

# European Register of ART for HIV patients: “CREAThE”

**Augusto Enrico Semprini MD**

President CREAThE

&

**Lital Hollander, MSc**

Esman Medical Consulting

[semprini@esman.it](mailto:semprini@esman.it)

# Lecture objectives

- To introduce CREAThE and the centres operating in the field of ART to couples with HIV
- To review the available evidence on safety and efficacy of assisted conception in HIV discordant couples
- To present the opportunities offered by proactive prospective follow up of couples (the Register)
- To explain the objectives of a European register on couples with HIV accessing ART

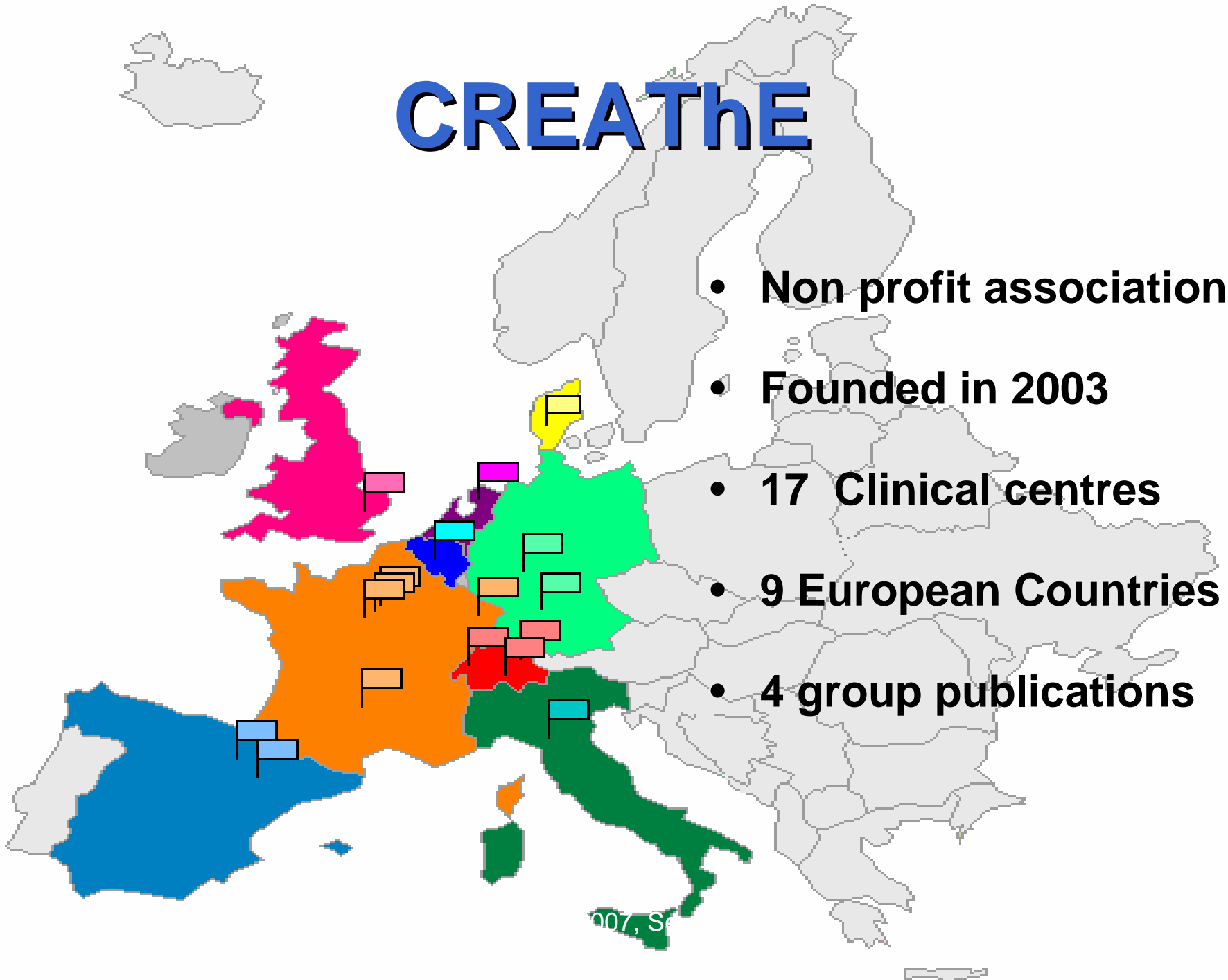


