HIV positive couples and ART : procedures, results

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A problem of health at the world level :

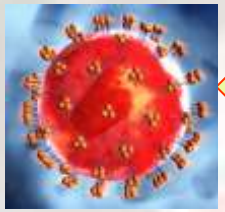
- **At least 40 millions persons infected by HIV around the world**
- **The majority of them are of reproductive age**
- **The HIV contamination is sometimes revealed by blood analysis prescribed during investigation of infertility**

In sero-different couples : the use of condoms is advised in order to avoid partner contamination,… but :

This behaviour induces artificial sterility….whereas : HAART procedures now allow them to make plans for the future (having a family)

Sero-discordant couples: two different situations

HIV



The male partner is contamined:

Aim: to prevent contamination of the female partner, then the baby

Consequence of using condoms: artificial sterility, although he is generally fertile

Art procedures: good results can be expected

The female partner is contamined:

Aim: to prevent contamination of the male partner

But: possibility of doing self inseminations

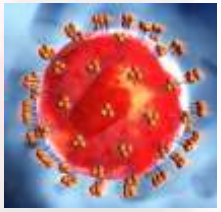
If no pregnancy occurs: misunderstood procedure

Or: revelation of infertility factor(s)

Art procedures: not so good results can be expected

Sero different couples with HIV-1 infected male partner

Sero discordant couples: contamination of the male partner

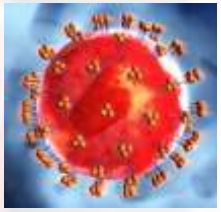


In the past: programmed intercourse during the female fertile period: several cases of contamination of the mother and the baby reported

1992: first description by Semprini of a « safe » procedure: artificial insemination of a virus free sperm sample

« sperm washing method »

