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ESHRE guideline: medically assisted reproduction in patients with a viral infection/disease†

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STUDY QUESTION: What is the recommended management for medically assisted reproduction (MAR) in patients with a viral infection or disease, based on the best available evidence in the literature?

SUMMARY ANSWER: The ESHRE guideline on MAR in patients with a viral infection/disease makes 78 recommendations on prevention of horizontal and vertical transmission before, during and after MAR, and the impact on its outcomes, and these also include recommendations regarding laboratory safety on the processing and storage of gametes and embryos testing positive for viral infections.

WHAT IS KNOWN ALREADY: The development of new and improved anti-viral medications has resulted in improved life expectancy and quality of life for patients with viral infections/diseases. Patients of reproductive age are increasingly exploring their options for family creation.

STUDY DESIGN, SIZE, DURATION: The guideline was developed according to the structured methodology for the development of ESHRE guidelines. After the formulation of nine key questions for six viruses (hepatitis B virus, hepatitis C virus, human immunodeficiency virus, human papilloma virus, human T-lymphotropic virus I/II and Zika virus) by a group of experts, literature searches and assessments were performed. Papers published up to 2 November 2020 and written in English were included in the review. Evidence was analyzed by female, male or couple testing positive for the virus.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Based on the collected evidence, recommendations were formulated and discussed until consensus was reached within the guideline group. There were 61 key questions to be answered by the guideline development group (GDG), of which 12 were answered as narrative questions and 49 as PICO (Patient, Intervention, Comparison, Outcome) questions. A stakeholder review was organized after the finalization of the draft. The final version was approved by the GDG and the ESHRE Executive Committee.

MAIN RESULTS AND THE ROLE OF CHANCE: This guideline aims to help providers meet a growing demand for guidance on the management of patients with a viral infection/disease presenting in the fertility clinic.

The guideline makes 78 recommendations on prevention of viral transmission before and during MAR, and interventions to reduce/avoid vertical transmission to the newborn. Preferred MAR treatments and interventions are described together with the effect of viral infections on outcomes. The GDG formulated 44 evidence-based recommendations—of which 37 were formulated as strong recommendations and 7 as weak—33 good practice points (GPP) and one research only recommendation. Of the evidence-based recommendations, none were supported by high-quality evidence, two by moderate-quality evidence, 15 by low-quality evidence and 27 by very low-quality evidence. To support future research in the field of MAR in patients with a viral infection/disease, a list of research recommendations is provided.

LIMITATIONS, REASONS FOR CAUTION: Most interventions included are not well-studied in patients with a viral infection/disease. For a large proportion of interventions, evidence was very limited and of very low quality. More evidence is required for these interventions, especially in the field of human papilloma virus (HPV). Such future studies may require the current recommendations to be revised.

WIDER IMPLICATIONS OF THE FINDINGS: The guideline provides clinicians with clear advice on best practice in MAR for patients with a viral infection/disease, based on the best evidence currently available. In addition, a list of research recommendations is provided to stimulate further studies in the field.

STUDY FUNDING/COMPETING INTEREST(S): The guideline was developed and funded by ESHRE, covering expenses associated with the guideline meetings, with the literature searches and with the dissemination of the guideline. The guideline group members did not receive any financial incentives, all work was provided voluntarily. A.D. reports research fees from Ferring and Merck, consulting fees from Ferring, outside the submitted work. C.P. reports speakers fees from Merck and MSD outside the submitted work. K.T. reports speakers fees from Cooper Surgical and Ferring and consultancy fees as member of the advisory board BioTeam of Ferring, outside the submitted work. The other authors have no conflicts of interest to declare.

DISCLAIMER: *This guideline represents the views of ESHRE, which were achieved after careful consideration of the scientific evidence available at the time of preparation. In the absence of scientific evidence on certain aspects, a consensus between the relevant ESHRE stakeholders has been obtained.*

Adherence to these clinical practice guidelines does not guarantee a successful or specific outcome, nor does it establish a standard of care. Clinical practice guidelines do not replace the need for application of clinical judgment to each individual presentation, nor variations based on locality and facility type.