# CREAThE

**CENTRES FOR REPRODUCTIVE  
ASSISTANCE TECHNIQUES IN  
hiv-INFECTED INDIVIDUALS IN  
EUROPE**

# CREAThE

- Non profit association
- Founded in 2003
- 17 Clinical centres
- 9 European Countries
- 4 group publications

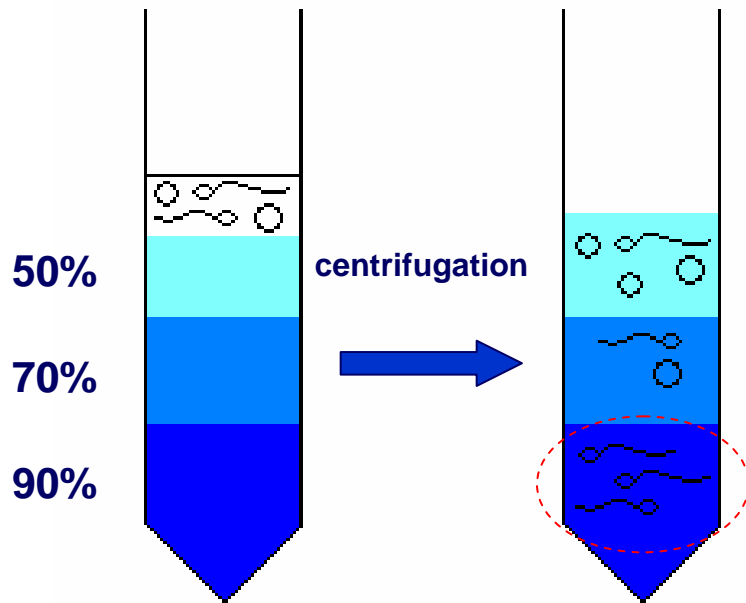


# Specific Objectives

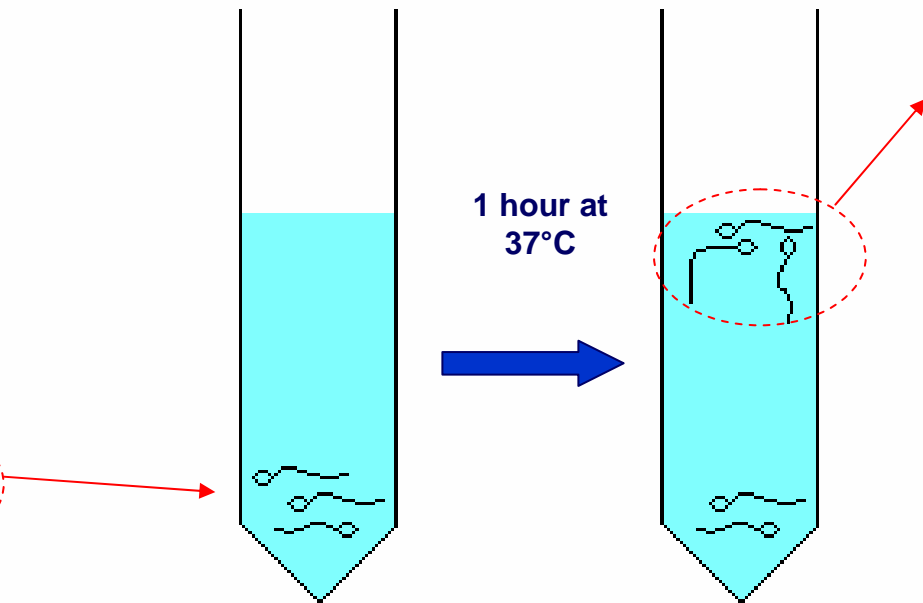
1. Improve the standards and availability of ART to couples with HIV
2. Issue recommendation for reproductive counselling and assistance of HIV couples
3. Collect data on treatment safety and effectiveness
4. Train new centres in countries where this method is currently not available
5. Inform regarding the availability and results of the method
6. Lobby with policy makers

