



Department of Urology, Pediatric Urology and Andrology



Virus infections and male infertility

HIV, hepatitis C, papillomavirus, Mumps

Adrian Pilatz

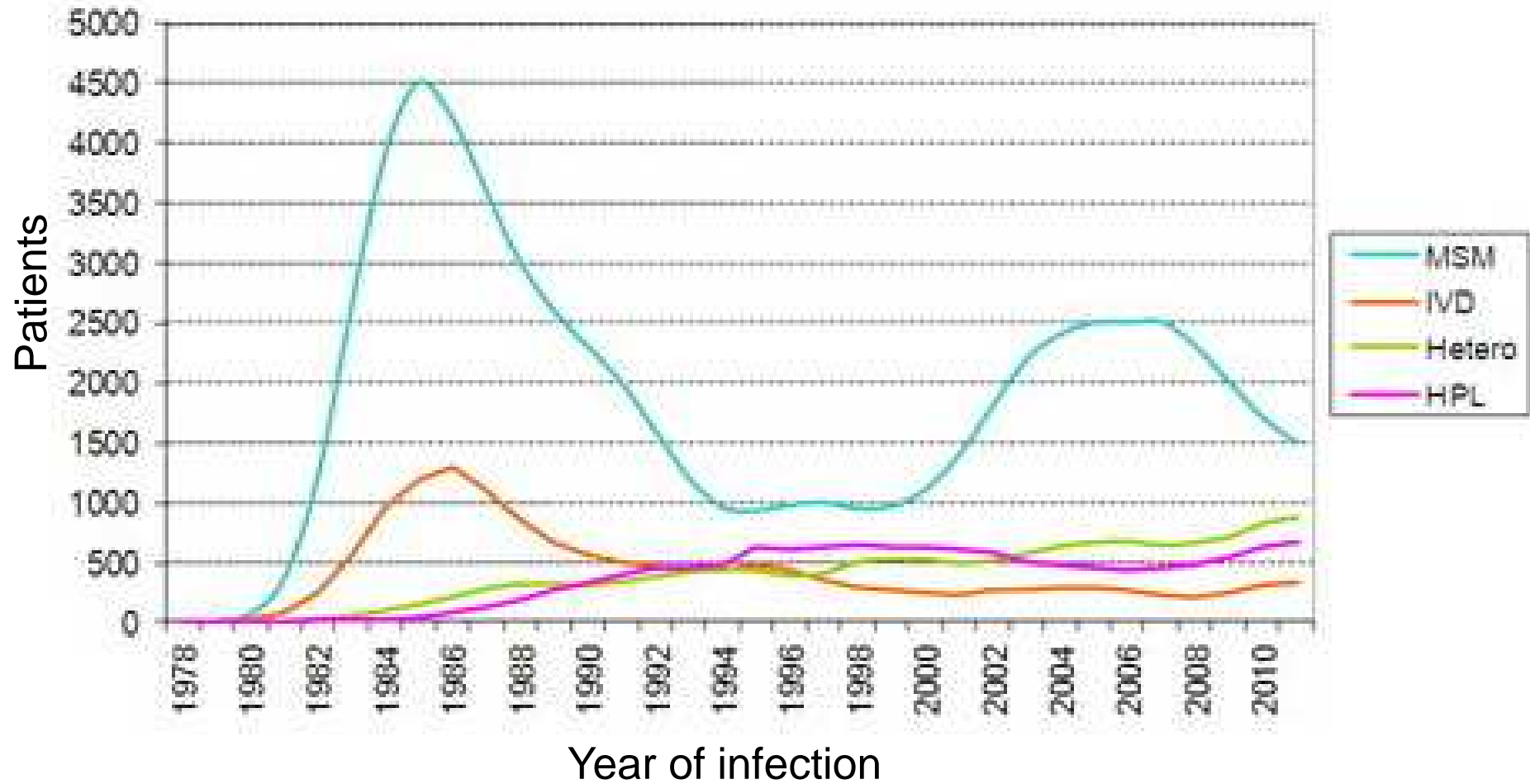
Department of Urology, Pediatric Urology and Andrology
Justus-Liebig-University Giessen, Germany
(Chairman: Prof. Dr. med. W. Weidner)