Sperm Washing method



Ejaculate

viral detection : seminal plasma
+ blood cells

final fraction

Density
gradients

50%
70%
90%

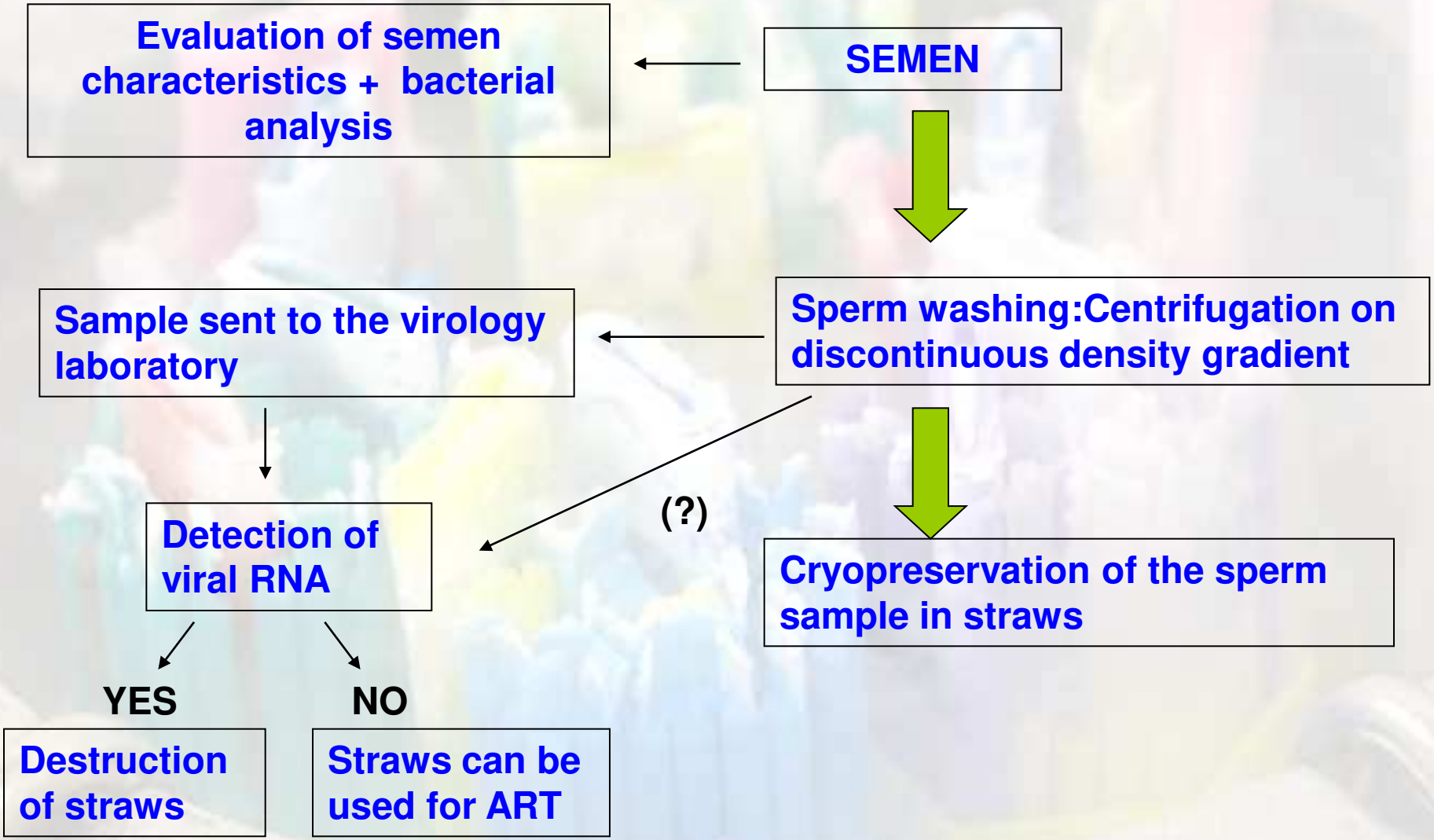
Washing
of 90%
fraction

1

2

Swim up

Treatment of semen : steps of procedure



Detection of RNA and DNA HIV-1 seminal Plasma: RNA + in 20% of cases

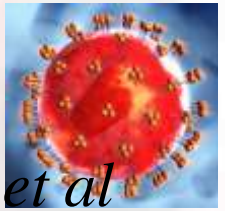
(5 - 277 000 copies/ml)

Cells rough semen		Cells Fraction 50%		final Fraction	
DNA	RNA DNA	DNA	RNA DNA	DNA	RNA DNA
26/476	39/478	14/265	15/262	0/422	0/461
5.5 %	8.2 %	5.3 %	5.7 %	0 %	0 %

Pasquier et al. AIDS 2000, Bujan et al.AIDS 2004

ANRS 096

Efficacy of the techniques of Sperm preparation



Double technique: more safe than one technique *Hannabusa et al*

Confirmed par Fiore et al 2005 **:**

RNA viral load	Percoll (density Gradient only)	Percoll + swim up
<50 000	négative	négative
100 000 - 500 000	positive	Négative
1 - 3 millions	Positive	positive

Limits of the procedure

- **Related to the infection**
- Very high level of viral load in blood and/or semen
- Low count of CD4 in blood (<200/mm3)
- Man not in good health

Related to the problem of infertility:

-severe oligozoospermia (the virology lab Cannot give reliable results)

-azoospermia: TESE: sperm washing unsafe

Alterations of sperm characteristics in HIV+ men

	HIV N=190	Control N=218		
Volume (mL)	3.3 [1.6]	3.9 [1.9]		*<0.01**
pH	8.2 [0.3]	7.9 [0.3]		*<0.01**
Motility a (%)	32.8 [17.2]	37.4 [14.1]		*<0.05**
Motility b (%)	6.4 [4.5]	6.2 [3.6]		*NS*
Forward Motility a+b (%)	39.2 [16.2]	43.6 [13.8]		*<0.05**
Vitality (%)	68.8 [15.3]	69.7 [13.3]		*NS*
Concentration (10^6/mL)	108.3 [96.8]	96.7 [88.2]		*NS*
Total sperm count (10^6 per ejaculate)	330.9[287.7]	353.8[317.9]		*NS*

