ASSISTED REPRODUCTION WITH SPERM FROM HIV-INFECTED MEN

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Alpha 2008
Istanbul, Turkey
May, 2008

Editor's corner

FERTILITY AND STERILITY

Vol. 51, No. 5, May 1989
Printed in U.S.A.

Retroviruses and reproduction

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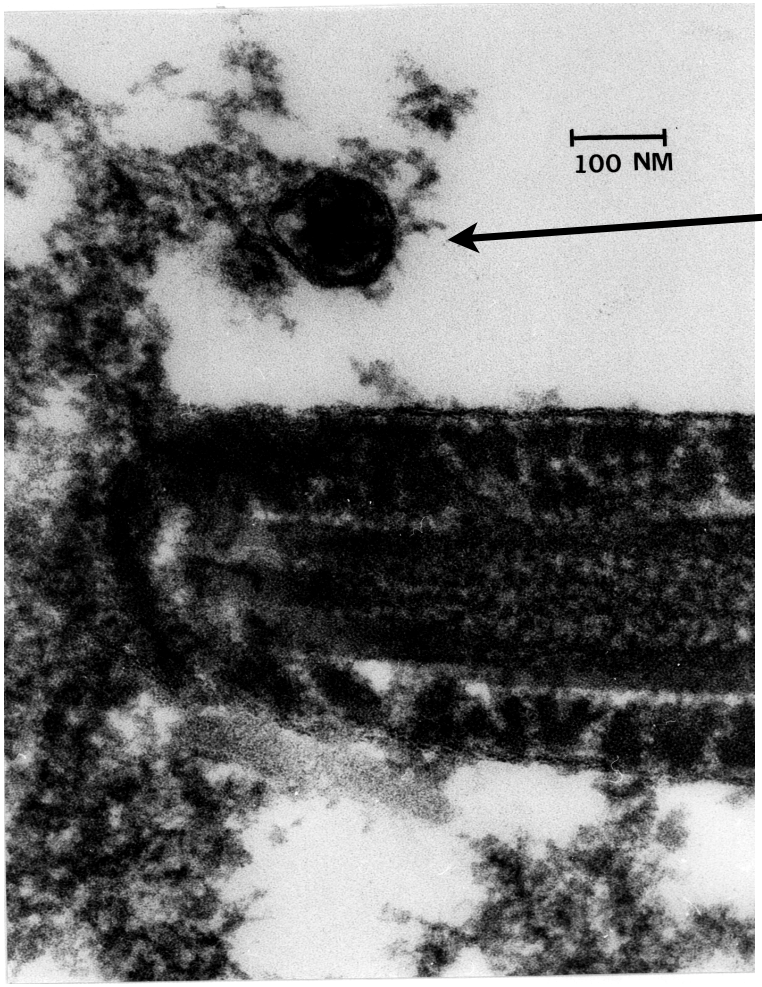
The venereal transmissibility of human immunosuppressive virus (HIV) and human T-cell leukemia virus, I (HTLV-I) impacts reproductive medicine in a number of ways. The possibility of HIV transmission by donor semen has received prompt and appropriate attention, with most centers using only cryopreserved semen stored according to quarantine guidelines for monitoring possible seroconversion of donors. As the incidence of HIV-positive pregnant women rises, obstetric units are evolving safeguards for medical staff attending deliveries. Counseling women at risk for HIV infections about the possible outcome to offspring is becoming increasingly necessary. Some centers for assisted reproductive technology require mandatory screening of patients for HIV antibody as a safeguard for their laboratory and medical staff.

However, a consequence of the venereal transmission of human retroviruses that has not received widespread attention is the impact on reproduction per se. That the impact will be a negative one is due to

1983:



Reported:
First Int'l Aids Congress, 1985;
AIDS 1:419, 1988

First electron micrograph of HIV in semen

The Need:

By 1987, >20,000 men and boys with hemophilia infected with HIV through clotting factors

Thousands of men and women infected by blood transfusion and IV drug abuse

1990: First Congress on "AIDS and Reproduction," Genoa, Italy
"Sperm washing" and IUI advocated by Augusto Semprini

1991: Centers for Disease Control: "IUI with sperm from HIV infected men not proven safe"

The Goal:

Develop methods to reduce, hopefully eliminate, transmission of HIV from infected male to uninfected female attempting pregnancy.