HIV

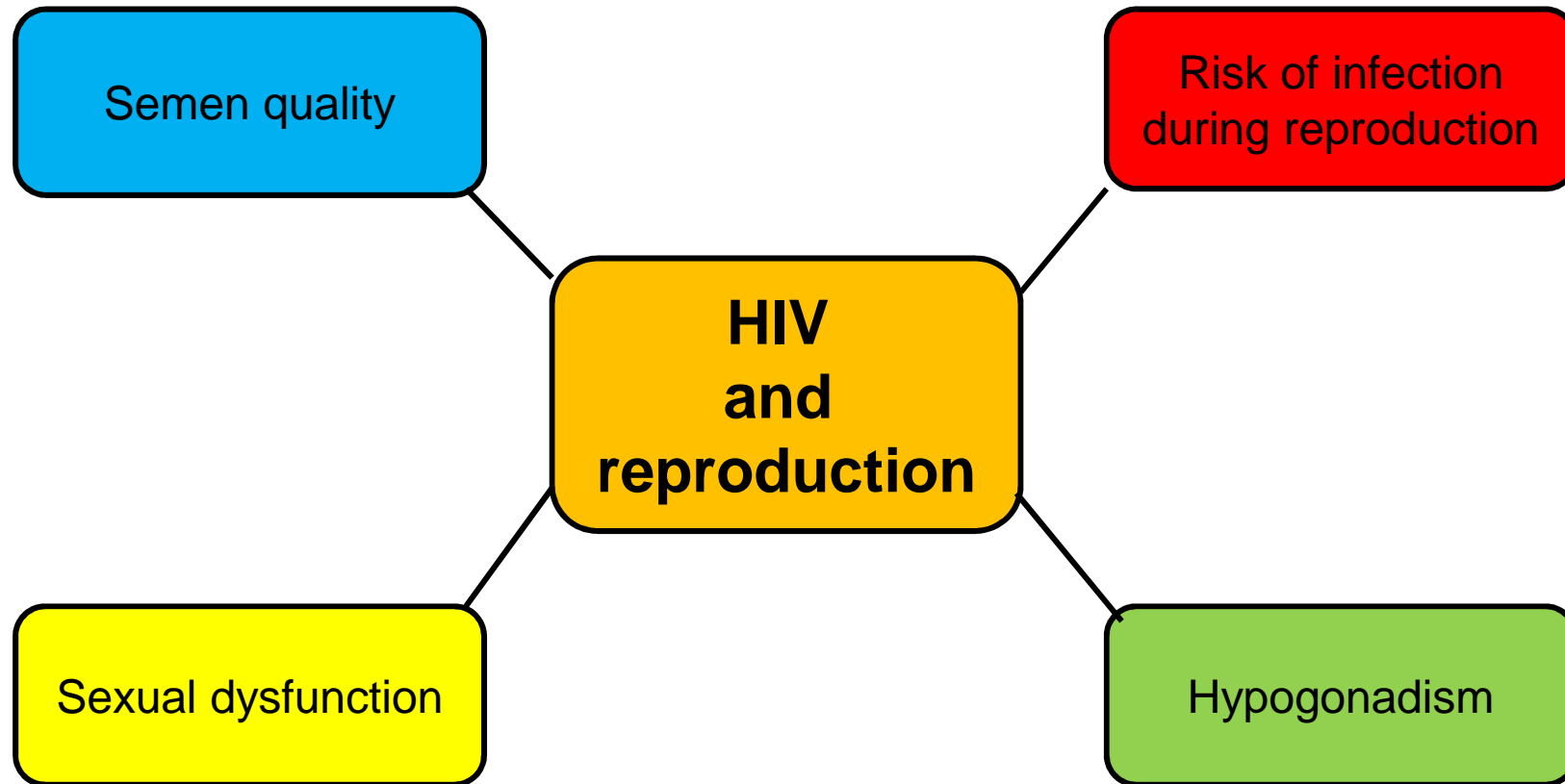
HIV in Germany

- Worldwide 34 Mio. infected with HIV
- Majority of newly infected men is heterosexual
- HIV infections in Germany: - 63.000 men
- 15.000 women
- Estimated new diagnoses of HIV 2012:
 - 3400 men: - thereof 2500 MSM,
- thereof 900 late presenters
 - 400 women
- Under antiretroviral therapy: 52.000 men and women
- Therapy costs ART 10.000 - 15.000 € per year and person

