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Opinion paper

Facts and myths in serological screening of ART couples

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Abstract

Serological screening of couples attending for ART therapy is now common practice. The frequency of such screening is a topic of debate as few publications have addressed this question. Emerging evidence shows that the ART population has similar prevalence of infectious diseases compared with the general EU population. The need to pursue repeat screening is mainly related to the risk of seroconversion in this highly selected population. The evidence presented here shows that seroconversion among cohabitating ART couples is negligible. Even if a theoretical risk of seroconversion during therapy exists, with correct laboratory practice the risk of cross-contamination is negligible as laboratory processing eliminates the infective risk. As such ART laboratory processing of contaminated samples becomes an indication rather than a risk. To strengthen the evidence it is recommended that data on prevalence and incidence should be prospectively collected by all ART units.

Key words: **ART, assisted reproduction, European reports, incidence, prevalence, serological viral screening, seroconversion risk.**

The context of the European Tissues and Cells Directive in ART

Providers of assisted reproduction services are required by law to test the donors of reproductive cells for blood borne viral (BBV) infections prior to Assisted Reproduction Technology (ART) treatments.

Annex III of Directive 2006/17/EC sets the requirements namely that in partner donation, where reproductive cells are processed/ stored or cryopreserved, biological tests must be carried out to assess the risk of cross-contamination (European Commission (2006a) Commission Directive 2006/17/EC). While the donation by non-partners is no different to organ donation and strict screening criteria have been in place for many years now, partner donation is fundamentally different in that the couples are cohabitating.

Intense debate has taken place in relation to the need and the timing of repeat serological screening in ART couples that have previously screened negative. While no evidence existed to prove seroconversion in ART couples is occurring, similarly no evidence existed to prove it did not, until recently (Wingfield and Cottell, 2010; Hughes et al., 2011). Unfortunately too late, as the law already forces ART clinics to test all ART receiving couples for HIV, HepB antigen and antibody as well as HepC at the time of "each donation".

The purpose of this paper is to summarise existing evidence in relation to the prevalence and incidence (real risks of seroconversion) of blood borne viruses in the context of partner donation ART in cohabitating couples.

Does the ART population have a different infectious risk?

A schematic representation of the ART process and how the 5 steps in reproductive tissues partner donation relate to the Tissues and Cells Directive is presented in Figure 1.

To assess if the ART population is different from the general European population we identified the prevalence of HIV, HepC, HepB infections in ART couples and European populations and searched the evidence as regards the incidence (risk of

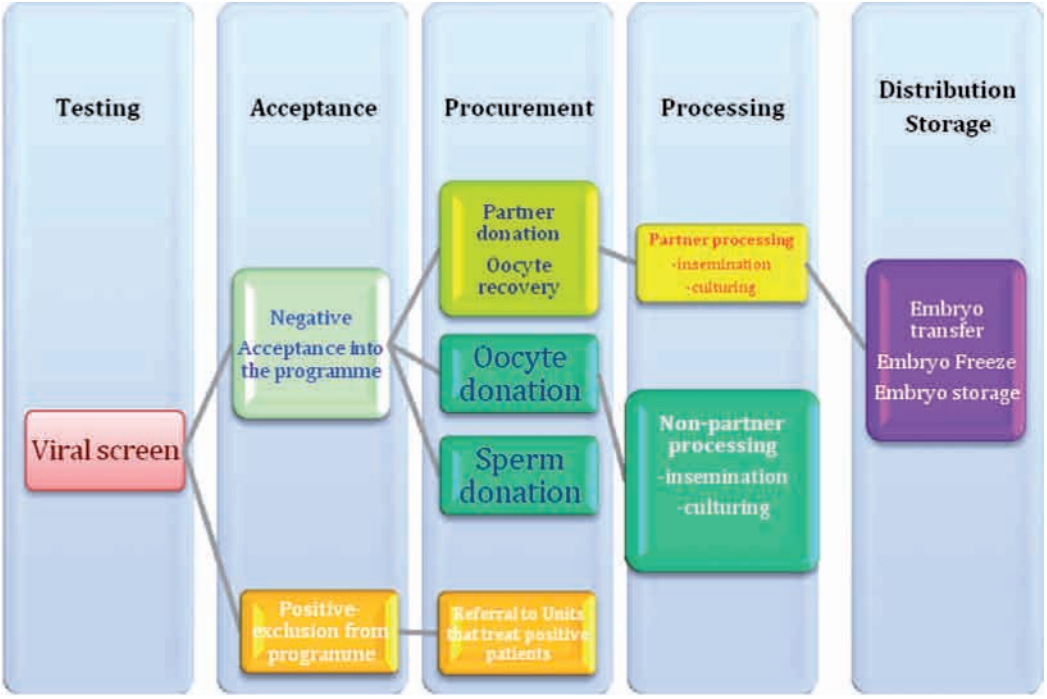

Fig. 1. — Context of EUTCD in the ART process (partner donation)

seroconversion) from published scientific peer-reviewed literature or Official European Reports.

a. What is the prevalence of infectious diseases in the ART population?