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Key words: viral disease / hepatitis B virus / hepatitis C virus / human immunodeficiency virus / human papilloma virus / human T-lymphotropic virus I/II / Zika virus / cross-contamination / medically assisted reproduction / ESHRE guideline

WHAT DOES THIS MEAN FOR PATIENTS?

Patients living with a viral infection/disease now have a longer life expectancy and improved quality of life, which leads them to think about family creation. In some cases, the pregnancy can establish spontaneously and safely, while in certain circumstances medically assisted reproduction (MAR) treatments are required to help couples achieve a pregnancy. When embarking on MAR, patients and practitioners have to explore the best treatment options that reduce the risk of transmission of the virus and result in the highest chances of getting pregnant. This is where the present guideline aimed to bring clarity through evidence from the literature and expert opinion in order to increase the safety of therapy and offer reassurance to all involved, patients and practisers alike.

The current paper summarizes the ESHRE Guideline on MAR in patients with a viral infection/disease providing clinicians with evidence-based recommendations on how to manage these patients in the fertility clinic with the aim to prevent/reduce the risk of horizontal (person to person) and vertical viral transmission to the baby. In addition, the guideline also provides recommendations on providing information regarding the risks of vertical viral transmission to the newborn. The full guideline and a patient leaflet are available on https://www.eshre.eu/VirusGuideline.

Introduction

The development of new and improved anti-viral medications has resulted in improved life expectancy and quality of life for patients with viral infections/diseases. Patients of reproductive age are increasingly exploring their options for family creation. The management of medically assisted reproduction (MAR) in patients with a viral infection is regulated rather strictly in some European countries, however, not in all. While viral testing of all patients embarking on MAR is compulsory in Europe, detailed guidance on the correct conduit once a patient tests positive and wishes to proceed with MAR is lacking. This guideline aims to help providers meet a growing demand for guidance on the management of patients with a viral infection/disease presenting in the fertility clinic, and in particular the ones proceeding with MAR treatments.

Materials and methods

The guideline was developed according to a well-documented methodology that is universal to ESHRE guidelines (Vermeulen *et al.*, 2020). The guideline development group (GDG) was composed of members of the ESHRE Special Interest Group (SIG) Safety and Quality in ART, Ethics and Law and members of the former task force on Viral Diseases, with the addition of experts in the field, including a virologist.

In short, 61 key questions were formulated by the GDG, of which 12 were answered as narrative questions and 49 as PICO (Patient, Intervention, Comparison, Outcome) questions. For each PICO question, databases (PUBMED/MEDLINE, Cochrane library, EMBASE and GIM) were searched from inception to 3 November 2020, limited to studies written in English. From the literature searches, studies were selected based on the PICO questions, assessed for quality and summarized in evidence tables. GDG meetings were organized where the evidence and draft recommendations were presented by the assigned GDG member and discussed until consensus was reached within the group. Each recommendation was labeled as strong or weak and a grade was assigned based on the strength of the supporting evidence (High ⊕⊕⊕⊕, Moderate ⊕⊕⊕◯, Low ⊕⊕◯◯, Very low ⊕◯◯◯). Good practice points (GPPs) based on clinical expertise were added, where relevant, to clarify the recommendations or to provide further practical advice. One 'research only' recommendation was also made, and this intervention should be applied only within the context of research, with appropriate precautions and ethical approval.

Strong recommendations should be used as a recommendation to be applied for most patients, while weak recommendations require discussion and shared decision-making.

For the narrative questions, a similar literature search was conducted. Collected data were summarized in a narrative summary and conclusions were formulated.

The guideline draft and an invitation to participate in the stakeholder review were published on the ESHRE website between 18 February and 1 April 2021. All comments were processed by the GDG, either by adapting the content of the guideline and/or by replying to the reviewer. The review process was summarized in the review report (Supplementary Data I), which is published on the ESHRE website (www.eshre.eu/Guidelines). Overall, 65% of the 109 comments resulted in an adaptation or correction in the guideline text. The full guideline document, the literature study and evidence tables can be found on the ESHRE website (www.eshre.eu/virusguideline).

This guideline will be considered for update 4 years after publication, with an intermediate assessment of the need for updating 2 years after publication.

