SRBT WEBINAR

Infectious Disease and the Infertility Patient:

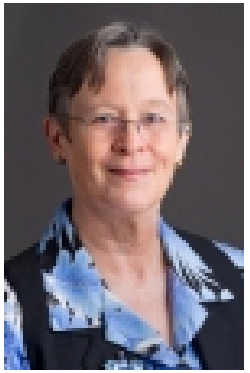
July 14, 2015: Patient Evaluation and Laboratory Safety
July 21, 2015: Fertility Treatment for Infected Patients

Hosts:

SRBT Sue Gitlin, Ph.D.,
Chair, SRBT Education

CRYOPORT Shannon Curiel, Business Development Manager, Cryoport

Erma Z. Drobnis, Ph.D., HCLD



- PhD from U California Davis on the biophysics of sperm-oocyte interaction in mammals
- Post doc training under Drs. John Crowe and Jim Overstreet
- Research faculty member at UCDavis in Ob/Gyn, Vet Medicine
- Currently, director of Andrology at University of Missouri, Columbia School of Medicine.
- Chair SMRU Traveling Scholars program
- In her 35+ years, studied diverse species, published multiple articles. Highlights:
  - Semen quality in urban vs rural areas
  - Sperm glycobiology
  - HIV discordant couples
  - HIV transmission at the endocervix

SOCIETY OF REPRODUCTIVE Biologists & Technologists
ASRM SRBT

Infectious Disease and the Infertility Patient

Part 2. Fertility Treatment for Infected Patients

Society of Reproductive Biologists & Technologists (SRBT)
Webinar 07-21-15

Erma Z. Drobnis, Ph.D., HCLD

University of Missouri, Columbia – School of Medicine
Missouri Center for Reproductive Medicine & Fertility

Slide Backgrounds: a rendering of the HIV virus by Ukrainian designer Alexey Kashpersky First prize winner of the Computer Graphics Society visualization competition 2012
http://www.cgsociety.org/index.php/CGSFeatures/CGSFeatureSpecial/autopack_challenge_winners

Infectious Disease and the Infertility Patient (covered in part 1)

- It is exciting to have registrants from 18 countries for this webinar!
- I am most familiar with U.S. regulations and accrediting bodies for clinical laboratories, and some are included; other regional regulations include NATA in Australia, CPA and HFEA in the UK, EU Tissues and Cells Directive and guidelines from the ISO, WHO and scientific societies that act and standards of clinical practice
- Homework: If you know the web location of regulations for your country (or if I missed relevant U.S. ones), please send them to me after the webinar

Participant Country		
Australia	Greece	Peru
Brazil	India	Saudi Arabia
Canada	Israel	Singapore
Costa Rica	Mexico	South Africa
Denmark	Nigeria	Spain
Germany	Pakistan	United States

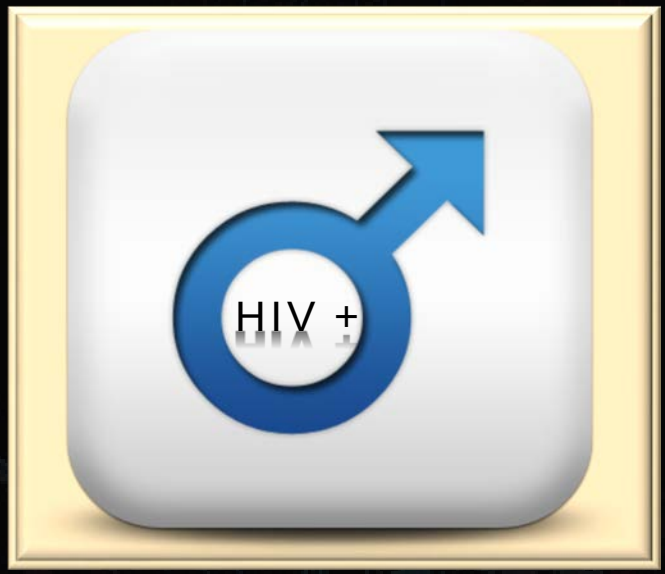
Infectious Disease and the Infertility Patient

Part 2. Fertility Treatment for Infected Patients

1. Counseling
2. HIV-discordant (focus on this because I work with these couples)
   a. Sperm Washing and IUI
   b. Sperm Washing and ICSI
   c. Intercourse with PrEP (Experimental)
   d. Reducing the Risk of HIV Infection
3. Other Viral Infections
   a. Hepatitis B
   b. Hepatitis C
   c. HTLV
   d. HPV
   e. HSV (genital herpes)
   f. CMV

Fertility Treatments for Serodiscordant Couples

- To prevent transmission of the virus to the seronegative partner, condoms must be used for each act of intercourse



- This means that the serodiscordant couple will need medical intervention in order to conceive a biologically-related child

Infectious Disease
and the Infertility Patient

Counseling

Fertility Treatments for Serodiscordant Couples

- Treatment for serodiscordant couples who desire a biologically-related child begins with counseling
- If the woman is seropositive and the man is seronegative, IUI is an appropriate treatment with ART if indicated
- If the man is seropositive and the woman is seronegative, emphasize that the safest options are donor insemination, adoption and remaining childless
- The greatest risks of all treatments involving semen from the infected man are infection of the woman and/or the resulting child
- The options and risks differ for each disease, but all are based on:
  - Reducing the man's viral load
  - Reducing exposure and susceptibility of the woman

Fertility Treatments for Serodiscordant Couples

HIV – Overview

HIV-discordant couples have been treated by three methods:

1. Specialized sperm washing for IUI
   - Widely used outside the U.S. but has gained less acceptance here
2. IVF with ICSI
   - Considered to be the safest method by U.S. practitioners (although this is not considered the case elsewhere)
   - Outside the U.S. used in cases of IUI failure or other indications for ART
3. Unprotected Intercourse once at the time of ovulation
   - Previously not allowed under CDC regulations but now a possibility due to the 2014 Pre-Exposure Prophylaxis (PrEP) guidance

Infectious Disease
and the Infertility Patient

HIV – historical note

Transmission of HIV by Insemination – Historical Note

- 1990 U.S. report: a woman became HIV-positive after 3 consecutive IUIs with sperm from her HIV-positive, hemophiliac husband[1,2]
- For one of IUI treatments, sperm were washed in buffer but not separated from other cellular contaminates, notably leukocytes
- This remains the only documented case of HIV-transmission resulting from assisted reproductive treatment of an HIV-discordant couple
- This one case continues to have profound effects on our practice

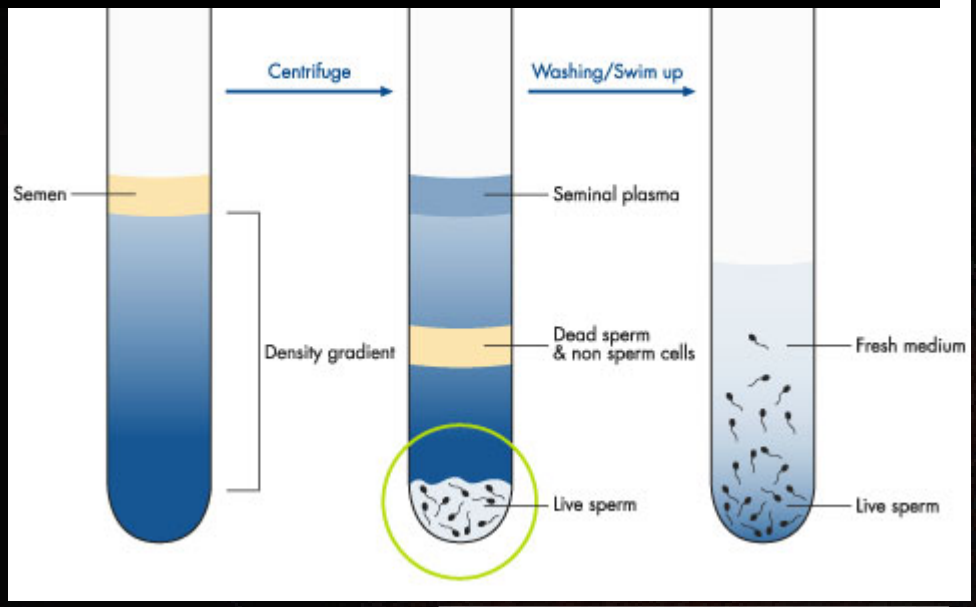
1. Wortley et al., 1998; 2. CDC, 1990

Infectious Disease
and the Infertility Patient

HIV – Sperm “Washing”