Bujan et al, 2004

Results of inseminations

84 couples, 298 cycles, 1 insémination per cycle

56 pregnancies : 18.8% /cycle

47 deliveries
9 misarriages : 16.1%

52.4% of couples had a baby

Bujan et al. Fertil Steril 2004

cumulative rate of pregnancies

	HIV-1 serodiscordant couples	Control group IUI	Control group ICI
Couples	84	90	192
Couples including second pregnancy	95	105	212
Women age	33,16 +/-4,45	32,59 +/-4,06	32.71 3.92
Insemination cycles	298	336	654
pregnancies	56	48	88
Pregnancy rate per cycle	18,79	14,29	13.46 *
Pregnancy rate per couple	57.14	48.89	40.10 *
Pregnancy rate within fisrt three cycles			
Miscarriages	9	10	14
Miscarriages rate per pregnancy	16.07	20.83	15.91
Delivery	44	37	68
Baby take home rate	52,38 (44/84)	41,11 (37/90)	35.42 **
Multiple pregnancy rate	14,89 (7/47)	15,79 (6/38)	9.09

* p<0.05, ** p<0.01 compared with serodiscordant couples

Bujan et al. Eur. Obst. Gyn. 2007

Table II. Outcome of intrauterine insemination (IUI) cycles in 581 couples

Couples (*n*)	581
Number of IUI cycles (*n*)	2400
Clinical pregnancies (*n*)	456
Clinical pregnancy rate per IUI cycle (%)	19
Clinical pregnancy rate per couple (%)	78
Miscarriages (*n*)	54
Miscarriage rate in total number of pregnancies (%)	12
Tubal pregnancy (*n*)	5
Ongoing pregnancy (*n*)	72
Number of deliveries (*n*)	325*
Multiple pregnancy rate (%)	4
Maternal seroconversion (*n*)	0
Congenital seroconversion (*n*)	0

* 337 newborn babies.