By definition, the prevalence of infections in the population is the proportion of individuals that are diagnosed as infected at entry in the service. The incidence of infections (incidence of seroconversion) is defined as the proportion of individuals that are diagnosed as infected while they receive multiple ART treatments having had a negative screen initially. Data on prevalence of HIV, HepB and Hep C infection in the ART population have been published since 1999. The evidence to date, summarized in Table 1, comes from 4 papers analyzing patients attending ART clinics located in different countries (Abusheikha et al., 1999; Hart et al., 2001; Hughes et al., 2011; Pepas et al., 2011). A pan-European study has not yet been published.

b. Is if the prevalence of infectious diseases in the ART population different compared to the general population?

Data on prevalence of HIV, HepB and Hep C infection in the general population are very scarce. The two sources of information identified are the European HIV and AIDS Statistics (http://www.avert.org/hiv-aids-europe.htm) and the ECDC Technical Reports (2010). The last column in Table 1 presents this European data and clearly shows that the ART population has a lower prevalence of infectious diseases compared with the average prevalence in the general EU population. The one exception is the inner London HIV prevalence (Pepas et al., 2011) from a centre that treats HIV serodiscordant couples and where the prevalence is expected to be higher than the country average.

c. Is seroconversion likely?

As the law aims to reduce the incidence one must firstly measure this risk within the specific ART population. So, what is the risk that a patient or couple attending ART therapy will seroconvert during the treatment? Few publications have specifically measured the risk of seroconversion (Hughes et al., 2011; Pepas et al., 2011). Hughes et al. (2011) retrospectively analysed the viral screen results of patients attending a tertiary referral ART centre between 1998 and 2009. The risk of seroconversion following an initial negative screen for Hepatitis C, HIV, Hepatitis B surface antigen and Hepatitis core antibody (only from 2008) was measured. Of the 12,500 patients attending initially, 6500 had repeat testing during the studied interval. This population included patients undergoing IVF/ ICSI therapy, patients that had embryos cryopreserved and males attending for oncology cryopreservation, the latter groups required 6 months re-testing for the

Table 1. — Prevalence of blood borne viral infections in ART (published data only, n = individuals tested).

Test	Hart R. 2001 (n = 815)	Abusheikha N. 1999 (n = 4960)	Hughes C. 2011 (n = 12,700)	Pepas L. 2011 (n = 3,910)	General population
Country	**UK (London)**	**UK (Cambridge)**	**Ireland (Dublin)**	**UK (London)**	**EU**
HIV	0.13%	0.06%	0.007%	0.6%	**0.24%**
HepC	0.5%	0.5%	0.33%	0.4%	**0.4-3.5%**
HepB antigen	1.3%	0.5%	0.28%	1.7%	**0.1-7%**
Hep B core	0.4%	–	3.32%	–	–

transfer of material in long-term storage. No seroconversion from an initial negative state was identified in any of the studied groups.

The London group (Pepas et al., 2011) conducted a retrospective study of all virology screening tests undertaken over a three year period for individuals attending an assisted conception unit serving a high risk inner city population. They ascertained prevalence and seroconversion rates for HIV, hepatitis B and C. Of the 3910 ART individuals screened (from 2007 to 2009) a total of 422 individuals had a second full screening test and none seroconverted.

In a paper trying to answer the question if repeat screening is justified, Wingfield and Cottell (2010) published an elegant review regarding the risks of transmission of hepatitis B, hepatitis C and HIV in the ART setting. They specifically looked at the risk of transmission of viruses from the donor to the recipient (sexual partner) and from the donor to a non-partner (mix up of gametes or embryos); risk of cross-contamination in an ART facility which could lead to a risk of infection for other patients or staff; risk of cross-contamination of cryopreserved material and risk of seroconversion between testing and treatment. The evidence presented in the paper shows that when best practice ART procedures for gamete and embryo processing are employed, cross-contamination in the ART facility or horizontal or vertical transmission to a partner or neonate has never been documented, even among those known to be HBV-, HCV- or HIV-infected.

These findings support previous local reports (Abusheikha et al., 1999; Hart et al., 2001) and strengthen the evidence that the incidence of BBV is exceptional in cohabitating ART couples.