HIV incidence in Germany in different risk groups



HIV and male fertility



HIV and hypogonadism

- Prevalence between 3 and 20% of patients

(Crum-Cianflone et al., AIDS Patient Care STDS, 2007
Collazos et al., J Int Assoc Physicians AIDS Care, 2009
Moreno-Pérez et al., J Sex Med, 2010)

- **Cave:** Increased levels of SHBG result in high total testosterone

- Association between testosterone, patients age and duration of HIV infection (Moreno-Pérez et al., J Sex Med, 2010)

- Opioid intake: risk factor for hypogonadism

(Collazos et al., J Int Assoc Physicians AIDS Care, 2009)

- Hypogonadism associated with lipodystrophy

(Montano et al., Clin Endocrinol Metab. 2007)

HIV and sexual dysfunction

- Erectile dysfunction associated with: - BMI (Guaraldi et al., Antivir Ther, 2007)
 - Age, depression, duration of ART (Asboe et al., AIDS Care. 2007)
- Sexual life associated with general health status (Guaraldi et al., Antivir Ther, 2007)
- Antiretroviral therapy without an impact (Guaraldi et al., Antivir Ther, 2007)
- Sexual dysfunction associated with: - regular drug consumption
 - unemployment(Lau et al., J Sex Med, 2008)

HIV and semen quality

- Advanced disease (AIDS):
 - impaired spermatogenesis with changes in testicular morphology
 - increase in immature sperm cells (Dondero et al., Hum Reprod, 1996)
 - testicular atrophy (Krieger et al., J Infect Dis, 1991)
- Type of antiretroviral therapy: probably no negative impact
(Robbins et al., J Infect Dis, 2001, van Leeuwen E et al., AIDS, 2008)
- Sperm quality is stable in HIV infected patients without antiretroviral therapy during 12 months (van Leeuwen E et al., Fertil Steril, 2008)

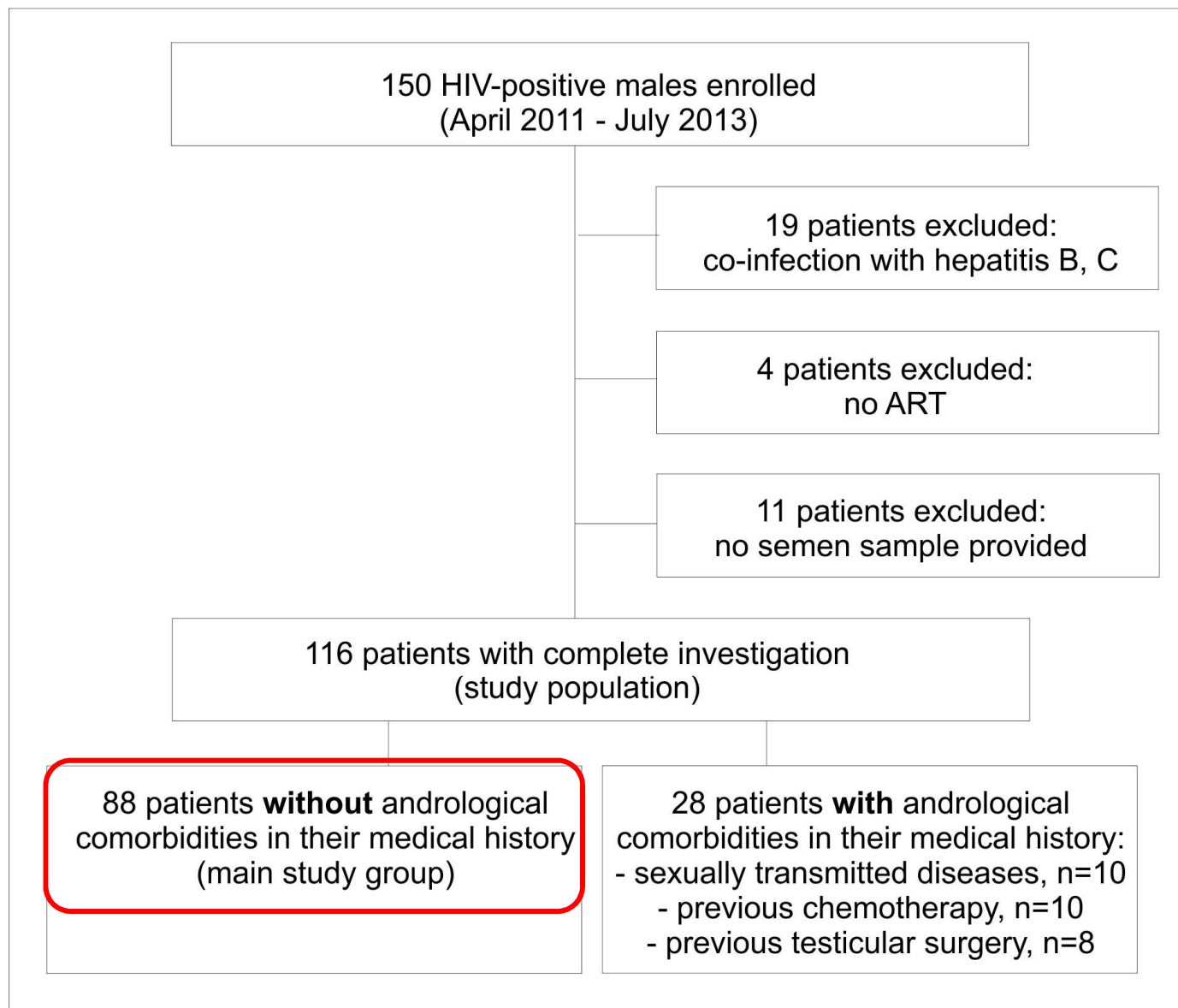
Summary of studies investigating sperm quality in HIV-positive patients