Fertility Treatments for Serodiscordant Couples - HIV
"Sperm Washing" for IUI

- Sperm washing reduces HIV from the sperm suspension to undetectable levels in most specimens
- Currently over 5000 inseminations reported worldwide without seroconversion of woman or resulting child



3. Semprini et al, 1992

Fertility Treatments for Serodiscordant Couples - HIV
"Sperm Washing" for IUI (continued)

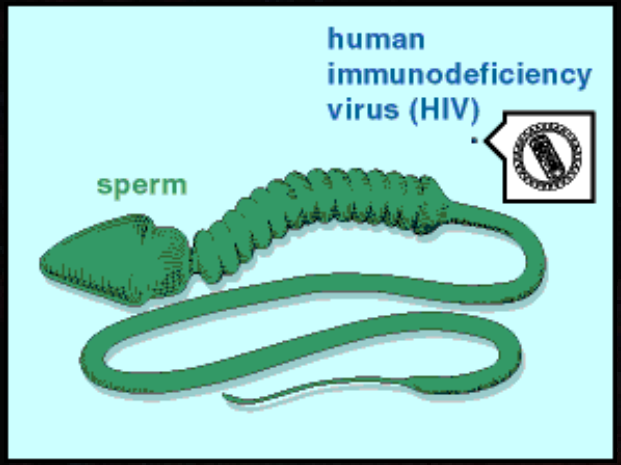
- IUI for HIV-discordant couples is standard of care in many countries, for example, the Society of Obstetricians & Gynaecologists of Canada recommends IUI with special sperm washing for HIV-discordant couples, followed by IVF if unsuccessful[4]
- In Europe, there have been over 4500 published cases of HIV-Discordant IUI or IVF without a single infection of the partner or resulting child[5-7]
- In the US, practitioners have been reluctant to adopt these methods, but current CDC regulations and ASRM guidelines support their use

Carole Gilling-Smith, MD, PhD

4. Loutfy et al, 2012; 5. Gilling-Smith et al., 2006; 6. Anderson et al., 2010; 7. Vitorino et al., 2011

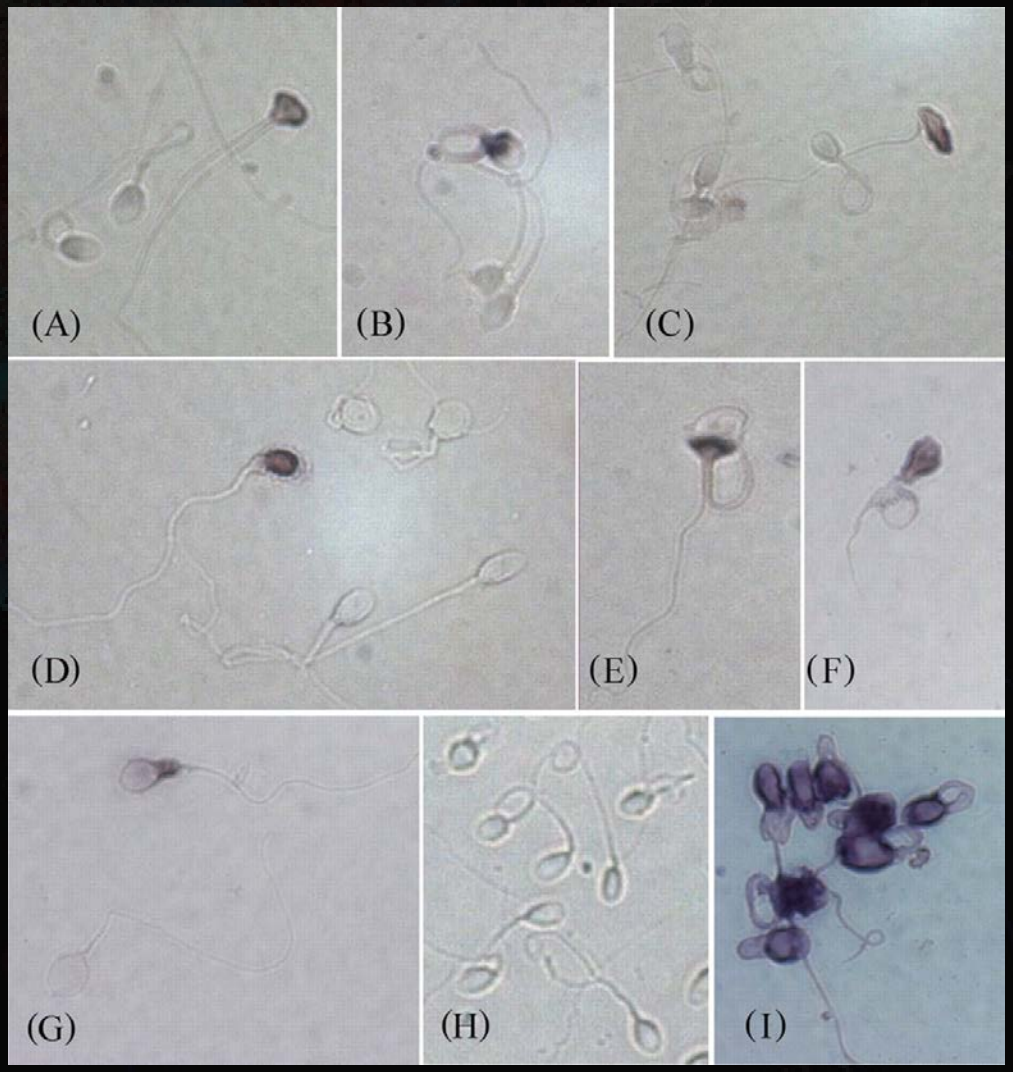
Is HIV Associated with the Sperm Cell? Remains Some Controversy

- Most scientists accept that there is no association of HIV with washed, motile sperm using PCR for HIV DNA/RNA[1,2]
- Although there are no HIV receptors on the sperm surface, HIV attaches avidly to sperm via sperm surface mannose or heparin sulfate receptors[10-16]
- Leukocytes in semen are the main mode of HIV infection[17]



8,9. Quayle et al 1997, 1998; 10. Kim et al., 1999; 11,12. Baccetti et al., 1991, 1994; 13. Barboza et al., 2004; 14. Bandivdekar et al., 2003; 15. Fanibunda et al., 2008; 16. Ceballos et al., 2009; 17. Nicopoullos et al , 2010

Is HIV Associated with the Sperm Cell? Remains some Controversy (continued)



- HIV may infect or adhere to morphologically abnormal sperm in semen[18]
- Highly motile sperm selected from semen of HIV-infected men usually have undetectable HIV nucleic acid levels[19]

In situ HIV-1 DNA detection in sperm cells of seropositive Subjects

(H) Is an uninfected donor

18. Muciaccia , 2007
19. Anderson et al., 2010

Fertility Treatments and the Potential for Disease Transmission

2014 CDC Recommendations for HIV Prevention

Conception methods that reduce the risk of sexual and perinatal transmission in HIV-discordant couples