# 1987: Sperm washing for HIV discordant couples

## Density gradient



## Swim-Up



# REMOVAL OF p18 IMMUNOREACTIVE CELLS FROM THE SEMEN HTLV-III/LAV SEROPOSITIVE MEN


Augusto E Semprini, A Vucetich, E Morandi, CL Parravicini, G Pardi and AE Beer. Colloque INSERM, Vol. 154, 1987, pp 462

A cytopsin preparation of washed spermatozoa, supernatant and the second fraction of the ejaculate were tested against a monoclonal anti-p18 antibody by immunoperoxidase technique. Washed sperm of seropositive and seronegative men were non-reactive, while many mononuclear cells and those in the second fraction of seropositive males were strongly reactive. Experiments are under way to test the possibility of safe intrauterine insemination with processed semen of HIV-positive men desiring a child.

## **1992: INSEMINATION OF HIV-NEGATIVE WOMEN WITH PROCESSED SEMEN OF HIV-POSITIVE PARTNERS**

**85 HIV-discordant couples were screened for fertility; 29 women were found suitable for a timed insemination course with the processed semen of their HIV-positive partner. None of the inseminated women seroconverted and 17 pregnancies were achieved in 15 women. All 10 infants born to these mothers remain HIV seronegative.**

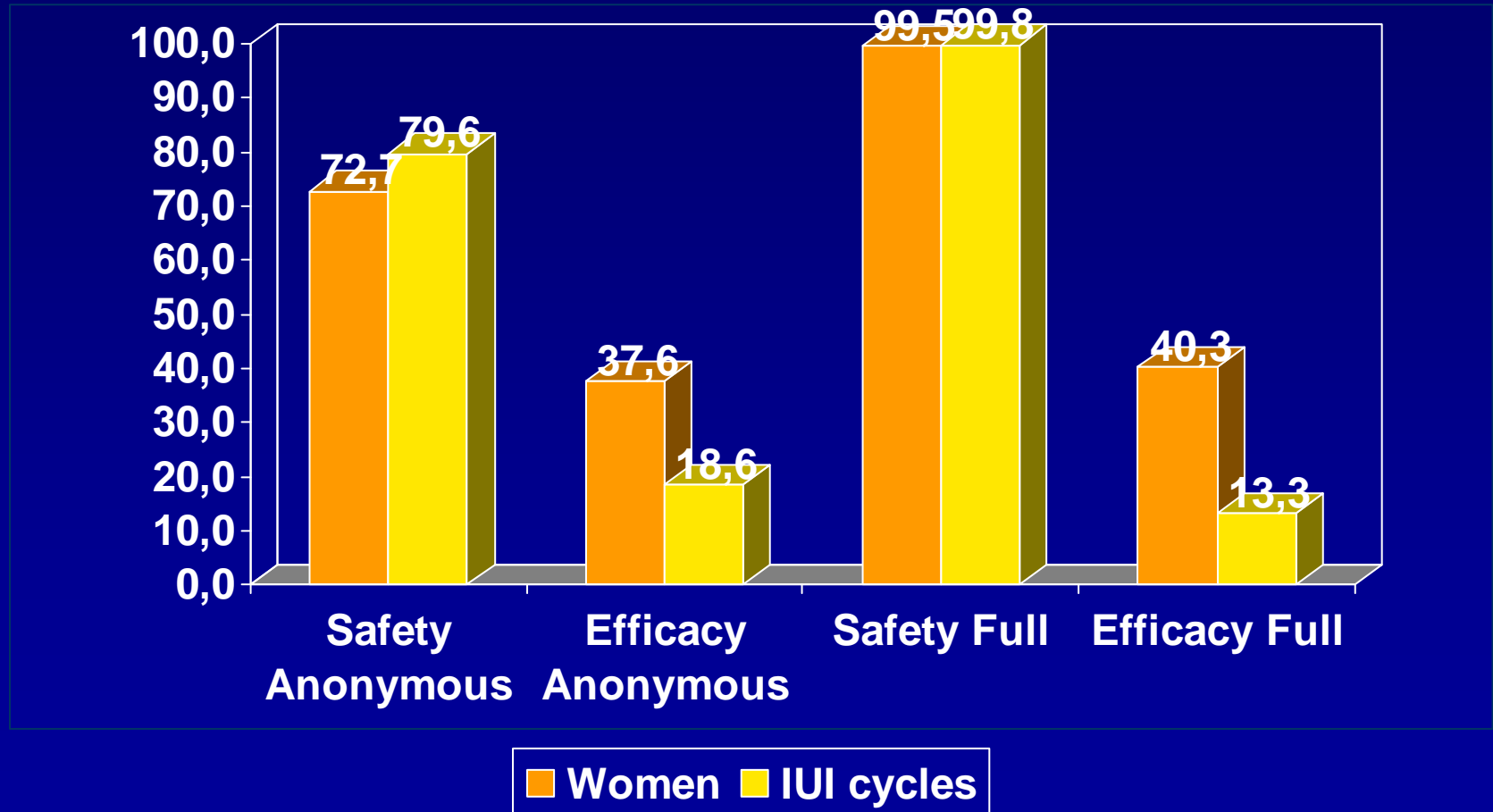
**(Semprini et al. - Lancet 1992; 340: 1317-19)**