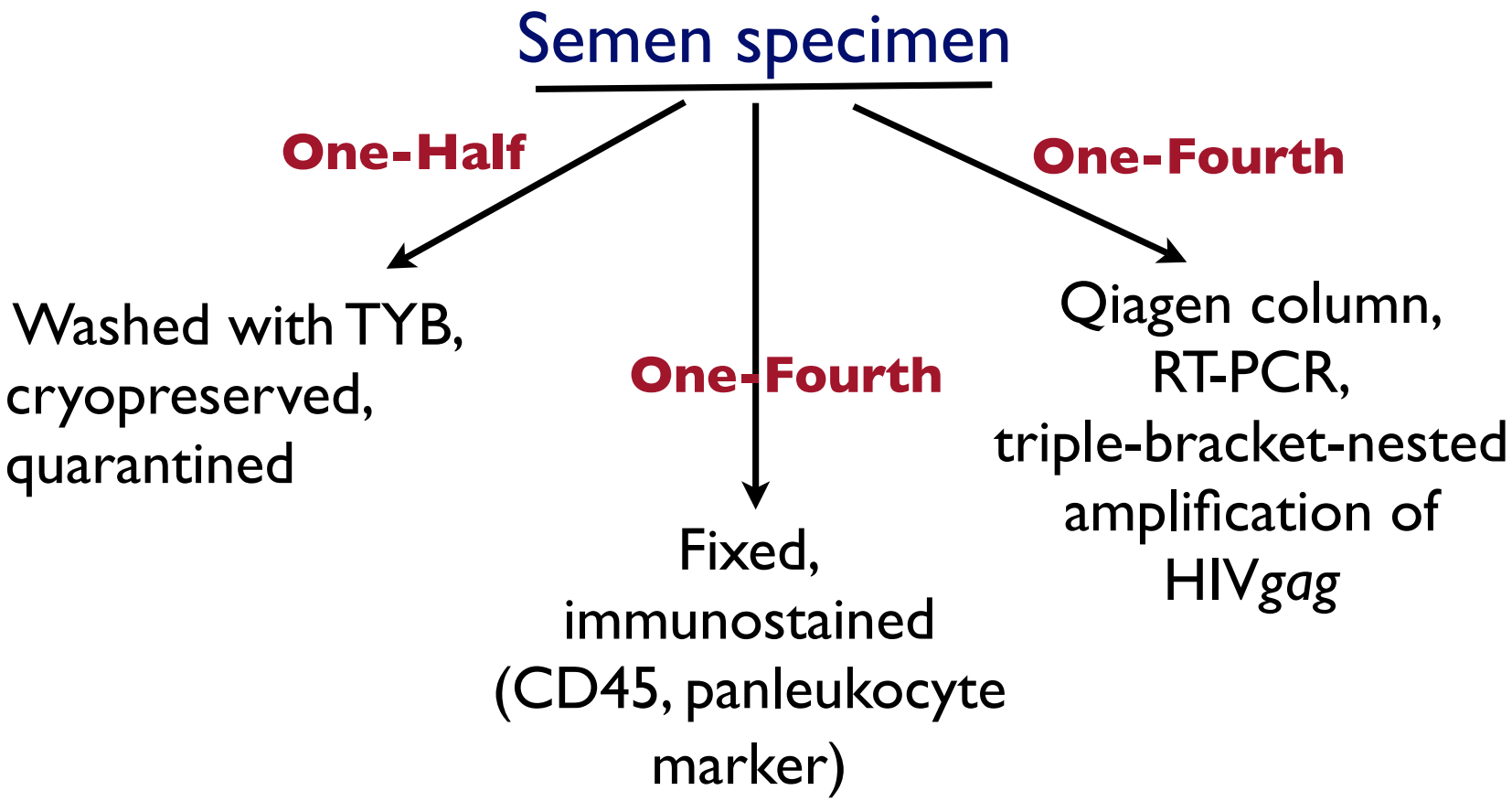
The Hope:

HIV infection in the male would be regarded as a form of male factor infertility

The Plan:

Develop sensitive assays for HIV and HIV-infected cells to eliminate the use of sperm from semen with detectable virus.