The future in ART screening

Screening of couples attending for ART services is precautionary in order to protect other clients receiving treatment from inadvertent exposure during manipulation or storage of their reproductive cells or inadvertent exposure as a result of a mix-up of reproductive cells. It also aims to protect staff in the service from inadvertent exposure during manipulation.

The question remains what happens if an undiagnosed seropositive patient (recent seroconversion) undergoes ART treatment.

The process stages where cross-contamination in the context of ART could occur are circled in Figure 2. While initial experience with donor sperm artificial insemination did portrait a negative picture in relation to the risks of cross-contamination (Morgan and Nolan, 1986; Araneta et al., 1995; Ross et al., 1998; Mayer, 1999), with documented HIV and STD transmission, developments in sperm processing in the IVF laboratory (ESHRE guideline on laboratory practice) have proven revolutionary.

As such, while initially the use of unprocessed semen from HIV positive males resulted in partner infections, multiple recent studies have proven that ART sperm preparation eliminates the risk of horizontal or vertical transmission in serodiscordant couples (male positive) and has now become an indication and recommended good clinical practice.

Pioneer work by Semprini et al. (1992) showed that gradient centrifugation followed by a swim-up procedure effectively removed HIV-1-infected cells from the semen of HIV-seropositive men. In the 29 cases reported, seronegative women were treated with washed sperm from HIV positive partners. No seroconversion occurred in the female partners after multiple treatments and none of the 10 newborn resulting from treatment was infected.

Honeck et al. (2005) showed that after 10 years of assisted procreation, there has been no case of horizontal or vertical transmission of HCV, HBV or HIV after specimen preparation. Similarly, (Garrido et al., 2009) in a 4-year follow-up study showed no presence of HCV in final sperm fraction after ART preparation and no newborn transmission of HCV. Furthermore, the European CREAThE network, following on the work of Semprini, published (Bujan

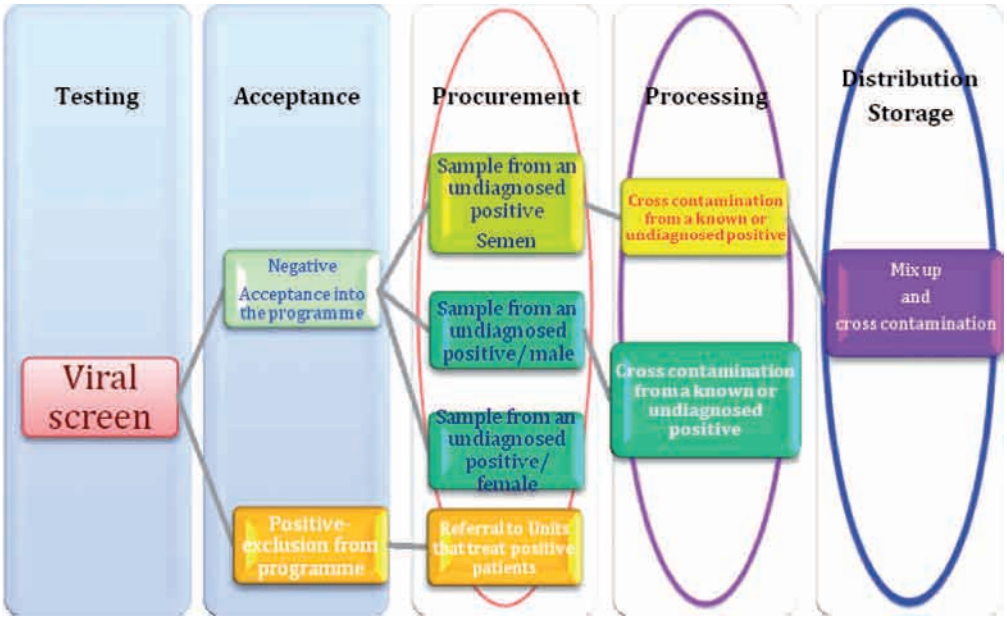

Fig. 2. — Steps where cross-contamination can occur in ART

Table 2. — Serological screening of ART couples: Recommendations.

1. Data on prevalence and incidence should be prospectively collected from all ART units.
2. Units should individualise the repeat screening schedule according to risk of their own ART population.
3. ART Units should pool data for a clear national picture.
4. National data should be required by ESHRE in order to prove beyond doubt that the risk is far less than after other medical interventions.
5. Laboratory practice should be uniform and conform to established ESHRE standards
6. There is a need for an ART specific European law as the circumstances are different from organ and tissue donation.

et al., 2007) their results on 3390 ART cycles and reported no risk of maternal contamination in HIV discordant couples.