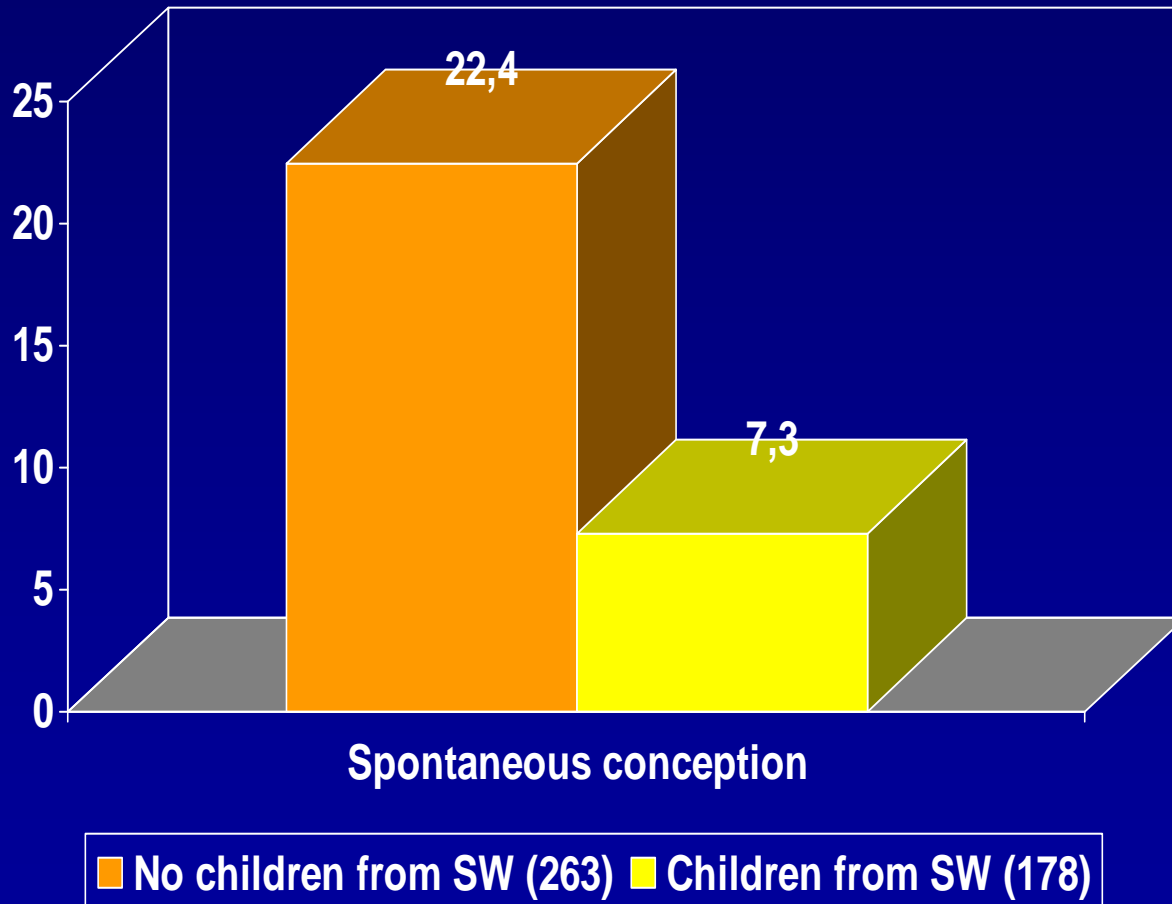
# 2000 – 2005: “HIV-1 infection risk in women inseminated with washed semen from HIV-1 positive partner – a retrospective analysis” - CONRAD