Study	Patients	ART(%)	Control group	Volume (ml)	Concentration	Motility	Morphology
Krieger, 1991	21	50	40 sperm donors	n.s.	n.s.	n.s.	n.s.
Crittenden, 1992	39	48	51 sperm donors, hemophiliacs	n.s.	n.s.	reduced	not done
Dondero, 1996	21	76	30 donors, healthy men	n.s.	reduced	reduced	reduced
Muller, 1998	250	35	38 proven fertile	reduced	reduced	reduced	reduced
Duloust, 2002	189	95	79 PWTI	reduced	n.s.	reduced	n.s.
Diehl, 2003	31	77	7 healthy men	not done	n.s.	n.s.	not done
Nicopoulos, 2004	106	55	234 PWTI	reduced	reduced	reduced	reduced
Garrido, 2004	73	70	73 PWTI	n.s.	n.s.	n.s.	not done
Bujan, 2007	190	91	218 proven fertile	reduced	n.s.	reduced	n.s.
Cardona-Maya, 2009	16	0	16 no data	n.s.	n.s.	reduced	reduced
Pavili, 2010	31	100	31 healthy men	n.s.	not done	reduced	reduced

PWTI, partner of women with tubal infertility

→ Studies largely heterogeneous (ART, controls)

HIV and semen quality



HIV and semen quality

Parameter	Patients without comorbidities (n=88)	WHO 2010 reference values	Patients (%) outside WHO reference
Volume (ml)	2.4 (0.2-6)	1.5 ^a	19 (21.6)
pH value	8 (7.1-9.3)	≥7.2 ^b	1 (1)
Sperm concentration (10 ⁶ /ml)	42.4 (0-425)	15 ^a	19 (21.8)
Total sperm count (10 ⁶)	75.2 (0-1487.5)	39 ^a	23 (26.4)
Progressive motility (%)	41 (0-69)	32 ^a	25 (29.4)
Sperm vitality (%)	76 (12-94)	58 ^a	5 (6)
Normal morphology (%)	4 (0-14)	4 ^a	40 (47.6)
Alpha-glucosidase (mU/ejaculate)	43.6 (7-165)	≥20/ejaculate ^b	11 (14.5)
Fructose (μmol/ejaculate)	18.5 (0.02-88.56)	≥13/ejaculate ^b	31 (35.9)
Zinc (μmol/ejaculate)	6.5 (0.42-37.24)	≥2.4/ejaculate ^b	14 (18.9)
Peroxidase-pos. leukocytes (10 ⁶ /ml)	0.1 (0-15.7)	<1 ^b	15 (17)
Elastase (ng/ml)	84 (10-2500)	<250 ^c	25 (32.5)

