

HIV: FERTILITY, SUB-FERTILITY, INFERTILITY

SA HIV Clinicians Society Conference **25-28 November 2012**

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Outline

1. Fertility: A critical question
2. Sub-fertility: impact of HIV infection and HAART
 - Female fertility
 - Male fertility
3. Infertility: role of infertility clinic
 - Failed 'home plan'
 - Sperm washing for HIV + men
 - Management of HIV positive infertile couples

HAART: antiretroviral therapy

ART: Assisted reproductive techniques (IUI/IVF/ICSI)

A Critical Question

Is this couple fertile?

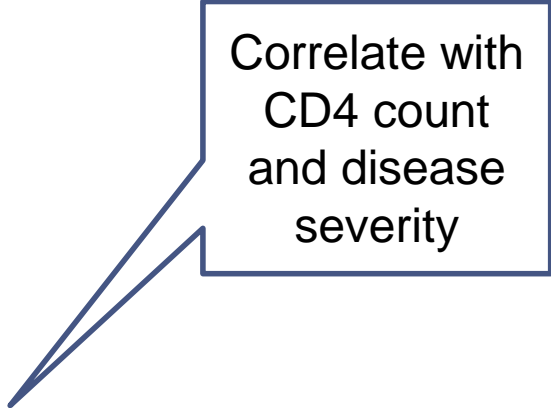
- **Compromised fertility**
 - History of PID, ectopic pregnancy, tubal surgery
 - Irregular menstruation
 - Clinical examination suggesting pathology
 - Infertility: failure to conceive after 1 year regular unprotected intercourse
- **Reasons for concern**
 - High background rate of infertility
 - Impact of HIV on fertility
 - Risks of unprotected intercourse without benefit

HIV and Fertility

HIV: Female fertility and fecundity

- Pelvic inflammatory disease
- Ovarian dysfunction
 - Ovulatory dysfunction
 - Secondary amenorrhea
 - Reduced ovarian reserve
- Coital frequency

- Pregnancy loss
- Neonatal / infant death



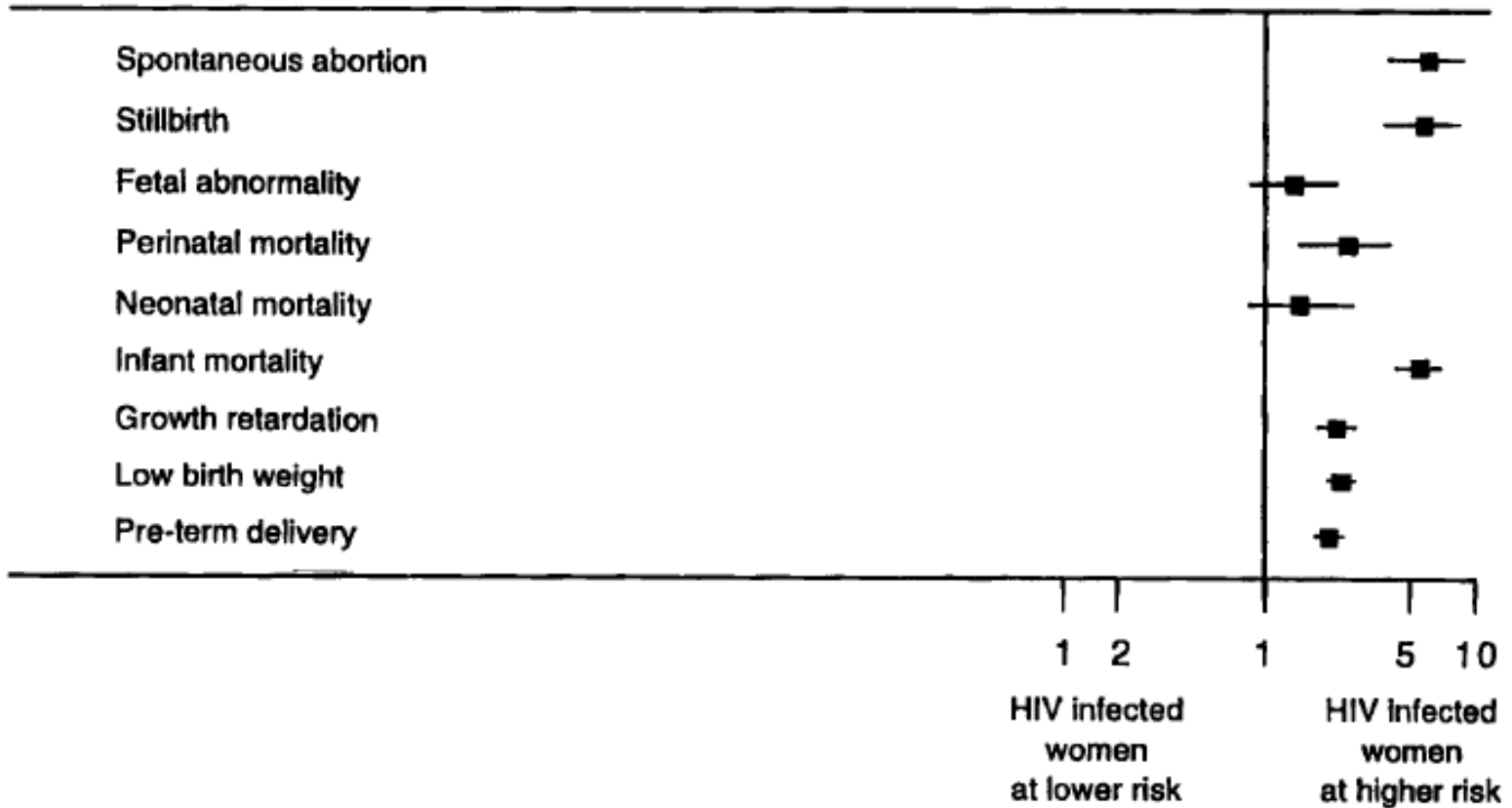
Correlate with
CD4 count
and disease
severity