As all recent evidence shows that ART processing is a recommended procedure to eliminate the risk of contamination in serodiscordant couples even if male seroconversion occurs during this interval with appropriate laboratory practice the risk of potential cross-contamination from a seroconverted patient is negligible.

Unfortunately there is no rigorous data collection at European level that will allow a clear picture to emerge. Nevertheless the evidence to date clearly shows that screening at each oocyte collection is excessive as seroconversion in the circumstances of ART co-habitating couples is negligible. Furthermore, rigourous methodology in the lab reduces rather than increases the risk of contamination and cross-contamination being an established technique to reduce the transmission burden from parent to child. A clear indication rather than a risk.

Considering the mounting evidence that serological screening in ART is overprescribed it is worthy of note that efforts have been made to introduce changes to the Annex III of Directive 2006/17/EC with regard to certain technical requirements for testing of tissues and cells and in particular point 4.2 of this Annex. Having considered the literature and clinical practice evidence, the Competent Authorities and the Regulatory Committee of the European Commission have recently met to draft a final version of the amendment, which should be officially published soon.

Conclusion

1. The ART population has a lower/ similar prevalence of infectious diseases compared with the general EU population.
2. Seroconversion in the cohabitating ART population is negligible.
3. All evidence to date shows that ART is a RECOMMENDED PROCEDURE to eliminate the risk of contamination in serodiscordant couples.
4. No proven case of contamination from ART in human ART applications exists.

Medical treatment follows the primum non nocere principle. As such, any potential benefits of an

intervention and protection from harm should be balanced by the costs and potential negative effects of the intervention. In the case of serology screening for ART couples while testing prior to treatment is recommended, the current screening frequency is not justified by clinical practice knowledge and literature evidence. Even if a theoretical risk of seroconversion during therapy exists with correct laboratory practice the risk of cross-contamination is negligible as laboratory processing eliminates the infective risk.

References

Abusheikha N, Akagbosu F, Marcus S et al. Viral screening and assisted conception treatment – the Bourn Hall experience. J Assist Reprod Genet. 1999;16:337-9.

Araneta MR, Mascola L, Eller A et al. HIV transmission through donor artificial insemination. JAMA. 1995;273(11):854-8.

Bujan L, Hollander L, Coudert M et al. Safety and efficacy of sperm washing in HIV-1 serodiscordant couples where the male is infected: results from the European CREAThE network. AIDS. 2007;12, 21(14):1909-14.

ECDC Technical Reports. Hepatitis B and C in the EU neighbourhood: prevalence, burden of disease and screening policies. Technical Report ECDC (European Centre for Disease Prevention and Control). 2010: 1-51.

European Commission (2006a) Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

European HIV and AIDS Statistics (http://www.avert.org/hiv-aids-europe.htm)

Garrido N, Gil-Salom M, Martinez-Janaloyas JM et al. 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(3):1012-5.

Hart R, Khalaf R, Bickerstaff H et al. Screening for HIV, hepatitis B and C infection in a population seeking assisted reproduction in an inner London hospital. BJOG. 2001;108: 654-6.

Honeck P, Weigel M, Kwon ST et al. Assisted procreation in cases of hepatitis B, hepatitis C or human immunodeficiency virus infection of the male partner. Hum Reprod. 2005;21:1117-21.

Hughes C, Grundy K, Emerson G et al. Viral screening at the time of each donation in ART patients: is it justified? Hum Reprod. 2011;26:3169-72.

Mayer KH. Risks of human immunodeficiency virus transmission from artificial insemination from an infected donor. Pediatr Infect Dis J. 1999; 18:310-1.

Morgan J, Nolan J. Risk of AIDS with artificial insemination. N Engl J Med. 1986; 314(6):386.

Pepas L, Macmahon E, El Toukhy T et al. Viral screening before each cycle of assisted conception treatment is expensive and unnecessary: a survey of results from a UK inner city clinic. Hum Fertil (Camb) 2011;14(4):224-9.

Ross RS, Elgas M, Roggendorf M. HIV-1 transmission through artificial insemination. Lancet. 1998;351(9118):1812-3.

Semprini AE, Levi-Setti P, Bozzo M et al. Insemination of HIV-negative women with processed semen of HIV-positive partners. Lancet. 1992;340(8831):1317-9.

Wingfield M, Cottell E. Viral screening of couples undergoing partner donation in assisted reproduction with regard to EU Directives 2004/23/EC, 2006/17/EC and 2006/86/EC: what is the evidence for repeated screening? Hum Reprod. 2010; 25:3058-65.