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

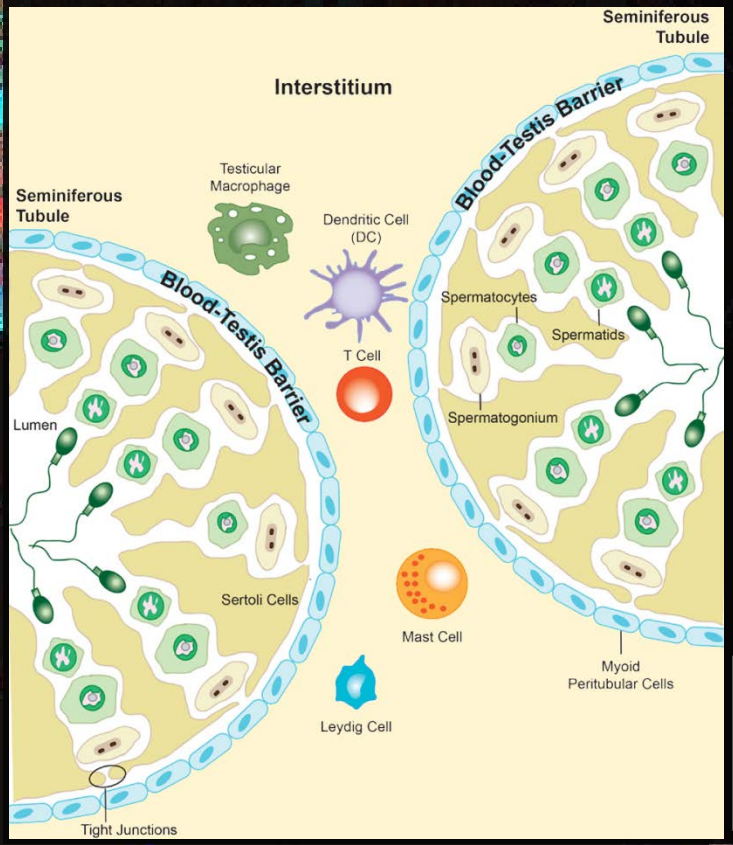
"For couples in which the man is HIV-infected and can access assisted conception methods, these options include

- preconception semen analysis to determine semen volume and any abnormal sperm characteristics that may influence conception decisions (because repeated semen exposure could result in HIV infection but not lead to conception or a viable fetus).
- intrauterine artificial insemination, in vitro fertilization, or intracytoplasmic sperm injection, using semen or sperm from an HIV-uninfected donor, or if donor semen or sperm is an unacceptable option, sperm from the HIV-infected man that has undergone procedures that remove seminal fluid that may contain HIV ("sperm washing")." [20]

20. CDC, 2014 http://stacks.cdc.gov/view/cdc/26062

Co-infections with Other Organisms

- HIV-positive patients are more likely to have co-infections that affect their fertility[21]
- Opportunistic infections associated with HIV can cause orchitis and/or epididymitis



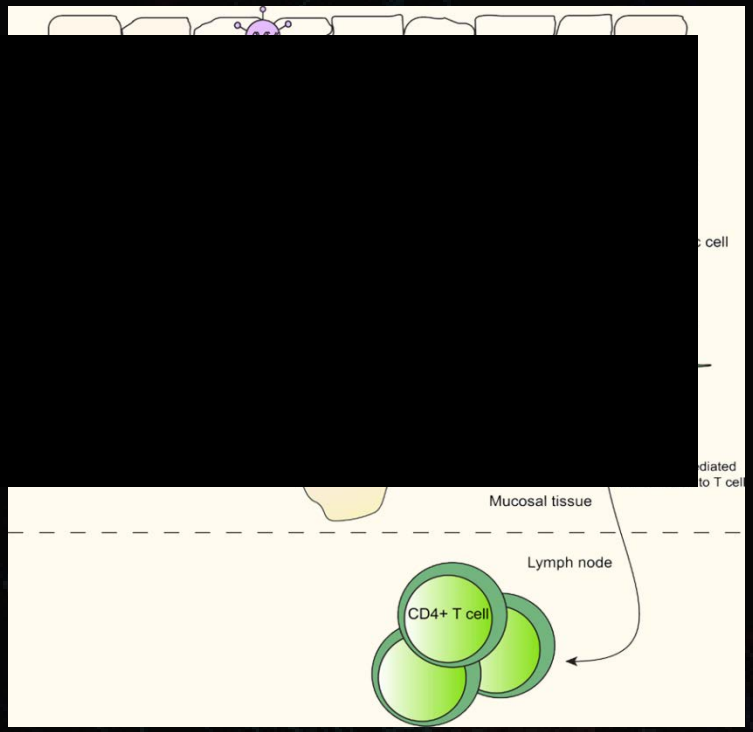
- Sexually transmitted infections also more common[22-23]
- HIV reduces the protective immunity of the genital tract, allowing co-infection with other pathogens[19,24,25]
- HAART restores some immunity, making it easier for the male to resist secondary genital infections

19. Anderson et al., 2010; 21. Kushnir and Lewis, 2011;
22. Sewankambo et al., 1997; 23. Mbulawa et al., 2009;
24. Politch et al., 2009; 25. Savasi et al., 2008

Co-infections with Other Organisms (continued)

[redacted]

- Lower fertility (e.g., from PID)
- Increased susceptibility to HIV due to inflammation and erosion of the genital tract epithelium[26,27]

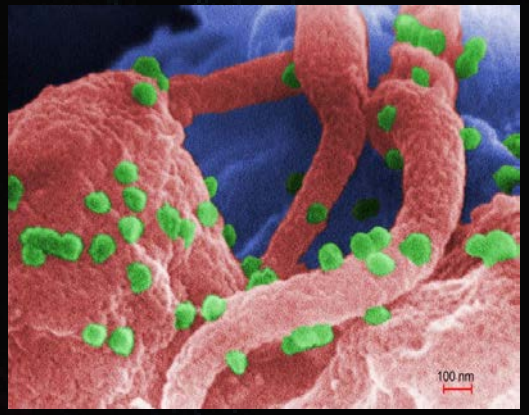


- Some organisms are more difficult to remove from sperm by washing than HIV (e.g., HPV)[28]
- For men with HCV/HIV co-infections – it may be possible to collect testicular sperm, which have been found to be free of virus[29]

26. Quinn et al., 2000 27. Gavin and Cohen, 2004 28. Foresta et al., 2011 29. Garrido et al., 2009

Fertility Treatments for Serodiscordant Couples - HIV

PCR to Detect HIV after "Sperm Washing"



- About 3-8% of washed specimens contain detectable HIV virus after "sperm washing" and cannot be used[5,7,17,30]
- As this is within the range of false positive results for this test, these may represent samples that test positive but contain no HIV virus
- It remains controversial if this test is required, particularly for men with undetectable viral loads-many clinics do not test for virus
- PCR requires up to 20 hours during which the processed sperm lose some viability
- Cryopreservation of the washed sperm is used by some groups so PCR can be done before the day of insemination[31]

5. Gilling-Smith et al, 2006; 7. Vitorino et al, 2011; 17. Nicopoullos et al, 2011; 30. Perisco et al, 2006; 31. Bujan et al 2007a

Ovarian Stimulation

- Due to the risk involved, conception per insemination should be optimized[3]
- In many European centers using for HIV-discordant IUI, ovarian stimulation and/or ovarian monitoring and ovulation induction are used for all cycles[5,25]