Meta-analysis

31 Studies: 1983- 1996

HIV INFECTED WOMEN VERSUS HIV UNINFECTED WOMEN

**Peto Odds Ratio
(95%CI)**



HIV and male fertility

Correlate with CD4 count and disease severity

- Male hypogonadism: reduced testosterone
- Reduced libido, ejaculatory dysfunction
- Abnormal spermatogenesis

World J Urol (2012) 30:23–30

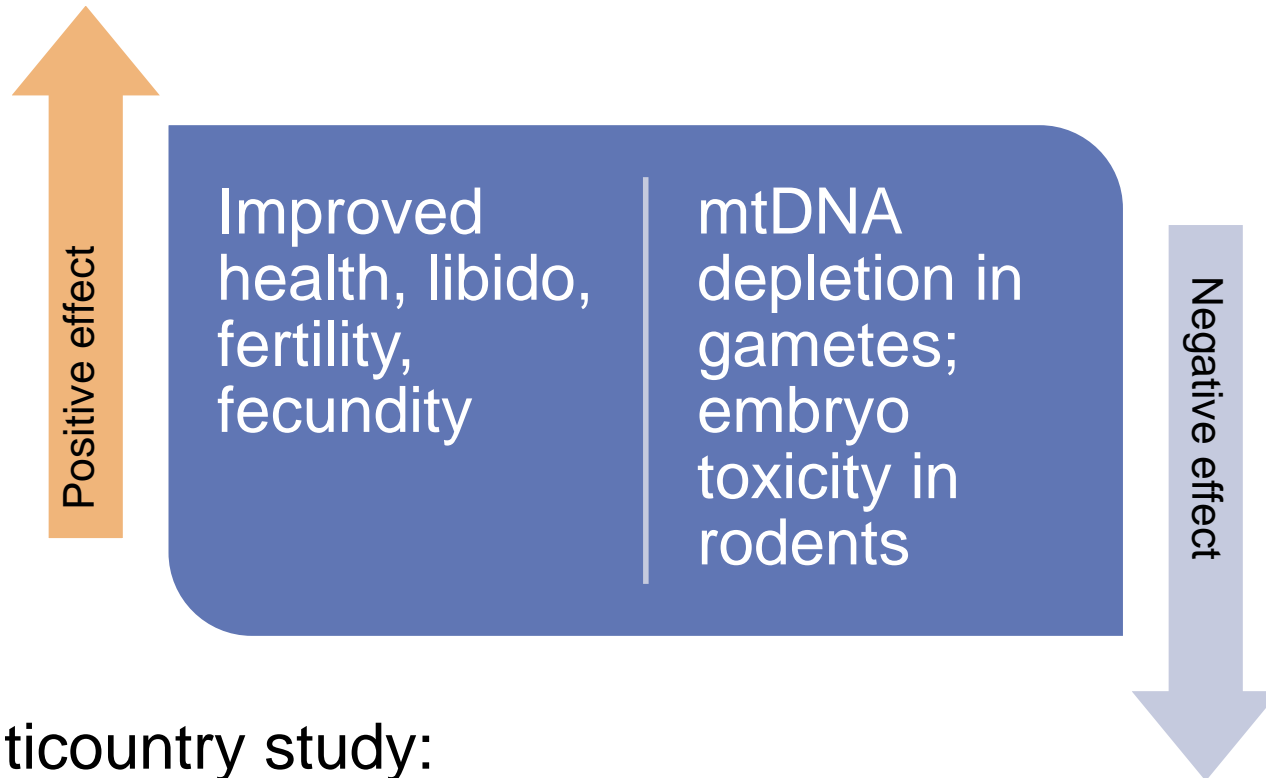
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Table 3 Published studies comparing semen parameters between HIV patients and controls