^abased on lower 5th percentiles,

^bconsensus parameters

^clocal lab criteria

Correlation between semen parameters and markers of HIV disease

	CD4 cell count (n=88)	CDC Status (n=88)		Duration of disease (n=88)	Duration of ART (n=88)	Positive viral load ^a (n=88)	Number of drugs in ART (n=88)	Seminal penetration score of antiretroviral drugs (n=88) ^b	Nadir CD4 cells (n=68)	Maximal viral load (n=59)
		ABC	123							
Volume (ml)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
pH value	NS	NS	r=0.239, p=0.026	NS	NS	NS	NS	NS	NS	NS
Sperm concentration (10 ⁶ /ml)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Total sperm count (10 ⁶)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Progressive motility (%)	NS	NS	NS	NS	NS	NS	NS	NS	r=-0.291, p=0.019	r=0.502, p<0.001
Sperm vitality (%)	NS	NS	NS	NS	r=-0.228, p=0.037	NS	NS	NS	NS	r=0.364, p=0.006
Normal morphology (%)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Alpha-glucosidase (mU/ejaculate)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Fructose (μmol/ejaculate)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Zinc (μmol/ejaculate)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Peroxidase+ leukocytes (10 ⁶ /ml)	NS	NS	NS	NS	r=0.228, p=0.033	NS	NS	NS	NS	NS
Elastase (ng/ml)	NS	r=0.239, p=0.038	NS	NS	NS	NS	NS	NS	NS	NS

NS not significant

^aMann-Whitney U test

^bscore calculated according to Lambert-Niclot 2011

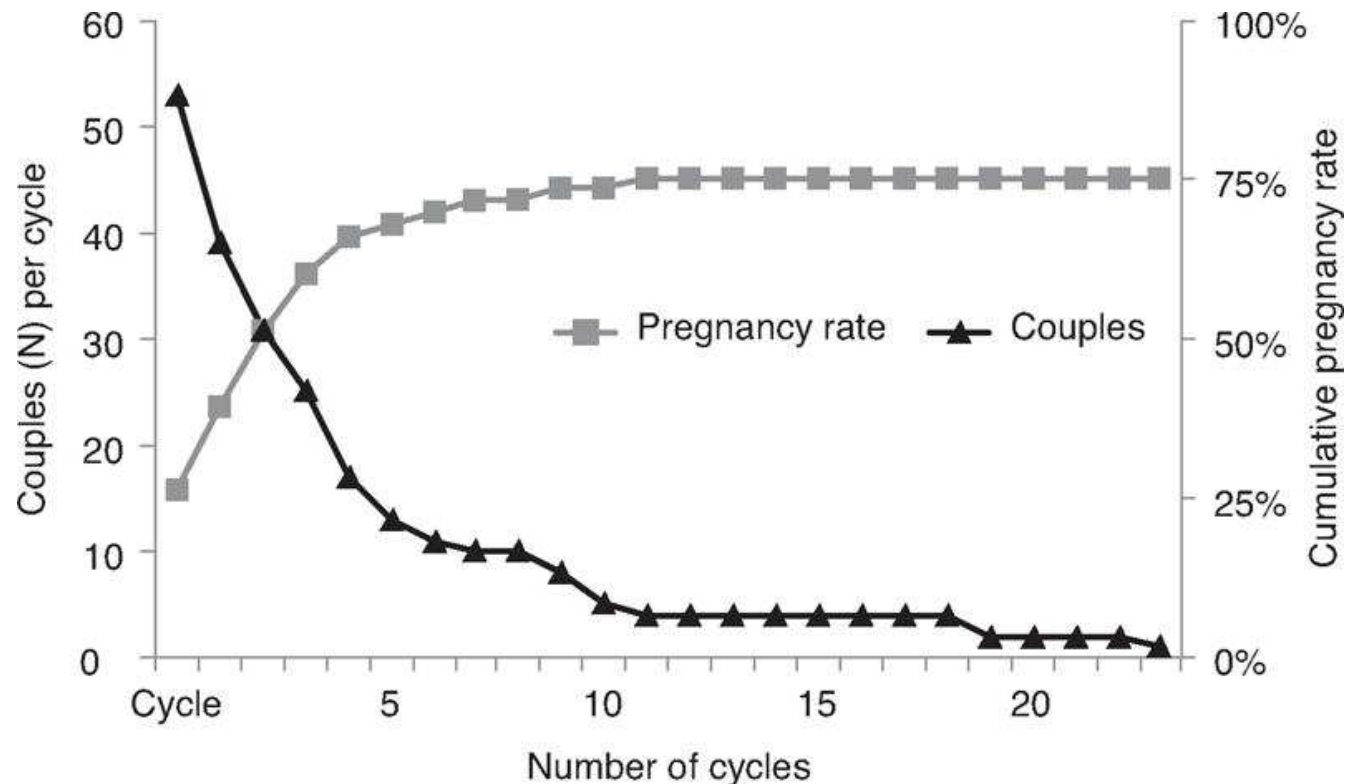
→ HIV surrogate parameters are not suitable for predicting semen quality