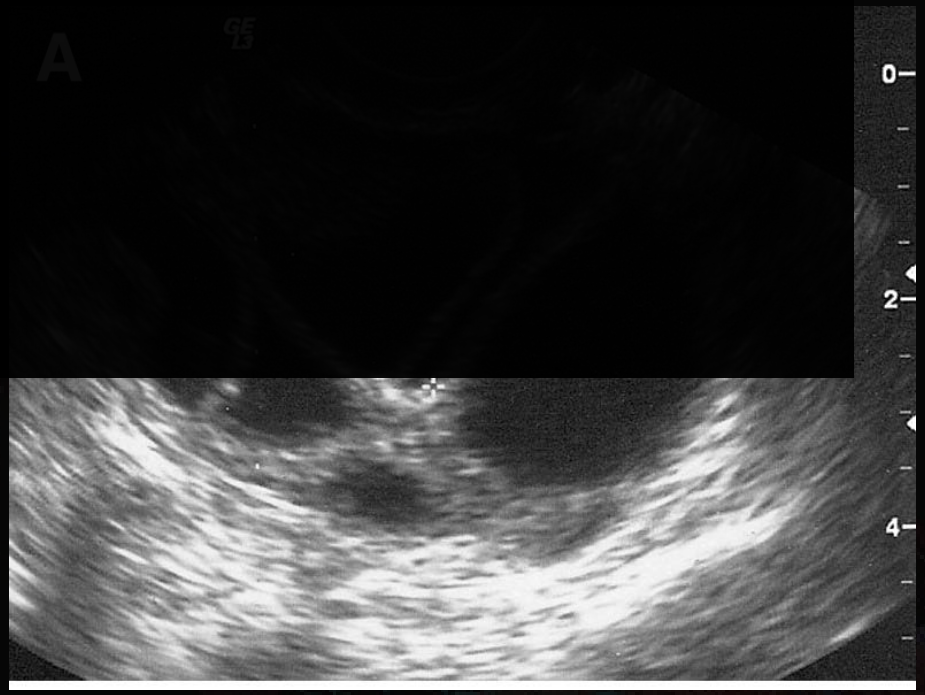


Photo from Oktay et al. Fertil Steril. 2010 Jul;94(2):753.e15-9.

3. Semprini et al., 1992 5. Gilling-Smith et al 2006 25. Savasi et al., 2008

Fertility Treatments for Serodiscordant Couples - HIV

IVF/ICSI (intracytoplasmic Sperm Injection)

- Outside the U.S., ICSI is generally used only in patients with an indication other than HIV-status[4,5,25,32]
- Some advise against ICSI for HIV-infected men because it could introduce HIV virus into the oocyte[5,33,34]
- The only clinical research of sperm washing for HIV-positive men in the U.S. used ICSI exclusively
  - No evidence that ICSI is safer than IUI
  - Minimize costs by use of IUI for some couples
- Risk/benefit analysis must consider the higher success rate of IVF/ICSI compared with IUI: each attempt is associated with some risk and IVF/ICSI reduces the number of exposures per pregnancy

4. Loutify et al, 2012; 5. Gilling-Smith et al, 2006; 25. Savasi et al, 2007; 32. Ohl et al, 2003; 33,34. Bujan et al, 2006, 2008.

Infectious Disease
and the Infertility Patient

HIV – PrEP

Fertility Treatments for Serodiscordant Couples - HIV

Lack of Access to Care is a Public Health Issue

As is true for other diseases, many HIV-discordant couples lack access to care:

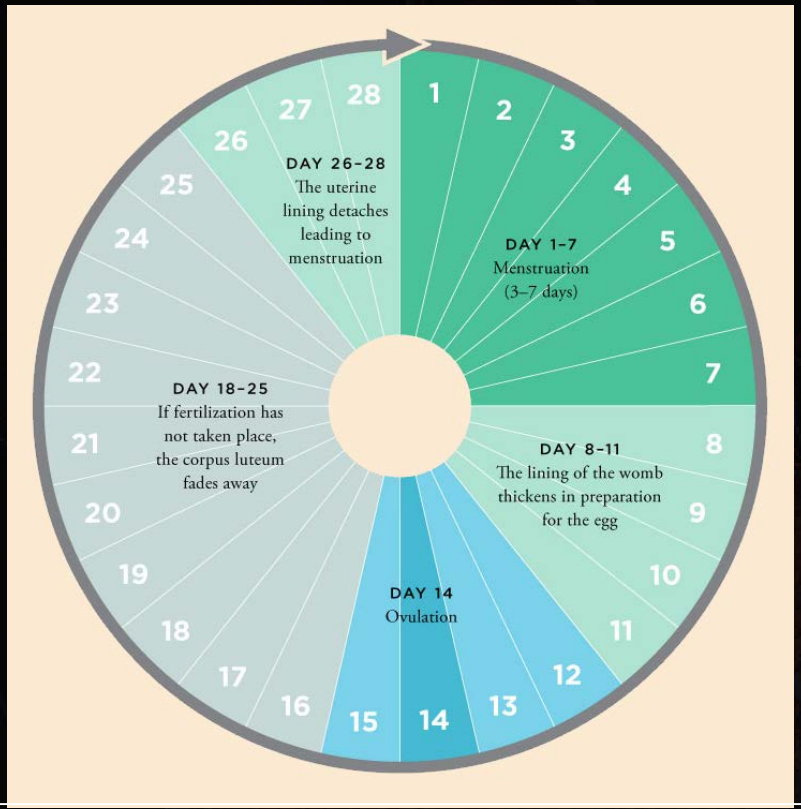
- Lack access to a clinic offering reproductive treatment to HIV-discordant couples
- If not covered by insurance (as it is not in most of the US), the use of ART can be very costly:

one cycle of IVF costs 20% of the median household income in the US

Fertility Treatments for Serodiscordant Couples - HIV

Lack of Access to Care is a Public Health Issue

- Study of 50 HIV-discordant couples[35]
- Significant number had tried timed intercourse without condom protection in order to have a child
- Others said they would consider this if assisted reproduction was not available
- Seroconversion rate of the woman using this approach without medical intervention was more than 4%[36], which is unacceptable
- 2014 CDC guidelines on pre-exposure prophylaxis (PrEP) opens the door to using this method more safely



35. Klein et al., 2003; 36. Mandelbrot et al, 1997

Fertility Treatments and the Potential for Disease Transmission

2014 CDC Recommendations for HIV Prevention

"PrEP should be discussed with heterosexually-active women… whose partners are known to have HIV infection (i.e., HIV-discordant couples) as one of several options to protect the uninfected partner during conception and pregnancy so that an informed decision can be made in awareness of what is known and unknown about benefits and risks of PrEP for mother and fetus."

20. CDC, 2014 http://stacks.cdc.gov/view/cdc/26062

Fertility Treatments and the Potential for Disease Transmission

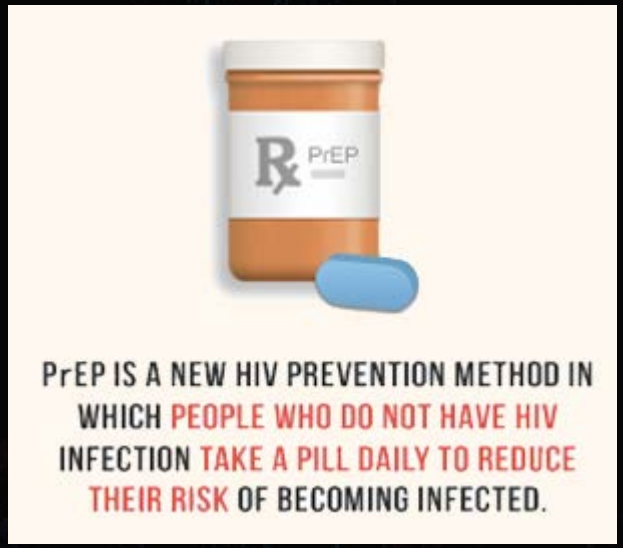
2014 CDC Recommendations for HIV Prevention (continued)

- What is not covered by the CDC guidelines is that use of PrEP and unprotected intercourse is safest if under the treatment of a reproductive medicine practitioner
- The practitioner can ensure that:
  1. The couple's fertility is compatible with high fertility
  2. Unprotected intercourse is limited and well-timed
  3. The risks of HIV transmission are reduced to near zero

20. CDC, 2014 http://stacks.cdc.gov/view/cdc/26062

What is PrEP?