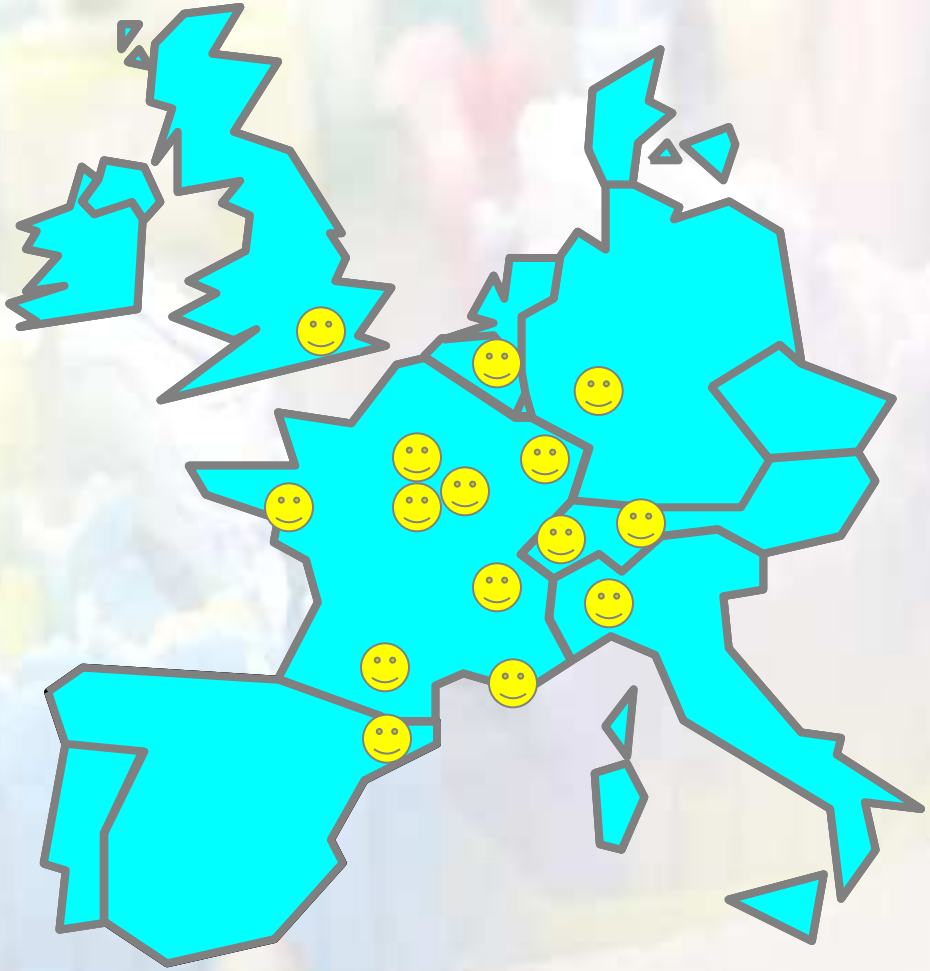
Savasi et al, 2007

RESULTS OF A COLLABORATIVE EUROPEAN NETWORK

CREAThE

Boston

Israel



Results CREAThE (1989-2003)
patients – ART cycles

country	Centre	Couples	lost	IUI	IVF	ICSI	Frozen emb	total
Belgium	Bruxelles	10	0	31	9	0	0	40
France	Paris	149	0	252	0	134	4	390
	Strasbourg	55	0	6	1	90	12	109
	Toulouse	83	0	298	0	1	0	299
Germany	Mannheim	29	0	62	1	13	1	77
Italy	Milan	588	74 (12.6%)	1883	73	133	30	2119
UK	Londres	57	0	115	23	23	2	163
Switzerland	St Gallen	65	0	193	0	0	0	193
TOTAL		**1036**	**74** (7.1%)	**2840**	**107**	**394**	**49**	**3390**

Bujan et al, AIDS, 2007

CREAThE AMP-VIH (1989-2003)

	IIU	ICSI	FIV	TEC	Total	p
Couples	853	262	76	40	1231	
Cycles	2840	394	107	49	3390	
Pregnancy rates /cycle %	15.1	30.6	29	20.4	17.5	< 0.001
deliveries/cycle %	11.5	15.8	20.8	14.3	12.3	< 0.05
Pregnancy per couple %	42.5	43.1	38.2	25	41.9	> 0.05
deliveries/couple %	35.1	21	26.3	17.5	30.9	< 0.01

Risk of contamination : 0 (95%CI: 0-0.09%)

Bujan et al, AIDS, 2007

Sero different couples with HIV-1 infected female partner

- Contrary to the former situation, very few data are available
- Artificial inseminations are generally poorly efficient, since self inseminations have been already practised without any success
- The results of IVF/ ICSI are also not so good than in the general population

	Group I Seropositive women	Group II Seronegative controls	Group III Overal Seronegative population
Age (years)	35.8	35.9	34.4
Cancelled cycles (%)	15.2	4.9[a]	6.9[a]
Total dose of rFSH injected (IU)	2898	2429[c]	2107[c]
Duration of stimulation (days)	13.3	11.7[b]	12.1[b]
Estradiol on the day of hCG (pg/ml)	1393	1391	1524
No. of oocytes	10.6	8.3	10.7
No.of mature oocytes	7.0	6.3	7.6
No embryos obtained	4.7	3.7	4.8
Fertilization rate (%)	67	60[b]	63[a]
Percentage of good quality embryos	38	35	41
No. of transferred embryos	2.0	2.4	2.1
Clinical pregnancy rate (%)	16.1	19.6	26.1[a]

Outcome of ICSI in HIV-1-positive women (group I), seronegative controls matched with regard to age and oocyte retrieval period (group II), and overall population of seronegative women treated at our facility (group III) (*Terriou et al, 2005*)

SERO CONCORDANT COUPLES

The couple can generally be considered as sterile, since intercourses are rarely protected

Solution: ART (IVF / ICSI)with sperm wasing and freezing as described earlier

Efficacy: No reliable data from the litterature

Conclusion :HIV infected male partner:

ART with sperm washing is a safe mean to have a baby, without risking of contamination of the female partner, and thereby the baby

In the absence of negative clinical arguments:
Artificial insemination must be the procedure of choice:
Simple method and very good results: > 20% pregnancies /cycle; > 50% deliveries/ couple

If the procedure is correctly conducted:
No risk of contamination of the partner

Conclusion: other cases

- **HIV infected women / seroconcordant infected couples**
- Generally: problems of sterility! Requiring IVF or ICSI rather than IU inseminations

- Data more scare and not so good
- Hypothesis: HIV contamination *per se* could be a factor of infertility in women

Questions and concerns

Is it reasonable to permit or advice couples where the male partner is contamined but with an undetectable viral load, to stop the use of condoms and have babies by « natural means »?

« Licence to love »

Pietro Vernazza et al. AIDS 2006

Pablo Barreiro et al. Hum. Reprod. 2007

Caution: in some cases, viral RNA is detected in semen but not in blood!