Risk of infection during reproduction

- Viral load in blood correlates with viral load in semen
- Assisted reproduction is secure using density gradient techniques and swim-up methods (Vitorino et al., Fertil Steril, 2011)
- [Swiss commission on AIDS questions \(EKAF\)](#):
 - HIV-infected patient is sexually not infective, if:
 - 1) Patient is under stable ART
 - 2) Patient has >6 months HIV viral load in blood below detection
 - 3) Patient has no further STIs

Natural reproduction in serodiscordant couples

- 46 serodiscordant couples (males HIV+, females HIV-)
- Preexposure prophylaxis with tenofovir and timed intercourse



→ Safe and high pregnancy rates

Hepatitis C

Hepatitis C - Facts and figures in Germany

- Prevalence: 0.4% = about 500.000 in Germany
- In 2010 n=5283 new HCV diagnoses
 - 2/3 males, 1/3 females
- Transmission route
 - 34% sexual contacts
 - 33% i.v. drug consumption
 - 22% surgery, invasive diagnostics
 - 12% tattoo
 - 12% blood products
 - 10% infections abroad

Hepatitis C und semen quality

- Impaired semen parameters in HCV patients

	HCV (27)	HIV (34)	HCV-HIV (41)	CONTROLS (130)
Volume (ml)	3 (2.2–3.2)	2.5 (2.1–2.9)	3 (2.6–3.2)	3 (2.5–2.9)
Sperm concentration × 10 ⁶	9.3 ^b (9.2–17.4)	24.7 (24.3–34.1)	22.3 (21.6–28.4)	27.1 (29.3–33)
Motility (a + b)	44.3 ± 22.2 ^a	48 ± 19.3	46.4 ± 20.3 ^a	57.3 ± 13.6
Viability (%)	70 ^b (59.6–70)	80 (75.1–82)	75 ^c (69.6–79.3)	80 (77.3–79.5)
Normal morphology (%)	25 ^a (26–33)	32 (30–36.3)	31 (29.2–33.7)	32.5 (32.7–35)
Sperm concentration × 10 ⁶ after treatment	1.5 ^b (1.3–2.2)	3.6 ^b (3.7–5.6)	3 ^b (2.8–4.1)	6.9 (6.7–7.5)
Progressive motility after treatment	80 (77–81)	80 (70–81)	80 (70–80)	80 (79–81)

². ^a*P* < 0.05; ^b*P* < 0.001; ^c*P* < 0.01.

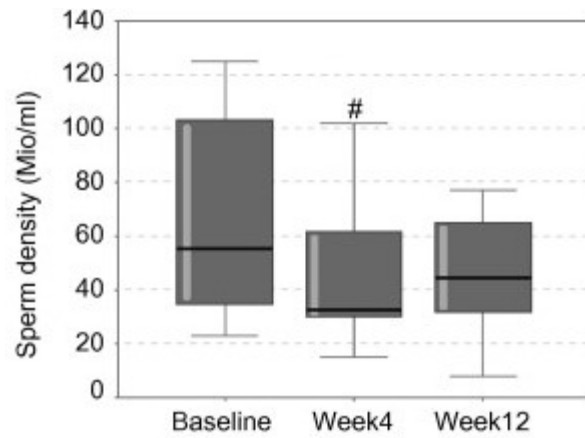
- **Cave:** - 90% of HIV infected patients under ART
 - HCV patients last 12 month no antiviral therapy
 - comorbidities not considered (i.v. drug consumption)