- Proactive retrospective follow up of HIV discordant couples treated in Italy
- Clinical database – 811 couples accessed treatment
- 2504 ART cycles, of which 2107 IUIs
- 16 years of follow up
- Activities:
  - Anonymous clinical dataset analysis
  - Request use of medical file data
  - Request update of serological data
  - Phone survey

# CONRAD – Proactive vs. passive surveillance

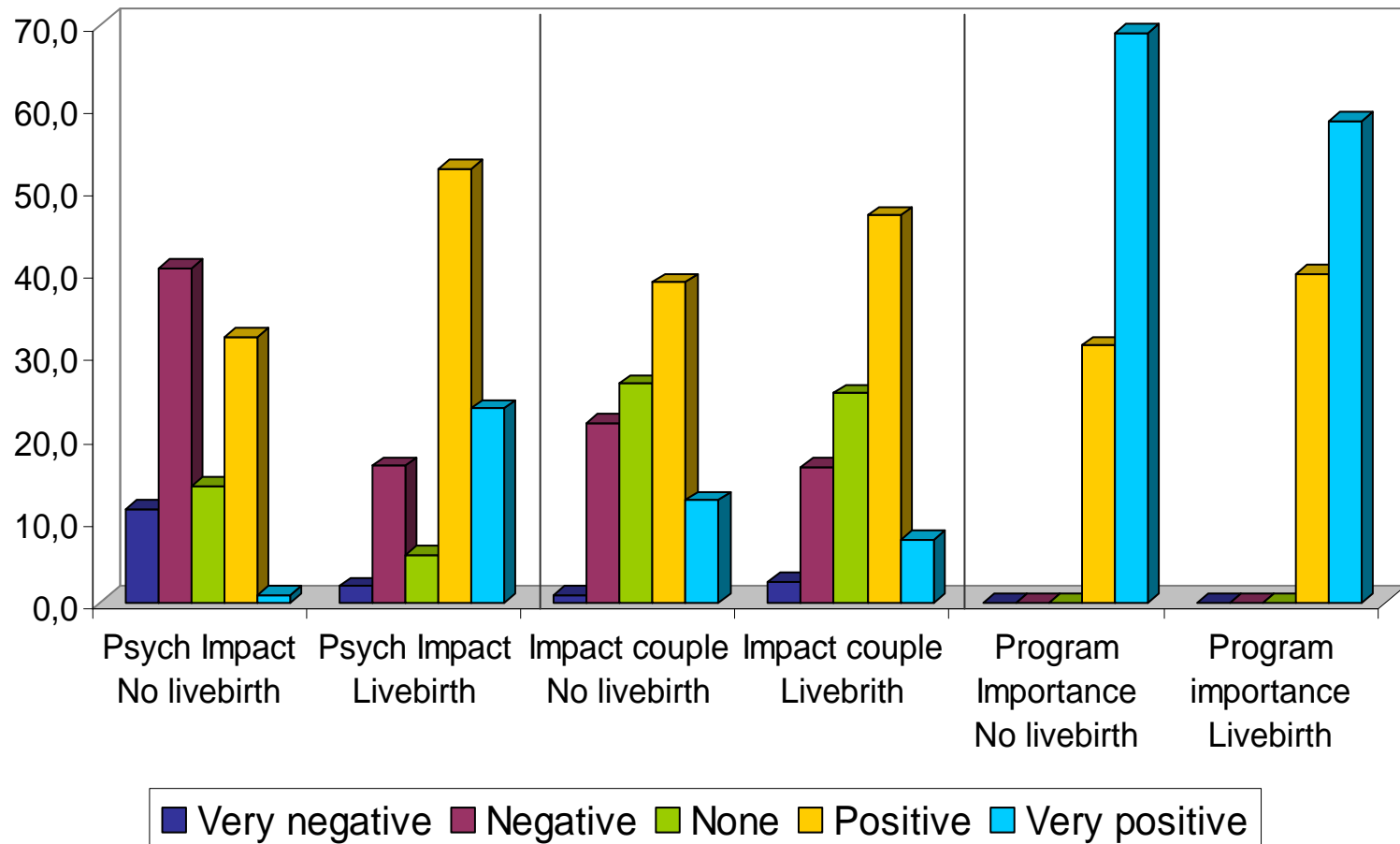


# CONRAD: Follow up findings



**HIV  
infection:  
one of 79  
women  
(1.2%)**

# CONRAD – Program impact



# 2003 – 2006: CREAThE – multicentre passive surveillance

- 9 CREAThE centres
- 1048 couples
- 3396 treatment cycles
  - 2840 intra-uterine inseminations
  - 107 IVF-ET
  - 394 ICSI
  - 49 embryo transfers

# Study centres



# Data collection parameters

## Cycle data :

- procedure
- date
- outcome
- cycle rank

## Patient data:

- age
- HIV history and treatment
- Gynaecological history
- Number of cycles

## Semen parameters<sup>†</sup>:

- before **and** after sperm processing
- spz concentration, motility, normal forms