- Pre-exposure prophylaxis for HIV
- Taken daily by persons at high risk for HIV infection, including HIV-discordant couples
- Oral
  - tenofovir disoproxil fumarate 300 mg (TDF)
  - emtricitabine 200 mg (FTC)
  - Brand name: Truvada
- Side effects are generally mild and include nausea



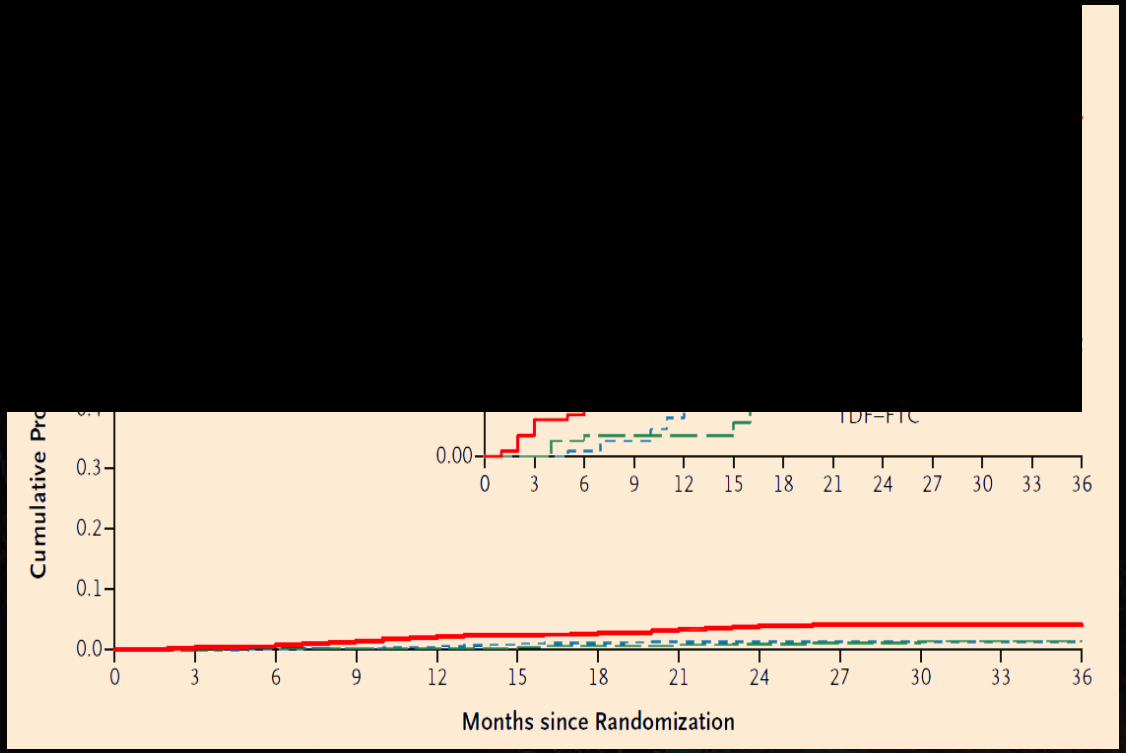
Fertility Treatments for Serodiscordant Couples - HIV

PrEP

- [redacted]
- [redacted]
- [redacted]

years

- PrEP (TDF/FTC) reduced HIV transmission by 80%
- Transmission was reduced by 90% in subjects with a positive blood test for the study drug



37. Baeten et al, 2012

Fertility Treatments for Serodiscordant Couples - HIV

Reducing Risk of HIV Transmission by Intercourse

Studies of HIV-discordant couples conducted primarily in African countries

General HIV-D population	**0.1% per coital act; 7% per year**
Male circumcision[38]	0% per year (n=50) for circumcised men 17% per year (n=137) for uncircumcised
HIV viral load[38]	0% per year (n=50) for copies < 1,500/mL 2% per year for copies < 35,000/mL 23% per year for copies > 50,000/mL
HART treatment[39]	0% per year (n = 149) if taking ART 9% per year (n = 476) if not taking ART
Genital ulcer disease[26]	9% per year (n=50) if without ulcer disease 12% per year (n=365) if with ulcer disease
Male HIV symptoms[40]	0.07% per coital act if asymptomatic 0.5% per coital act if advanced disease
Time from seroconversion[41]	0.82% per coital act for 0-5 mon 0.15% per coital act for 6-15 mon 0.10% per coital act for 16-35 mon 0.43% per coital act for 6-15 mon before death

26. Quinn et al, 2000; 38. Gray et al, 2001; 39. Del Romero et al, 2010; 40. De Vincenzi, 1994; 41. Wawer et al, 2005

Fertility Treatments for Serodiscordant Couples - HIV

Reducing Risk of HIV Transmission by Intercourse

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Fertility Treatments for Serodiscordant Couples - HIV

One Well-Timed, Unprotected Intercourse

The risk of HIV transmission by intercourse extremely low if:

- Monogamous relationship; avoiding rough sexual practices
- Condom use for every coital act except one per month at ovulation
- No IV drug use
- Man has been HIV-positive for at least one year
- Man has low viral load (< 200 copies/mL) and high CD4 count (> 250 cells/mL)
- Couple free of concomitant infections (BV, gonorrhea, chlamydia, syphilis, HPV, HBV, HCV)
- Normal vaginal examination monthly
- Male and Female genital tracts are free of lesions
- Man is circumcised
- Man is taking ART and woman is taking PrEP
- Fertility work-up to ensure potential for normal fertility

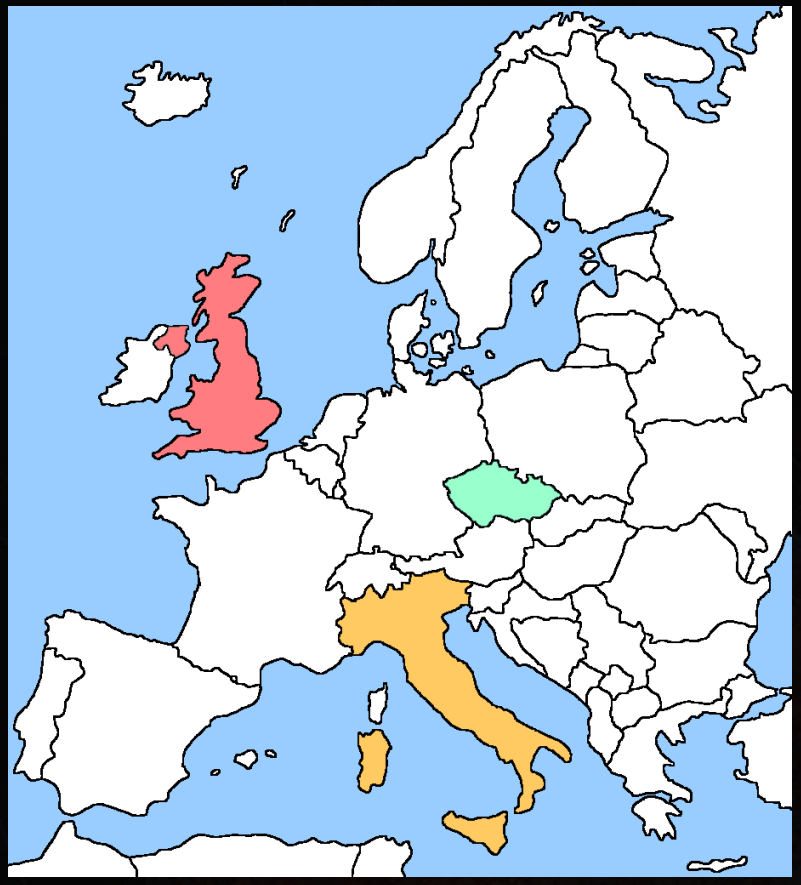
Currently 3 ongoing clinical trials in Europe to evaluate this treatment