Hepatitis C - Therapy

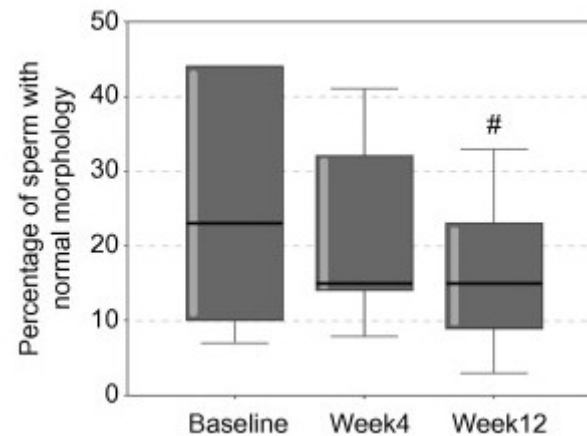
- Standard: Ribavirin plus interferon
 - Ribavirin in animals: - enrichment in semen (Hofer et al., J Hepatol, 2010)
 - teratogenic (Kochar et al., Toxicol Appl Pharmacol, 1980)
 - impairs sperm morphology
- **Contraception** during therapy and for a further of 6 months after treatment
- Since 2014 therapy without IFN/ribavirin:
 - Sofosbuvir (RNA polymerase inhibitor) plus simeprevir (protease inhibitor)
 - Sofosbuvir plus daclatasavir (Non-Structural Protein 5 inhibitor)
- Effective in up to 90% of patients to eradicate the virus

Impact of ribavirin on sperm quality

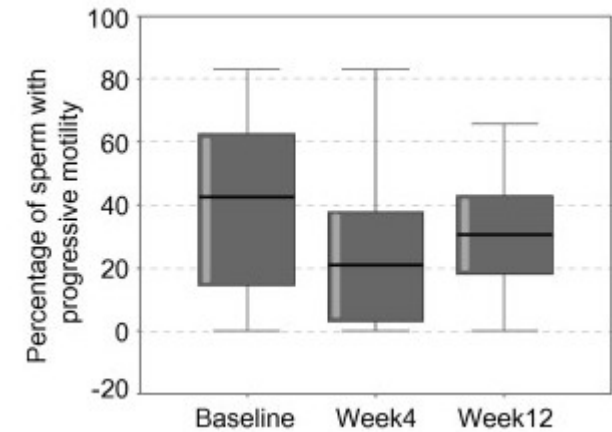
- 15 patients with hepatitis C before and under therapy with ribavirin



Concentration



Morphology



Motility

→ Impairment of sperm parameters during therapy with ribavirin

Impact of HCV on assisted reproduction outcome

- No negative impact of HCV on pregnancy rate achieved by IVF/ICSI

	HIV-female SDC [CG]	HIV-male SDC [CG]	HCV-female SDC [CG]	HCV-male SDC [CG]
Number of couples	52 [82]	28 [41]	22 [42]	28 [46]
Mean female age (years)	34.7 ± 4.9 [34.7 ± 4.8]	35.3 ± 4.3 [35.5 ± 4.4]	37.7 ± 3.9 [37.7 ± 3.9]	37.6 ± 3.1 [37.5 ± 3.0]
Trial rank	1.6 ± 0.9 [1.6 ± 0.8]	1.5 ± 0.7 [1.6 ± 0.8]	2.0 ± 1.0 [1.8 ± 0.8]	1.7 ± 0.9 [1.7 ± 0.9]
Infertility etiology %				
– Female pathology	59.6 [67]	21.4 [19.5]	50 [62]	35.7 [39.2]
– Male factor	40.4 [33]	78.6 [80.5]	50 [38]	64.3 [60.8]
Number of OR	94 [94]	44 [44]	45 [45]	49 [49]
Number of transfer (ET)	85 [88]	36 [36]	37 [42]	40 [41]
Mature oocytes/OR	6.4 ± 4.5 [7.3 ± 5.4]	7.3 ± 6.4 [7.4 ± 5.9]	5.6 ± 4.9 [6.0 ± 4.4]	7.5 ± 5.3 [4.8 ± 3.7] ^e
Fertilization rate %	68.2 [75.6] ^a	60.8 [71.8] ^b	71.1 [70.2]	54.7 [68.2] ^f
Cleavage rate %	69.75 [73.1]	62.6 [75.1] ^c	75.3 [63.6] ^d	54.45 [65.7] ^g
Transferred embryo/ET	1.96 ± 0.5 [1.94 ± 0.5]	2.08 ± 0.44 [1.92 ± 0.43]	2.14 ± 0.63 [1.87 ± 0.61]	1.95 ± 0.5 [1.67 ± 0.61]
Implantation rates %	10.8 [7.1]	10.7 [7]	5.1 [3.6]	12.8 [4.2]
Clinical pregnancies/OR %	15.96 [10.5]	18.2 [9.1]	8.9 [11.1]	14.3 [6.1]
Clinical pregnancies/ET %	17.65 [11.5]	22.2 [10.8]	10.8 [12.8]	17.5 [7.0]
Children born	14 [12]	6 [4]	2 [4]	8 [2]