Results

Key questions and recommendations

The current document summarizes all the key questions and the recommendations from the guideline 'Medically assisted reproduction for patients with a viral infection/disease'. Figures 1 and 2 provide a summary of the available evidence from the literature on the topics included in the recommendations. Further background information and the supporting evidence for each recommendation can be found in the full version of the guideline available at https://www.eshre.eu/VirusGuideline.

Hepatitis B virus

A summary of the management of medically assisted reproduction in patients testing positive for hepatitis B virus (HBV) can be found in Fig. 3.

	Virus detected in sperm	Virus detected in oocytes	Virus detected in placenta	Virus detected in breastmilk	Impact on MAR outcome	
HBV	Yes	Yes	Yes	Yes (HBsAg)	Contradictory data	No effect
HCV	Probably not	Probably not	Probably not	Probably not	Contradictory data	Contradictory data
HIV	No*	No	Contradictory data	Yes	No	Yes
HPV	Yes	No data	Contradictory data	Yes	Yes	Unclear
HTLV I/II	No data	No data	No data	Yes	No data	Probably not
ZIKV	Yes	No data	Yes	Yes	No data	No data

*Only viral-like particles the size of HIV have been detected in spermatozoa.

Figure 1. Summary of the available evidence on the topics included in the guideline. HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papilloma virus; HTLV I/II, human T-lymphotropic virus I/II; MAR, medically assisted reproduction; ZIKV, Zika virus.

	Type of infection	Vaccine available	Horizontal / sexual transmission	Horizontal transmission during MAR	Prevention of vertical transmission by CS	Vertical transmission via breastfeeding	Prophylaxis in neonate
HBV	Acute / Persistent	Yes	Yes	Yes → Vaccinate unaffected partner	Probably not	Probably not	Yes
HCV	Acute / Persistent	No	Limited	Limited	Probably not	Probably not	No
HIV	Acute / Persistent	No	Yes	Yes → Semen processing for males	If detectable viral load	Yes	Yes
HPV	Transient	Yes	Yes	Yes	Probably not	Probably not	No
HTLV I/II	Acute / Persistent	No	Yes	Yes	Unknown	Yes	No
ZIKV	Transient	No	Yes	Yes	Probably not	Unknown	No

Figure 2. Summary of further evidence on the topics included in the guideline. CS, caesarean section; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papilloma virus; HTLV I/II, human T-lymphotropic virus I/II; MAR, medically assisted reproduction; ZIKV, Zika virus.

HBV	Male testing positive	Female testing positive	Couple testing positive
Before MAR	Vaccinate non-infected partner		
	Consult with infectious disease / liver disease specialist		
		Discuss: - Risk of viral vertical transmission (not eliminated by MAR) - Newborn prophylaxis	
During MAR	IUI, IVF or ICSI depending on infertility work-up		
	Routine semen processing		
After MAR	Caesarean section not recommended		
	Breastfeeding not contra-indicated		
	Vaccination of the neonate	Vaccination of the neonate + HBIG administration	

Figure 3. Summary of management of medically assisted reproduction in patients testing positive for hepatitis B virus. HBIG, hepatitis B immunoglobulin; HBV, hepatitis B virus; MAR: medically assisted reproduction.

Prevention of transmission before medically assisted reproduction

Partners of hepatitis B virus (HBV)-positive individuals should be vaccinated.	Strong ⊕○○○
Barrier contraception should be used until the completion of the HBV vaccination protocol (Inaba *et al.*, 1979; Rosenblum *et al.*, 1992; Hou *et al.*, 1993; Huo *et al.*, 1998; Katoonizadeh *et al.*, 2018; Tufon *et al.*, 2019).	Strong ⊕⊕○○
Medically assisted reproduction (MAR) services staff should be vaccinated against HBV.	GPP
All patients with an active or chronic HBV-infection must be reviewed by an infectious disease/liver specialist before initiating any MAR treatment.	Strong ⊕○○○
Commencing with MAR treatments in patients positive for HBV should be a joint decision between the patient, their partner, the fertility doctor and the infectious disease/liver specialist.	Strong ⊕○○○
In the case of the female testing positive for HBV, the possibility of viral vertical transmission, the availability of vaccination during pregnancy and newborn prophylaxis should all be discussed.	GPP

