome of Rapid Liver Fibrosis in HIV-infected Men with AHCV

- Severe liver fibrosis with progression rates 5 times greater in the HIV+/AHCV cohort compared with pts who were HIV-seronegative at time HCV acquisition
- Concluded that HIV infection at the time of AHCV accelerates hepatic fibrosis beyond the accelerated rates documented in coinfection when HCV precedes HIV infection
- Age, immune dysregulation?

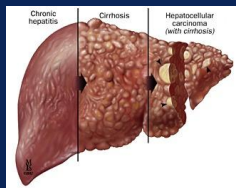
Fierer DS. Liver fibrosis during an outbreak of AHCV infection in HIV-infected men: a prospective cohort study. JID Sept 2008

AHCV Treatment

- HCV treatment more likely to work if initiated during acute phase, regardless of HIV status
 - SVR rates vary inversely with time from AHCV dx
Corey Viral Hep 2009
 - Treatment AHCV among HIV+ persons results in SVR rates 70-91% x 24 wks therapy
 - vs. 20-40% SVR HIV+ CHCV 48 wks
- Identification HCV in acute stage may
 - Increase SVR rates
 - Result in fewer persons progressing to CHCV
 - Reduce adverse effects and costs with shorter course therapy
 - Permit preventive intervention

Importance of Screening for AHCV HIV+MSM

- Spontaneous clearance less common among males than females
- Lack of symptoms associated with decreased spontaneous clearance
 - pointing to value of screening by risk
 - asymptomatic persons may benefit most from early treatment
- HIV+ individuals developing HCC more likely to be younger, male, HCV-infected



Missed Opportunities

- AHCV diagnosis is rarely made
- Most cases asymptomatic, sxs mild, non-specific
 - HCV has been thought to precede HIV infection in most cases
 - U.S. HIV guidelines endorse only HCV Ab testing at time of HIV diagnosis
- AHCV reports include small case numbers, identified serendipitously or retrospectively
- To date, AHCV has been diagnosed primarily through case finding by astute clinicians due to non-specific symptoms, ALT elevations, health care workers post-needlestick

McGovern B et al. CID 2006 Micallef JM et al. J Viral Hepat 2006

Changing Screening Practices

Most clinics think HCV screening is for IDU
< 50% 1,607 HIV+ MSM in 8 U.S. clinics were screened for HCV Hoover K CROI 2009

Miriam Immunology Center in 2006 instituted HCV re-testing for all HCV- patients with without a repeat test in the prior year

- First 6 mos, of 150 pts tested at routine visits, 9% found to have new HCV Ab since last test
- Median time between tests 3 yrs (2 mos - 15 yrs)
- 4 seroconverted within the year
- 1 HCC – consequence late dx

2007 European AIDS Clinical Society Guidelines for Treatment of HIV/HCV Coinfection

Reflect more aggressive approach

- Pt education: Mucosal traumatic sex practices with high risk of blood contact should be avoided
- Serological testing for HCV on initial physician visit and then annually thereafter
- HCV RNA for pts with risk factors (e.g., IDU, mucosal traumatic sex) who have unexplained increase in ALT and negative HCV Ab

Rockstroh. European AIDS Clinical Society guidelines for clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. HIV Med. Feb 2008;9(2):82-88.

Using ALT to trigger HCV screening

- ALT is cheap, relatively predictable, with individual variation
- HCV RNA detectable in blood 1-2 weeks after exposure with rapid increase in levels over subsequent days
- followed by rise in ALT
- ALT may rise more than 10-fold before declining

Acute HCV Pilot Study Providence RI (L Taylor et al)

- Participants recruited at the Miriam Immunology Center 11/07-5/08
 - 1200 HIV+ patients, 80% on HAART
 - Risk factor HIV: 1/3 MSM, 1/3 heterosexual, 1/3 IDU
 - 1/3 coinfecting chronic HCV
 - Eligibility:
 - Patients ≥ 18 years without chronic HCV
 - With drug and/or sexual HCV risk within prior 6 months
- Prospectively enrolled in 9-month study

HCV Risk Behavior

1. MSM any 1:
 - a. Traumatic sex
 - unprotected anal intercourse
 - unprotected fisting
 - bleeding during sex
 - b. STI
 - c. Stimulant or club drug use
 - d. > 5 sexual partners
 - e. Unprotected oral sex
2. MSM with HCV-infected sexual partner
3. IDU or intra-nasal drug use (any gender)
4. Unprotected traumatic sex/anal sex (any gender)

Miriam AHCV Study (Taylor et al)

- At 0, 3, 6 and 9 month routine clinic visits
 - Blood drawn for ALT, storage
 - Behavioral Risk Questionnaire (BRQ)
 - Risk reduction counseling, drug treatment
- ALT rise triggered HCV RNA testing
 - If normal baseline, tested if ALT rises by 20 IU/mL or exceeds 45 IU/mL
 - If ALT was already elevated, then new 1.5-fold increase led to testing
- 33% snorted or inhaled drugs; 20% shared straws; 4% injected drugs; 30% unprotected sex under influence drugs or alcohol
- One new AHCV case detected with 14.8 py f/u

AHCV Conclusions

- AHCV is increasing among HIV+ MSM
- Sexual and drug practices that transmit HCV are common, but providers tend not to ask
- If detected early, AHCV can be cured; if detected late, co-infection is associated with rapid progression to cirrhosis
- Increased detection could be facilitated by routine repeat Ab testing of all HIV+/HCV- patients in care, by monitoring ALT and having a low threshold to screen for HCV RNA, and by educating and discussing risk practices with patients regularly