Data for seronegative controls groups (CG) are in [].
 ET = embryo transfer; OR = oocytes retrieval; SDC = serodiscordant couples.

Mumps virus

Mumps orchitis – Historical data

Epidemiology

- Already described by Hippocrates
- Incidence of orchitis in Mumps is 18% (1468/8153)

Clinical presentation

- Mostly 4-5 days after parotitis
- Cases with orchitis preceding parotitis (n=30)
- Cases with isolated orchitis without parotitis (n=64)
- Epididymis may become involved before or after the testicle
- Bilateral orchitis 17% of cases (209/1208), 4-9 days lagged

Fertility

- Testicular atrophy in 55% (190/347, **Cave:** definition & timepoint)

Mumps orchitis – Current situation

Epidemiology

- Studies on smaller outbreaks
- Mumps orchitis possible after vaccination, but milder symptoms

(Tae et al., 2012)

Laboratory findings

- Moderate increase of CRP and α -Amylase (Gazibera et al., 2012, Tae et al., 2012)

Diagnostic issues

- Sensitivity of serology low (24-51%), specificity 82% (Krause et al., 2007)

→ Aim: PCR analysis

- Detection rate in saliva >85%, urine: 30% (Krause et al., 2007, Tan et al., 2012)
- Problem: with duration of disease detection rate decreases
- Exclude uropathogens & STIs

Mumps orchitis – Therapy

Natural course

- Self-limiting within 5-10 days

Supportive therapy

- Best rest
- Local cooling/warming
- NSAIDs

Specific therapy

- No standard
- Experimental: Interferon- α 2A/B (Yapanoglu et al., 2010, Yeniyol et al., 2000)

Mumps orchitis – fertility aspects

- Testicular atrophy (volume & histology) about 25%
(Bartak et al., 1973, Ternavasio-de la Vega et al., 2010)
- Increased FSH (Gazibera et al., 2012)
- No correlation between CRP values and semen parameters
(Gazibera et al., 2012)
- Bilateral Orchitis: ca. 60% Azoospermie (Gazibera et al., 2012)

Side	Azoospermia	Oligozoospermia	Normozoospermia
Unilateral, n (%)	5 (13%)	27 (69%)	7 (18%)
Bilateral, n (%)	9 (60%)	3 (20%)	3 (20%)

Team in Giessen

Dept. Urology & Andrology

F. Wagenlehner

H-C. Schuppe

J. Wolf

A. Paradowska-Dogan

W. Weidner

Dept. of Anatomy and Cell Biology

T. Lang

S. Bhushan

M. Fijak

M. Walecki

A. Meinhardt

Institute of Laboratory Medicine

C. Hudemann

H. Renz

Department of Urology, Protestant Hospital

D. Schultheiss

Institute of Medical Microbiology

H. Hossain

E. Domann

T. Chakraborty

Institute of Veterinary Anatomy

M. Bergmann

Institute for Medical Virology

C. Schüttler

Dept. of Anatomy and Cell Biology II

S. Karnati

E. Baumgart-Vogt

Institute of Biochemistry

G. Lochnit