Fertility Treatments for Serodiscordant Couples - HIV

One Well-Timed, Unprotected Intercourse

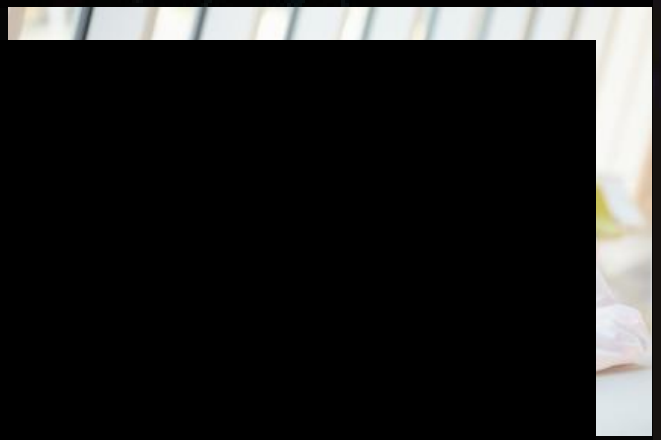
Currently 3 ongoing clinical trials in Europe to evaluate this treatment

- An ongoing Swiss trial, started in 2004, has had no seroconversion in 53 couples, and has had an overall pregnancy rate of 75% after 6 cycles[42]
- Preliminary data from a UK trial reports 13 couples with 11 pregnancies and no seroconversion[43]
- An Italian trial has been initiated[44]
- Treatment of HIV-discordant couples with PrEP and timed, unprotected intercourse remains experimental



42. Barreiro et al, 2007; 43. Whetham et al, 2014; 44. De Carli et al, 2014

Reducing the Risk of HIV Transmission While Using Intercourse to Establish a Pregnancy



- Male circumcision
- Manage man's HIV disease: reduction of the man's viral load with HAART and regular testing to confirm low viremia
- Pre-exposure prophylaxis (PrEP) for the woman
- Surveillance by monthly speculum exam for genital tract infections and inflammation, and testing for HBV, HCV, HTLV, HPV, trichomonas, chlamydia, gonorrhea, and syphilis
- Regular testing of the woman for HIV seroconversion

Infectious Disease
and the Infertility Patient

Other Viruses

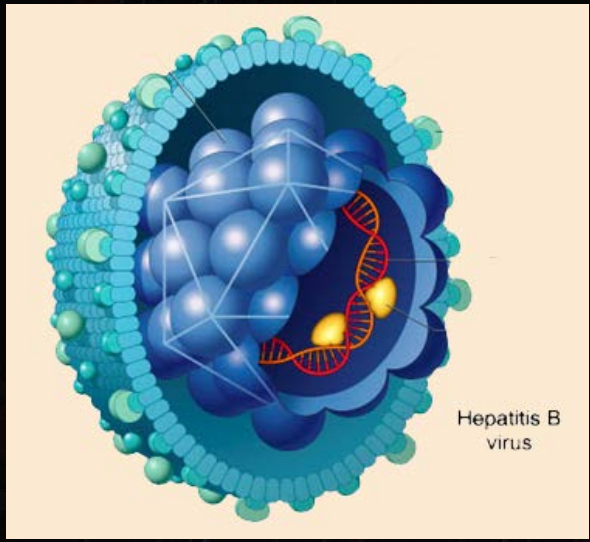
Hepatitis B: What is the Risk of Transmission by Needle Stick?

- If the source patient is known to be HIV-positive, the risk of infection of exposed employee is approximately 0.3%
- Prophylactic treatment with HAART reduces this risk
- Compare to the case in which the patient has hepatitis B: the risk of infection for non-vaccinated workers is approximately 30%
- The transmissibility of hepatitis B virus is very high

Fertility Treatments for Serodiscordant Couples

Hepatitis B Virus - Risks

- Approximately 25% after a single sexual contact of discordant couples results in seroconversion (*vs*. 0.1% for HIV)
- Risk to staff is much greater than for HIV
- Vaccination of the uninfected partner is effective

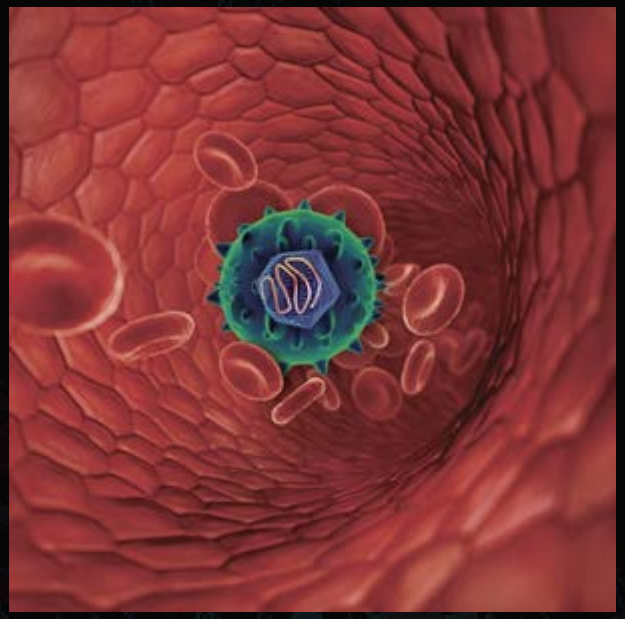


- Fertility treatments may be started once the vaccinated partner's anti-HBV surface antibody titer is positive
- If the female is the infected partner, newborn should receive immunoprophylaxis: HBV vaccine and immunoglobulin, with 2 vaccine boosters in the first 6 months
- Breastfeeding is not contraindicated

Fertility Treatments for Serodiscordant Couples

Hepatitis C Virus

- Infects nearly 5% of U.S. Population
- Small but measurable risk of sexual transmission via semen
- “Sperm washing” is effective at removing the virus because, like HIV, HCV is not associated with the sperm cell
- IVF/ICSI has also been shown to reduce the risk of transmission to the female

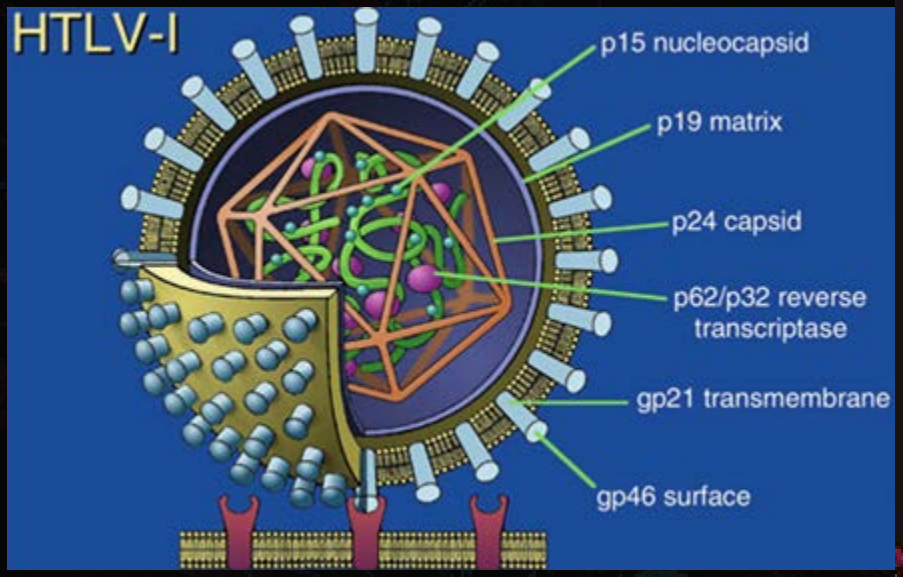


- Treatment with peginterferon alpha and ribavirin should be considered to reduce the viral load in the infected partner before fertility treatment
- Treatment for 48 weeks followed by 6 months post-therapy recommended before pregnancy is initiated because ribavirin is a category X medication
- Vertical transmission rate is low and breastfeeding is allowed

Fertility Treatments for Serodiscordant Couples

HTLV I & II (human T-lymphocyte virus)