## CD4 count

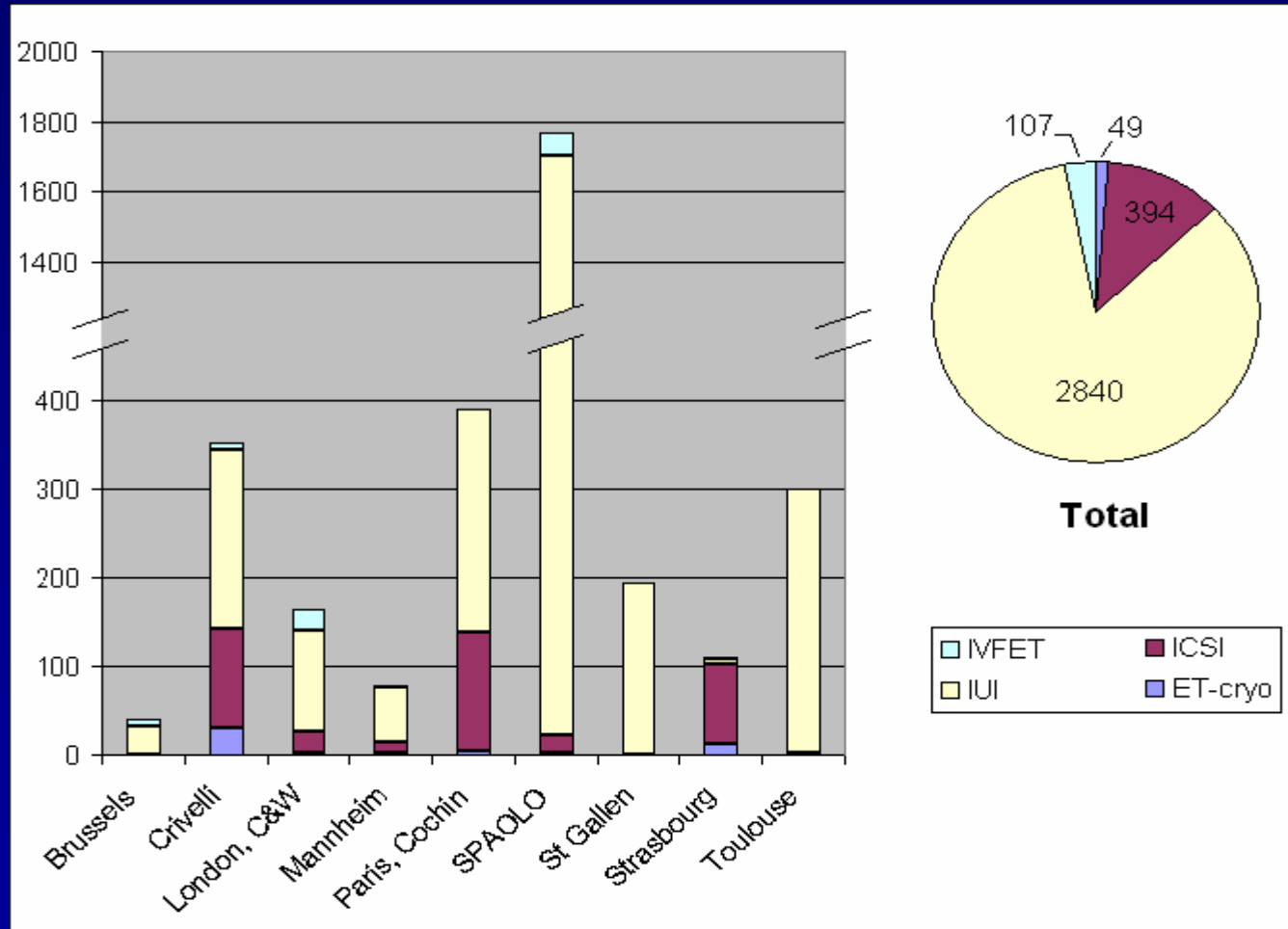
and

## FSH level<sup>‡</sup>

<sup>†</sup> last specimen provided before insemination.

<sup>‡</sup> last exams before insemination.

# Centre distribution of 3396 ART cycles



# Safety of Sperm washing + ART

- 3209 of 3396 treatment cycles had an HIV test 6 months or longer after with a follow-up rate of 94%
- All tests were negative
- Real contamination rate per cycle  $p$  is unknown.

# SW + ART vs. natural conception

- Mandelbrot : 92 deliveries/4 seroconversions
- CREAThE : 386 deliveries/ 0 seroconversion
- Fisher's exact  $P = 0.0013$

	Transmission	No Transmission	Total
Sperm washing + ART	0	386	386
Timed unprotected intercourse	4	88	92
Total	4	474	478

# Efficacy

- 580 pregnancies (rate per cycle 17.5%) in 499 women (rate per patient 48.2%)
- Pregnancy outcome:
  - 401 deliveries and 453 live births  
(360 singletons, 28 sets of twins - 2 neonatal deaths, 13 sets of triplets)
  - 111 failures  
(100 miscarriage, 8 extra-uterine pregnancies, 1 intra-uterine death, 2 TOP)
  - 68 missing data  
(21 ongoing and 47 lost of follow-up)