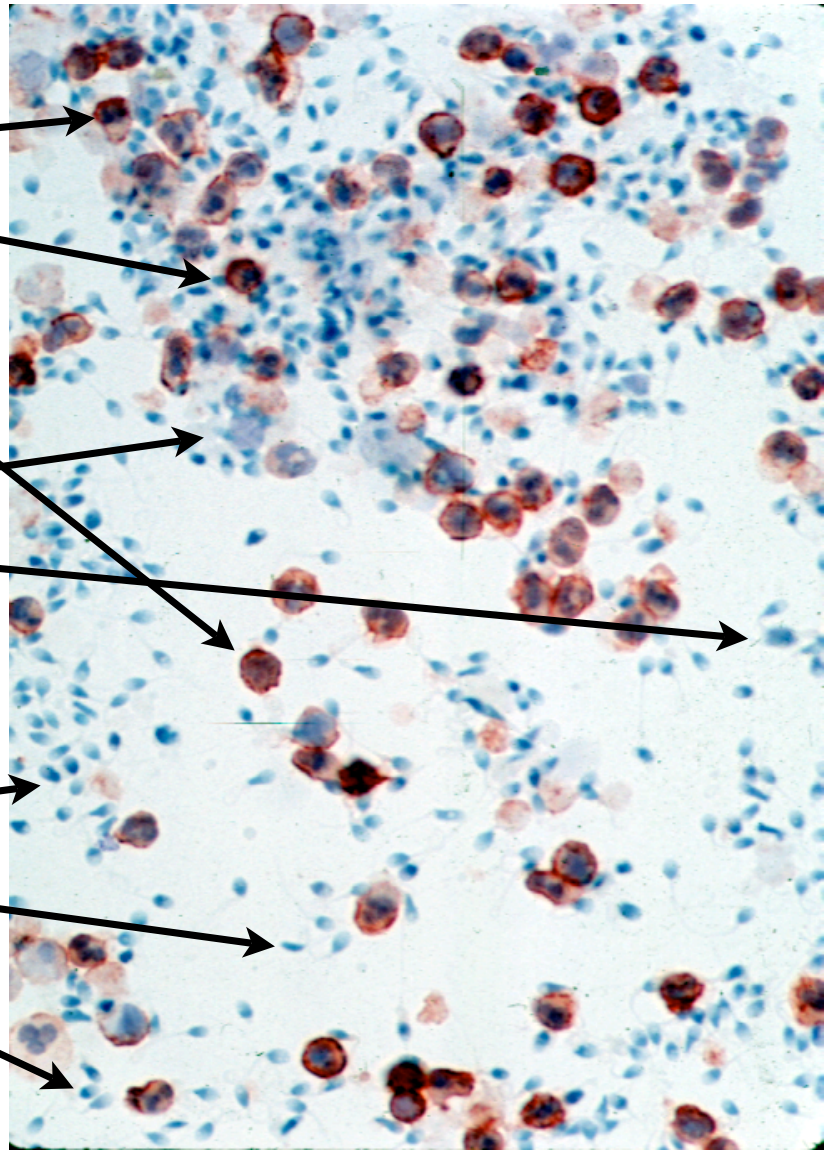
Semen HIV assays:



CD45+ leukocytes (red-brown)