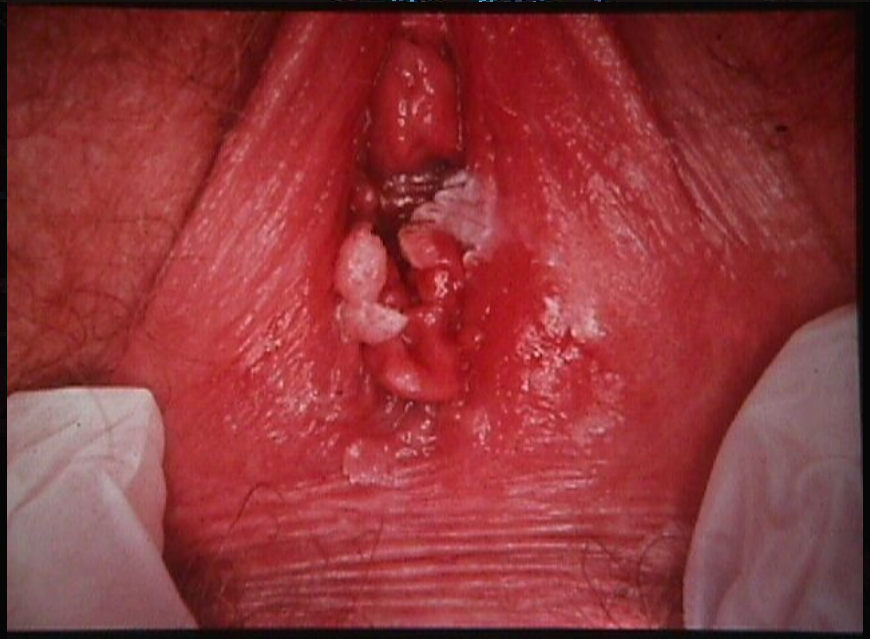
- HTLV-I Infects CD4 cells, causing adult T-cell leukemia (ATL) and HTLV-I associated myelopathy (HAM)
- HTLV-II infects CD8 cells, but does not cause disease
- Endemic rates in U.S. are very low (0.016%), primarily IV drug users



- "Sperm washing" is effective at removing the virus because, like HIV, HTLV is not associated with the sperm cell
- No treatments exist currently, but research into therapeutics and vaccines is ongoing. Experimental vaccines are effective in animal models.

Fertility Treatments for Serodiscordant Couples

HPV (human papilloma virus)



- Serodiscordancy is uncommon
- 50 genotypes that infect the genital tract; most do not cause disease
- About 50% of sexually active adults have been infected by one or more HPVs
- In semen, occurs as free virus or associated with epithelial cells
- Symptomatic HPV increases the susceptibility to infection by other viruses
- “Sperm washing” has limited effectiveness at removing the virus
- Vaccines are available for the HPVs causing disease symptoms
- Vertical transmission is common and occurs early in pregnancy as HPV can be detected in the placenta

Fertility Treatments for Serodiscordant Couples

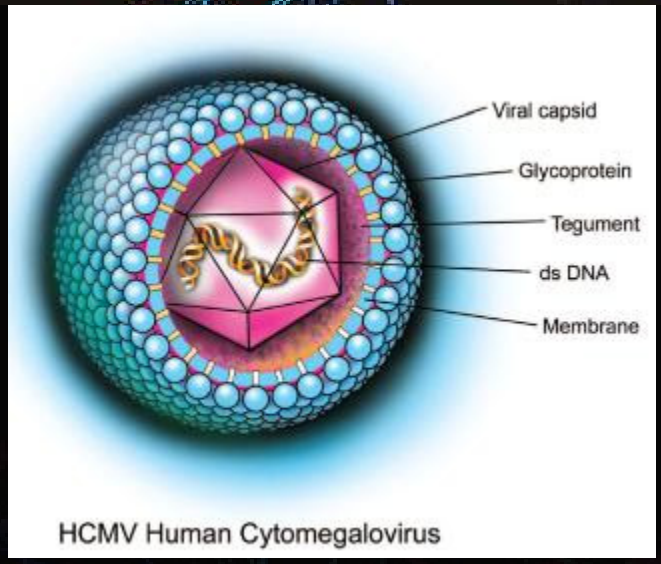
Genital Herpes – HSV-2 (herpes simplex-2)

- Endemic
- Can cause serious brain damage in the newborn
- Primary infection in early pregnancy can cause intrauterine infection of the fetus causing abortion, stillbirth and congenital anomalies
- Neonatal infection can cause death or brain damage with long-term disabilities
- 80-90% of newborn infections occur at birth, and transmission is highest if mother has primary infection in 3rd trimester
- Semen collection should be avoided when a lesion is present
- Treatment with antivirals (acyclovir or valacyclovir) to reduce viral load
  - Men can be treated to reduce HSV-2 shedding in semen
  - Women are treated during pregnancy to reduce vertical transmission, and can be delivered by C-section; Note: acyclovir is a pregnancy class B drug (no adverse effects in experimental animals; no good studies in women)
- "Sperm washing" may be effective because virus is not cell-associated

Fertility Treatments for Serodiscordant Couples

CMV

- Primary infection during early pregnancy causes infection in 3-5% of fetuses and can have serious complications, including neonatal death or long-term complications such as mental retardation, hearing loss, and blindness



HCMV Human Cytomegalovirus

- CMV is endemic and is the most significant cause of congenital viral infection in the U.S.; 9000 children per year are born with severe disabilities due to intrauterine infection
- No vaccine available, but vaccination is successful in experimental animals, and development of a human vaccine is ongoing
- “Sperm washing” may reduce the risk of CMV transmission

References

1. Wortley PM, Hammett TA, Fleming PL. Donor insemination and human immunodeficiency virus transmission. Obstet Gynecol 1998;91:515–518.
2. CDC. Epidemiologic notes and reports HIV-1 infection and artificial insemination with processed semen. MMWR 1990;39(15);249,255-256.
3. Semprini AE, Levi-Setti P, Bozzo M, Ravizza M, Taglioretti A, Sulpizio P, Albani E, Oneta M, Pardi E. Insemination of HIV negative women with processed semen of HIV-positive partners. Lancet 1992;340:1317–1319.
4. Loutify MR, Margolese S, Money DM, Gysler M, Hamilton S, Yudin MH. Canadian HIV pregnancy planning guidelines. J Obstet Gynaecol Can 2012;34:575-590.
5. Gilling-Smith, Nicopoullos, JDM, Semprini, AD, Frodsham, LCG. HIV and reproductive care-a review of current practice. Brit J of Gynecol. 2006;113(8):869-878.
6. Anderson RA, Brown D, Jackson EM, Feathergill KA, Bremer JW, Morack R, Rawlins RG. Feasibility of repurposing the polyanionic microbicide, PPCM, for prophylaxis against HIV transmission during ART. ISRN Obstet Gynecol 2011;2011:1-13.
7. Vitorino RL, Grinsztejn BG, Ferreira de Andrade CA, Hökerberg YHM, Vieira de Souza CT, Friedman RK, Passos SRL. Systematic review of the effectiveness and safety of assisted reproduction techniques in couples serodiscordant for human immunodeficiency virus where the man is positive. Fertil Steril 2011;95:1684–1690.
8. Quayle, AJ, Xu, C, Mayer, KH, Anderson, DJ. T lymphocytes and macrophages, but not motile spermatozoa, are a significant source of human immunodeficiency virus in semen. J Infect Dis 1997;176:960-968.
9. Quayle, AJ, Xu, C, Tucker, L, Anderson, DJ. The case against an association between HIV-1 and sperm: molecular evidence. J Reprod Immunol 1998;41: 127-136.
10. Kim, LU, Johnson, MR, Barton, S, Nelson, MR, Sontag, G, Smith, JR, Gotch FM, Gilmour JW. Evaluation of sperm-washing as a potential method of reducing HIV transmission in HIV-discordant couples wishing to have children. AIDS 1999;13:645–651.
11. Baccetti, B, Benedetto A, Burrini AG, Collodel G, Elia G, Piomboni P, Renieri T, Sensini C, Zaccarelli. M. HIV particles detected in spermatozoa of patients with AIDS. J. Submicr. Cytol Pathol. 1991;23:339-345.