# Pregnancy rate per procedure

<b>Procedure</b>	<b>Number</b>	<b>Missing data</b>	<b>%</b>	<b>I.C. 95%</b>	
IUI	420 / 2774	66	15.1 %	13.8%	16.5%
ICSI	120 / 392	2	30.6 %	26.0%	35.2%
FIV	29 / 100	7	29.0 %	20.1%	37.9%
ET-Cryo	10 / 49	0	20.4 %	9.1%	31.7%
Total	579 / 3315	75	17.5 %	16.2%	18.8%

# Conclusions retrospective analysis

- Number of cycles insufficient to prove safety.
- Nevertheless, no infection after SW + ART, as opposed to natural conception attempts.
- Pregnancy rate per cycle is constant for IUI.
- Higher pregnancy rate with IVFET / ICSI.
- Woman's age has a strong influence on inseminations results.
- Semen parameters have an influence on IUI results only.


# Retrospective analysis vs. European register

<b>Retrospective studies</b>	<b>European register</b>
Simple, centralized data entry	Dedicated trained personnel at centres
High number of patients	Time to accumulate significant numbers
Rigid format	Ongoing development of study instruments
Missing data / different data collection forms	Unified collections forms, fixed deadlines
Incomplete follow up	100% safety + efficacy follow up
No psychosocial dimension	Psychosocial / QoL batteries
Drop outs are lost to FU	Study and correction of failure correlates

# SHARE

## STUDYING HIV AND REPRODUCTION IN EUROPE

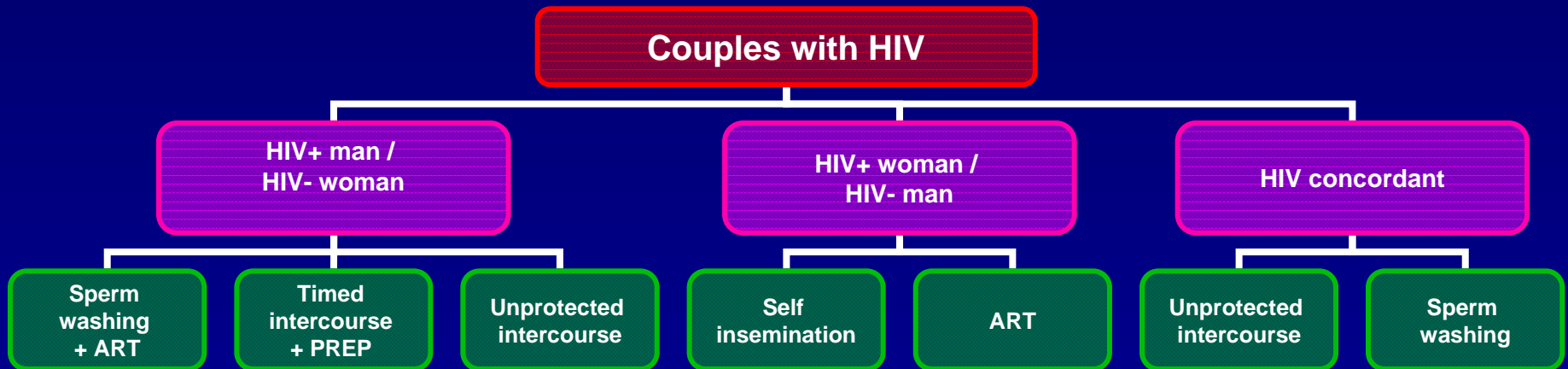
- European Register on HIV and reproduction
- Prospective cohort study
- 10 clinical centres – common database



# SHARE - Objectives

1. To evaluate the number of reproductive requests from couples with HIV in Europe
2. To monitor demographic and biological characteristics of HIV couples accessing assisted conception programs
3. To improve the safety follow up of the program
4. To collect data on biological and psychological determinants of failure to conceive
5. To estimate the rates of HIV transmission in Europe connected to spontaneous conception attempts
6. To assess the efficacy of different treatment and diagnostic protocols

# SHARE - flow



# SHARE - data

- Number couples requesting reproductive counselling / assistance
- Male/female infertility factors / correlation with antiretroviral medication
- Safety / efficacy of reproductive options
- Risk taking behaviour
- Quality of Life

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