Study	HIV patients	ART (%)	Control	Group	Volume (ml)	Concentration	Motility	Morphology
Krieger [30]	21	50	40	Sperm donors	n.s.	n.s.	n.s.	n.s.
Crittenden [31]	39	48	51	Sperm donors, hemophiliacs	n.s.	n.s.	Reduced	Not done
Dondero [35]	21	76	30	Donors, healthy men	n.s.	Reduced	Reduced	Reduced
Dulioist [33]	189	95	79	PWTI	Reduced	n.s.	Reduced	n.s.
Diehl [32]	31	77	7	Healthy men	Not done	n.s.	n.s.	Not done
Nicopoulos [29]	106	55	234	PWTI	Reduced	Reduced	Reduced	Reduced
Cardona-Maya [39]	16	0	16	No data	n.s.	n.s.	Reduced	Reduced
Pavili [36]	31	100	31	Healthy men	n.s.	Not done	Reduced	Reduced

PWTI partner of women with tubal infertility, *ART* antiretroviral therapy, *n.s.* no significant changes between HIV group and control group

HAART and Fertility



Multicountry study:

- 4531 HIV + women in sub-Saharan Africa
- HAART: Pregnancy Hazard ratio 1.74 (1.19-2.54)
- Behavioural and biomedical factors

Fertility assessment of HIV + couples

Cross-sectional study, 1998 – 2005, Spain

- 130 HIV+ women; 121 male partners (38 HIV+)
- HAART: 74% women, 84% men
- No history of infertility
- Pre-conception infertility investigations
 - High rate of HSG pathology (15.2%)
 - Abnormal semen analysis: 83.4% vs 41.7%

Role of the Infertility Unit

- Failed “home plan”
- Sero-discordant couple, HIV + male
- HIV + infertile couple

Initial evaluation

- CD4 count and viral load
- Screening for
 - Haemoglobin or full blood count
 - HIV test partner
 - Rubella, syphilis, cervical dysplasia
 - In resource-rich environments:
 - Hep A/B/C, CMV, Herpes simplex, toxoplasma
 - Genital secretions: gonorrhoea, chlamydia, trichomonas, bacterial vaginosis
- Routine infertility investigations:
Semen analysis, “D 21” progesterone, hysterosalpingography

Infertility Management

- Subject to underlying pathology
- Couple fully counselled
- No STDs or significant co-morbidity
- Adequate social circumstances
- Stable CD4, low viral load
- HAART: access, teratogenicity
- Appropriate facilities
 - Trained staff – multi-disciplinary team
 - Dedicated laboratory

Informed consent : risk reduction not risk free

Ethical Considerations

- HIV positive, infertile couple:
 - Physician has responsibility towards offspring
 - Withholding of treatment justified *if* reproduction considered to cause serious harm
- HIV positive, non-infertile couple
 - Able to procreate
 - Physician's role: Risk reduction only, moral obligation
 - No responsibility for adverse pregnancy outcome
 - Withholding of assistance unethical

*Pennings, J Med Ethics 2003, 29:321;
Shenfield, Hum Reprod 2004, 19:2454*

Sero-discordant couple, man HIV+

- Sperm detoxification procedure
 - Separate semen from sperm
- Assess viral load in aliquot of post-wash sperm (~100µl) : < 25 copies/ 10⁶ sperm
- Intra-uterine insemination
- Intra-cytoplasmic sperm injection (ICSI)

Intracytoplasmic sperm injection (ICSI)

Indication

- 2nd line treatment
- Infertility management
- Controversial: 1st line treatment
 - Spermatozoa appear to be free of HIV-1
 - Increased safety? : reduced exposure to sperm
 - Increased risk ? : accidental injection of free viral particle into oocyte
 - More expensive and invasive than IUI

Effectiveness and safety of ART

- Systematic review
- HIV sero-discordant couples, HIV + male
- With/ without infertility factors
- 17 publications
- 3900 IUI cycles
 - Median pregnancy rate per cycle: 18.1%
 - Median miscarriage rate: 15.6%
 - Cancellation rate: 5-9%

Median
PR
38.1%

IVF/ICSI 748 cycles	Cycles	PR/cycle %	Misc. Rate %	Seroconversion
Veiga, 1999	16	26.6	0	No
Marina, 2002	58	49.7	18.5	No
Sauer, 2002	55	45.4	20.6	No
Pena, 2003	113	38.1	25.7	No
Garrido, 2004	-	40.1	-	No
Chu, 2005	146	34.6	-	No
Chu, 2006	-	47.0	-	No
Manigart, 2006	62	17.7	33.3	No
Savasi, 2007	288	23.0	-	No

Reproductive Medicine Unit, GSH

2010-2012

IUI HIV pos women: n=16		
No. inseminations	31	
No. pregnancies	4	Incl. 1 miscarriage
Pregnancy rate	12.9% per insemination	25% per patient

IVF/ICSI HIV pos men: n=13		
No. ICSI cycles	18	All virus free
No. embryo transfers	16	
No. pregnancies	3	
Pregnancy rate	18.7% per ET	23% per patient

Summary

- Critical question
- Risk of sub-fertility in HIV infected individuals
- HAART: many benefits, some adverse effects

- Collaboration between HIV physicians and infertility specialists
- Barriers
 - Access to care
 - Additional laboratory requirements
 - Cost