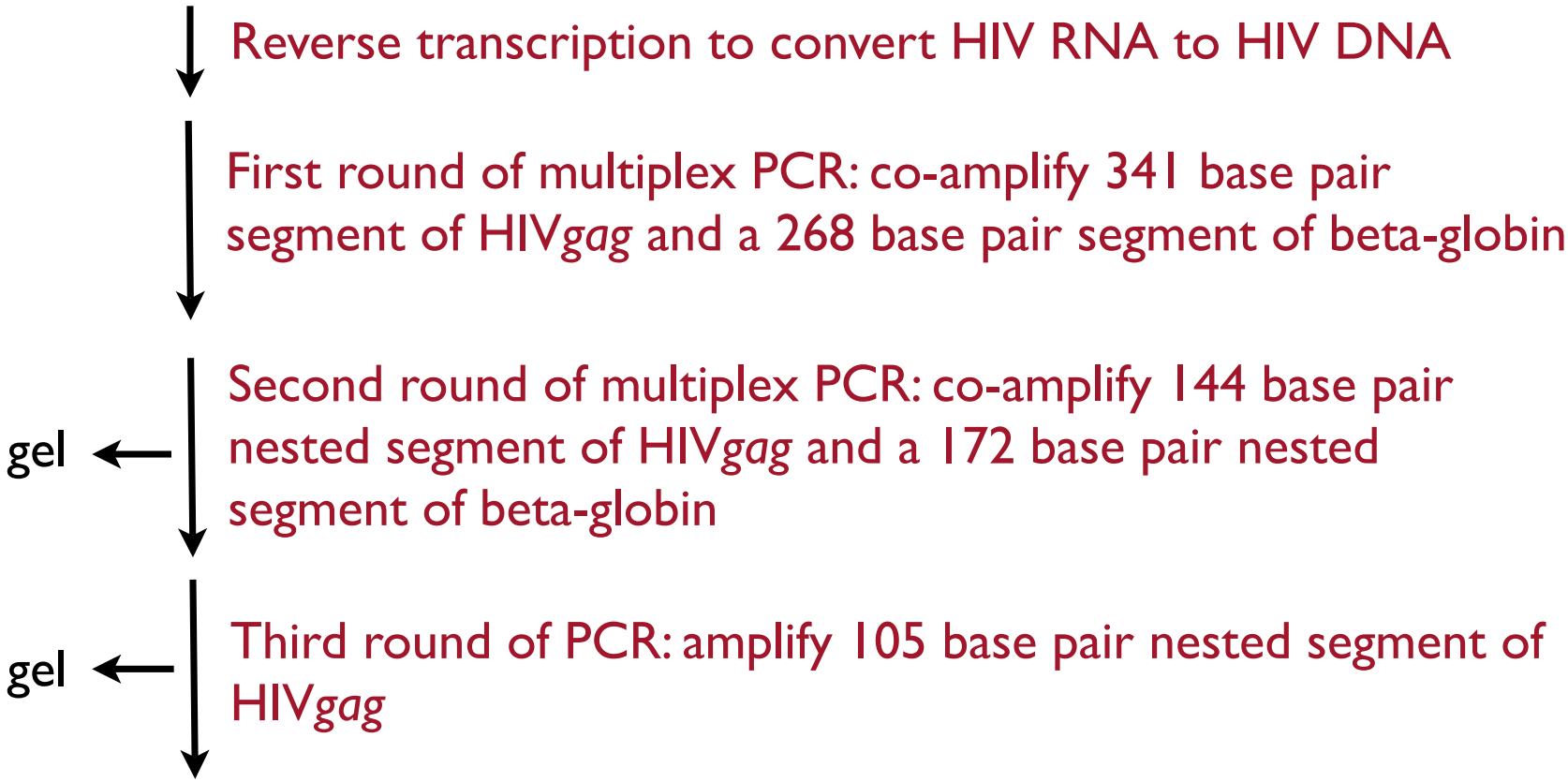
Immature germ cells (blue)

Mature sperm (dark blue)

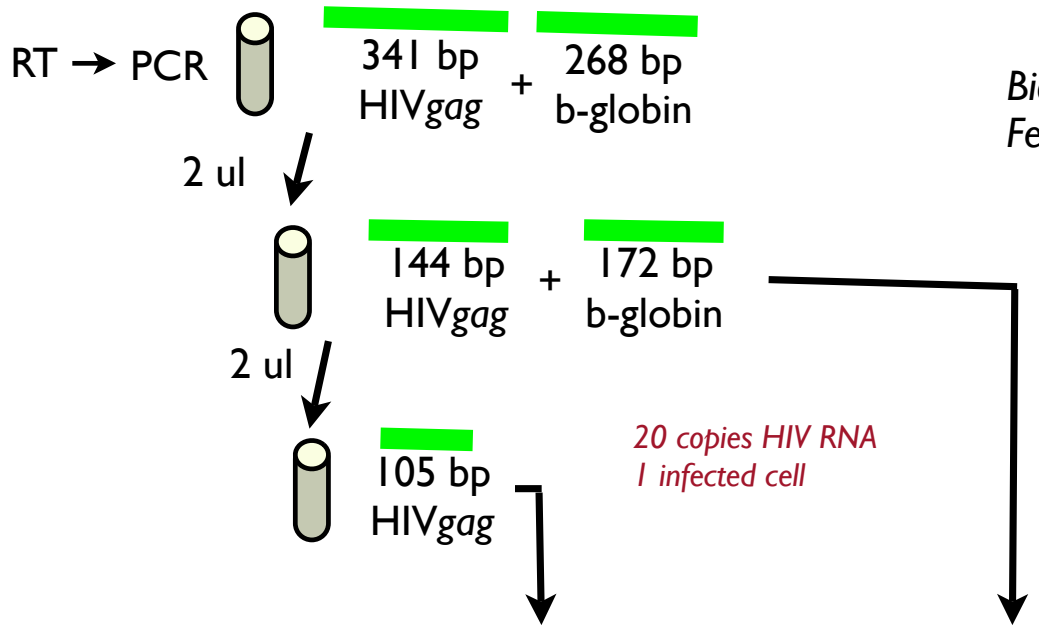


RT-PCR steps:

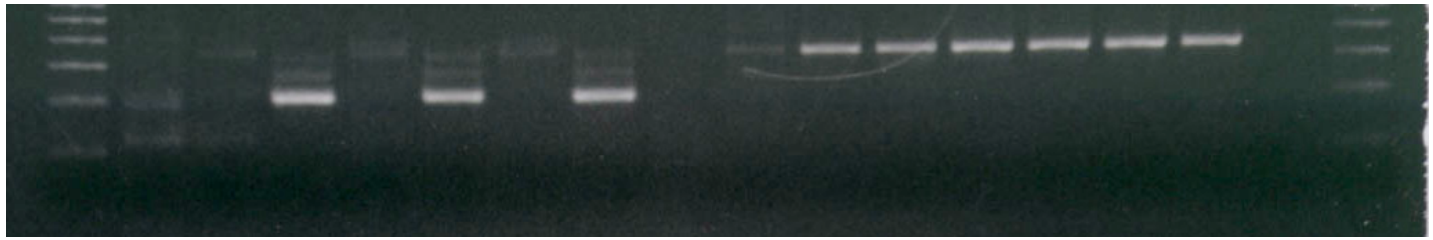
Semen cells and particles, but not sperm heads, lysed to release RNA and DNA:



RT-PCR steps:



Biotechniques 15: 128, 1993
Fertil Steril 60: 576, 1993



L 1 2 3 4 5 6 Pos Bl 1 2 3 4 5 6 Pos Bl L

HIV in sequential semen specimens:

Patient								
1	•		U		•	•		U
2	•	•			U		•	•
3	•		•		U		•	
4	•	•		•		•		U
5	•		U		U		•	
6	•		U		•			U
7	•		•		U			
8	U		U		U		•	U
9	•		U		U	•		
10	•		•	•		U		
11	•	U		•		U		
12	•		•		•			•
	1	2	3	4	5	6	7	8

Month of study

U = undetectable

• = HIV positive

Program steps:

(1) Interview with HIV counselor

a) Health status of male:
regular visits to infectious disease specialist;
no "minimum" blood viral load;
explain complex nature of HIV in semen;

b) Health status of female:
at risk for HIV infection (and possibly Hep C/B);
need for fertility evaluation;
need for follow-up HIV antibody testing;

c) Fertility clinic referral, if needed

d) Need to test baby sometime during the first year

Program steps:

(2) Submit semen specimens for testing, using overnight transport kit if not in Boston area

(3) Sperm from half of specimen is cryopreserved, remainder of specimen is tested for leukocytes, HIV virus, and HIV-infected cells

(4) If HIV detected, sperm discarded; fresh specimen is tested

(5) If two specimens in a row test positive for HIV, man may be referred to urologist, if suspect GU tract infection; or to infectious disease physician if adjustment to antiviral therapy is indicated.

Program steps:

(6) Cryopreserved sperm from two specimens with un-detectable viral burden stored until shipped to collaborating fertility treatment center

(7) Pregnancy attempted by IVF or oligospermia cup (NOT IUI)

(8) Female partner tested for HIV antibody at 3 weeks, 3 months and 6 months after pregnancy attempt -- whether or not pregnancy achieved

(9) Baby tested for HIV antibody within first year of life

Program began in 1996

Controversial, caught in hospital merger, became a public charity

First baby born in 1998

(Stephen Smith, "*Fertility Race*," Minnesota Public Radio)

Conceiving Ryan

by Stephen Smith of Americanradioworks
Minnessota Public Radio

2000-2006:

608 semen specimens from 262 men tested for HIV

107 (19%) semen specimens tested positive, discarded

151 couples proceeded to ART

69 pregnancies, 62 babies born, 10 sets of twins

As of September, 2007:

26 collaborating fertility clinics

71 Babies born, 8 ongoing pregnancies

All Moms and Babies test negative for HIV

CONCLUSIONS:

- AIDS will continue to change the world
- HIV disease will continue to challenge social mores and biomedical science
- Vaccine development will be a lengthy process
- Preventing disease spread will continue to be the responsibility of individuals
- “Safe sex” needs to be helped by new approaches

Hepatitis B infection:

- Infected blood
- Infected body fluids, including semen
- At delivery, if mom is chronically infected

Hepatitis B infection:

- 90% of adults clear acute infection within 6 months
- 10% of adults develop chronic infection and have detectable levels of virus in blood for many years
- chronically infected adults are contagious

Hepatitis B infection:

- 90% of infants infected at birth develop chronic infection
- at markedly increased risk of liver disease
- remain contagious for life

Hepatitis B:

- An hepadna virus -- DNA virion, reverse transcribed from an RNA intermediate
- Stable -- remains infectious on dry surfaces for more than a week
- Serum, saliva and semen are infectious

Hepatitis B treatment:

- Acute infection leads to jaundice within about two months, resolves within another two months
- Chronic infection may be treated with anti-virals: adefovir dipivoxil, interferon alfa, lamivudine, entecavir

Hepatitis B tests:

- Tests for serum antibodies:
  - anti-HBs (surface antigen)
    - response to infection or vaccination
  - anti-HBc (core antigen)
    - response to infection -- not a vaccination marker
  - IgM anti-HBc (core antigen)
    - indicates recent infection
  - anti-HBe: (“e” antigen)
    - indicates vigorous immune response

Hepatitis B tests:

- Tests for viral antigens in serum:
  - HBsAg (surface antigen)
    - indicates acute or chronic infection with active virus production
  - HBeAg: (“e” antigen)
    - indicates high degree of infectivity
- Tests for viral DNA in serum:
  - HBV-DNA
    - correlates well with infectivity

History of Hepatitis C:

- “Non-A, non-B” post transfusion hepatitis
- Cloned in 1989, Chiron Corporation team
- 1992, began to screen blood supply
- No vaccine
- Second viral epidemic treated by drug therapy instead of vaccine

Biology of Hepatitis C:

- RNA virus, Flavivirus family
- Double-shelled, enveloped, single-stranded RNA
- Encodes a single, 3000 amino acid polypeptide
- High mutation rate

Hepatitis C:

- Relatively stable -- remains infectious on dry surfaces for up to 4 days
- Has 6 subtypes

Hepatitis C infection:

- Infected blood
- Infected body fluids, including semen (?)
- Highest risk since 1992 = iv drug abuse

Hepatitis C infection:

- may be relatively asymptomatic and not require treatment
- more than half of acute infections become chronic
- chronic infection leads to:
  - cirrhosis in approximately 10% of patients
  - liver cancer in approximately 2% of cases

Hepatitis C treatment:

- Acute infection may resolve without anti-viral treatment
- Chronic infection may be treated with two anti-virals: interferon and ribavirin, usually in combination

Hepatitis C tests:

- Serum antibodies:
  - indicates past or present infection
- HCV RNA:
  - qualitative -- indicates present infection
  - quantitative -- useful to evaluate therapy
- Genotyping:
  - Type 1 most common in U.S.
  - Types 2 and 3 most responsive to therapy
- Liver Biopsy

Hepatitis C treatment:

- Interferon 2-alpha plus ribavirin:
- HCV RNA:
  - qualitative -- indicates subtype
  - quantitative -- useful to evaluate therapy
- Genotype:
  - Type 1 most common in U.S.
  - Types 2 and 3 most responsive to therapy

HIV, Hepatitis C, Hepatitis B:
Disease Course and Risk of Sexual Transmission

Summary:

HIV infection is life long, sexually transmitted by both virus particles and virus-infected cells

Hepatitis B infection usually resolves, carriers remain infectious for life, sexually transmitted by virus particles, stable for several days

Hepatitis C infection likely to become chronic, sexual transmission not well documented, stable for several days

Bacteria in Semen:

- 25 (56%) of 45 semen specimens from 22 (65%) of men were positive for abundant bacteria (>20,000 organisms/cc)
- Identification by cloning and sequencing species specific regions of 16s ribosomal DNA revealed gram-positive anaerobic cocci (GPAC) were the most frequently detected (13 specimens)
- Leukocytospermia did NOT predict semen bacteria
- Sperm morphology poorest in bacterial rDNA positive specimens

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(all inquiries strictly confidential)