References

12. Baccetti B, Benedetto A, Burrini AG, Collodel G, Ceccarini EC, Crisà N, Di Caro A, Estenoz M, Garbuglia AR, Massacesi A, Piomboni P, Renieri T, Solazzo D. HIV-particles in spermatozoa of patients with AIDS and their transfer into the oocyte. J Cell Biol 1994;27: 903-914.
13. Barboza JM, Medina H, Doria M, Rivero L, Hernandez L, Joshi NV. Use of atomic force microscopy to reveal sperm ultrastructure in HIV-patients on highly active antiretroviral therapy. Arch Androl 2004;50:121–129.
14. Bandivdekar AH, Velhal SM, Raghavan VP. Identification of CD4-independent HIV receptors on spermatozoa. AJRI 2003; 50:322–327
15. Fanibunda SE, Velhal SM, Raghavan VP, Bandivdekar AH. CD4 independent binding of HIV gp120 to mannose receptor on human spermatozoa. J Acquir Immune Defic Syndr 2008;48:389–397.
16. Ceballos A, Lenicov FR, Sabatté J, Rodrígues CR, Cabrini M, Jancic C, Raiden S, Donaldson M, Pasqualini RA, Marin-Briggiler C, Vazquez-Levin M, Capani F, Amigorena S, Geffner J. Spermatozoa capture HIV-1 through heparin sulfate and effi ciently transmit the virus to dendritic cells. J Exp Med 2009; 206:2717-2733.
17. Nicopoullos JDM, Almeida P, Vourliotis M, Goulding R, Gilling-Smith C. A decade of sperm washing: clinical correlates of successful insemination outcome. Hum Reprod 2010;25:1869–1876.
18. Muciaccia B, Corallini S, Vicini E, Padula F, Gandini L, Liuzzi G, Lenzi A, Stefanini M. HIV-1 viral DNA is present in ejaculated abnormal spermatozoa of seropositive subjects. Hum Reprod 2007;22:2868–2878.
19. Anderson DJ, Politch JA, Nadolskia AM, Blaskewicza CD, Pudneya J, Mayer KH. Targeting Trojan Horse leukocytes for HIV prevention. AIDS 2010;24:163–187.
20. CDC, Health Resources and Services Administration, NIH, American Academy of HIV Medicine, Association of Nurses in AIDS Care, International Association of Providers of AIDS Care, the National Minority AIDS Council, and Urban Coalition for HIV/AIDS Prevention Services. Recommendations for HIV Prevention with Adults and Adolescents with HIV in the United States, 2014. http://stacks.cdc.gov/view/cdc/26062. December 11, 2014.
21. Kushnir VA, Lewis W. Human immunodeficiency virus/acquired immunodeficiency syndrome and infertility: emerging problems in the era of highly active antiretrovirals. Fertil Steril 2011;96:546-553.
22. Sewankambo N. Gray RH. Wawer MJ. Paxton L. McNaim D. Wabwire-Mangen F. Serwadda D. Li C. Kiwanuka N. Hillier SL. Rabe L. Gaydos CA. Quinn TC. Konde-Lule J. HIV-1 infection associated with abnormal vaginal flora morphology and bacterial vaginosis. Lancet 1997;350:546 –550.

References

23. Mbulawa ZZA, Coetzee D, Marais, DJ, Kamupira M, Zwane E, Allan B, Constant D, Moodley JR, Hoffman M, Williamson A-L. Genital Human papillomavirus prevalence and human papillomavirus concordance in heterosexual couples are positively associated with human immunodeficiency virus coinfection. J Infec Dis 2009:199:1514-1524.
24. Politch JA, Mayer KH, Anderson DJ. Depletion of CD4RT cells in semen during HIV infection and their restoration following antiretroviral therapy. J Acquir Immune Defic Syndr 2009;50:283–289.
25. Savasi V, Parrilla B, Ratti M, Ferrazzi E. Reproductive assistance in HIV-1 discordant couples. Curr Opin Obstet Gynecol 2008;20:205–210.
26. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, Meehan O, Lutalo T, Gray RH, for the Rakai Project Study Group. Viral load and heterosexual transmission of human immunodefficiency virus type 1. N Engl J Med 2000; 342: 921–29.
27. Galvin SR, Cohen MS. The role of sexually transmitted diseases in HIV transmission. Nat Rev Microbiol 2004;2:33-42.
28. Foresta C, Pizzol D, Bertoldo A, Menegazzo M, Barzon L, Garolla A. Semen washing procedures do not eliminate human papilloma virus sperm infection in infertile patients. Fertil Steril Fertility & Sterility 2011; 96(5):1077-82.
29. Garrido N, Gil-Salom M, Martınez-Jabaloyas JM, Meseguer M. First report of the absence of viral load in testicular sperm samples obtained from men with hepatitis C and HIV after washing and their subsequent use. Fertil Steril 2009;92:1012-1014.
30. Persico T, Savasi V, Ferrazzi E, Oneta M, Semprini AE, Simoni G. Detection of human immunodeficiency virus-1 RNA and DNA by extractive and in situ PCR in unprocessed semen and seminal fractions isolated by semen-washing procedure. Hum Reprod 2006; 21:1525–1530.
31. Bujan L, Sergerie M, Kiffer N, Moinard N, Seguela G, Mercadier B, Rhone P, Pasquier P, Daudin M. Good efficiency of intrauterine insemination programme for serodiscordant couples with HIV-1 infected male partner: a retrospective comparative study. Eur J Obstet Gynecol Reprod Biol 2007; 135:76–82.
32. Ohl J, Partisani M, Wittemer C, Schmitt MP, Claudine C, Stoll-Keller F, Rongieres C, Bettahar-Lebugle K, Lang JM and Nisand I. Assisted reproduction techniques for HIV serodiscordant couples: 18 months of experience. Hum Reprod 2003;18:1244–1249.

References

33. Bujan L, Daudin M, Pasquier C. Choice of ART programme for serodiscordant couples with an HIV infected male partner Hum Reprod 2006;21(5): 1332-1333.
34. Bujan L, Gilling-Smith C, Hollander L, Venazza P. Lack of clinical and scientific evidence to justify the systematic use of ICSI in HIV-serodiscordant couples wishing to conceive where the male partner is infected. 2008;91:e1-e2.
35. Klein J, Pena JE, Thornton MH, Sauer MV. Understanding the motivations, concerns, and desires of human immunodeficiency virus 1-serodiscordant couples wishing to have children through assisted reproduction. Ostet Gynecol 2003;101:987–94.
36. Mandelbrot L, Heard I, Henrion-Geant E, Henrion R. Natural conception in HIV-negative women with HIV-infected partners. Lancet 1997;349:850–851.
37. Baeten JM et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med 2012;367:399-410.
38. Del Romero J, Castilla J, Hernando V, Rodríguez C, García S. Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross sectional and prospective cohort study. BMJ 2010;340:c2205-13.
39. de Vincenzi I. A longitudinal study of human immunodeficiency virus transmission by heterosexual partners. European Study Group on Heterosexual Transmission of HIV. N Engl J Med 1994;331(6):341-346.
40. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, Kiwanuka N, Kigozi G, Kiddugavu M, Lutalo T, Nalugoda F, Wabwire-Mange F, Meehan MP, Quinn TC. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. J Infect Dis 2005;191:1403-0409.
41. Barreiro P, Castilla JA, Labarga P, Soriano V. Is natural conception a valid option for HIV-serodiscordant couples? Hum Reprod 2007;22:2353-8.
42. Whetham J, Taylor S, Charlwood L, Keith T, Howell R, McInnes C, Payne E, Home J, White D, Gilleece Y. Pre-exposure prophylaxis for conception (PrEP-C) as a risk reduction strategy in HIV-positive men and HIV-negative women in the UK. AIDS Care 2014;26:332-6.
43. De Carli G, Palummieri A, Liuzzi G, Puro V. Safe conception for human immunodeficiency virus-discordant couples: the preexposure prophylaxis for conception alternative. Amer J Obstet Gynecol 2014;210:90.

That's All Folks!

Thank You....