Assisted reproduction techniques and impact on outcomes

The cause of infertility should dictate the specific technique (IUI/IVF/ICSI) used for MAR in couples where one or both partners test positive for HBV (Nie *et al.*, 2019).	Strong ⊕○○○
Women infected with HBV should be informed that MAR does not eliminate the risk of vertical transmission.	GPP
HBV can be detected in sperm cells, oocytes, granulosa cells and embryos. This equates with a theoretical risk of vertical HBV transmission that remains to be proven.	*Conclusion*
Existing evidence cannot clarify if the presence of HBV-infection in the male impacts the outcomes of MAR. Multiple studies showed no differences in reproductive outcomes following MAR when comparing seronegative with HBV-seropositive women.	*Conclusion*

Prevention/reduction of transmission during assisted reproduction

Men testing positive for HBV should be informed that no current semen preparation technique can select HBV DNA-free spermatozoa for use in MAR.	GPP
Routine semen processing according to the ESHRE 'Guideline on good practice in the IVF laboratory' should be used when performing MAR in men testing positive for HBV.	GPP
Based on the current evidence, HBV DNA testing on seminal fluid or sperm is not recommended (Ayoola *et al.*, 1981; Hadchouel *et al.*, 1985; Qian *et al.*, 2005; Fei *et al.*, 2015).	Strong ⊕○○○

Reducing/avoiding vertical transmission

Cesarean delivery is not recommended on the basis of maternal HBV positivity alone (Chen *et al.*, 2019).	Strong ⊕⊕○○
Breastfeeding is not contra-indicated in women testing positive for HBV (Zheng *et al.*, 2011).	Conditional ⊕⊕○○
All neonates born to HBV-positive couples should be vaccinated (Lee *et al.*, 2006; Schillie and Murphy, 2013).	Strong ⊕⊕⊕○
Administration of hepatitis B immunoglobulin (HBIG) in addition to vaccination is recommended for children born to mothers testing positive for HBV (Jin *et al.*, 2014; Machaira *et al.*, 2015).	Strong ⊕⊕○○
HBIG administration should follow local or national guidelines.	GPP

Hepatitis C virus

A summary of the management of medically assisted reproduction in patients testing positive for hepatitis C virus (HCV) can be found in Fig. 4.

Prevention of transmission before medically assisted reproduction

In a monogamous heterosexual relationship of more than 12 months, there is no indication for the use of barrier contraceptives to reduce the risk of hepatitis C virus (HCV) transmission in a serodiscordant-infected couple (Ackerman *et al.*, 1998).	Conditional ⊕⊕○○
All patients with an active or chronic HCV-infection must be reviewed by an infectious disease/liver specialist before initiating any medically assisted reproduction treatment (MAR).	GPP
Commencing with MAR treatments in patients positive for HCV should be a joint decision between the patient, their partner, the fertility doctor and the infectious disease/liver specialist.	Strong ⊕○○○
In the case of the female testing positive for HCV, the possibility of viral vertical transmission should be discussed prior to MAR treatment.	GPP

Assisted reproduction techniques and impact on outcomes

The cause of infertility should dictate the specific technique (IUI/IVF/ICSI) used for MAR in couples where one or both partners test positive for HCV (Garrido *et al.*, 2004; Nesrine and Saleh, 2012; Savasi *et al.*, 2013).	Strong ⊕○○○
Women testing positive for HCV should be informed that MAR does not eliminate the risk of vertical transmission.	GPP
The possibility of HCV RNA presence in oocytes cannot be excluded. However, the risk of Hepatitis C transmission through the use of reproductive material remains to be proven.	*Conclusion*
There are contradictory results evaluating effects of male HCV-infection on infertility treatments outcomes. Although the fertilization rate has been reported significantly lower in couples with HCV-RNA-positive men, other studies report that HCV-infection does not affect the IVF-ICSI cycle outcomes in these couples.	*Conclusion*
There are contradictory results evaluating effects of female HCV infection on infertility treatments outcomes. Although some studies report significantly reduced implantation rates, higher cycle cancelations, and higher FSH use in HCV positive women, other report no significant differences.	*Conclusion*

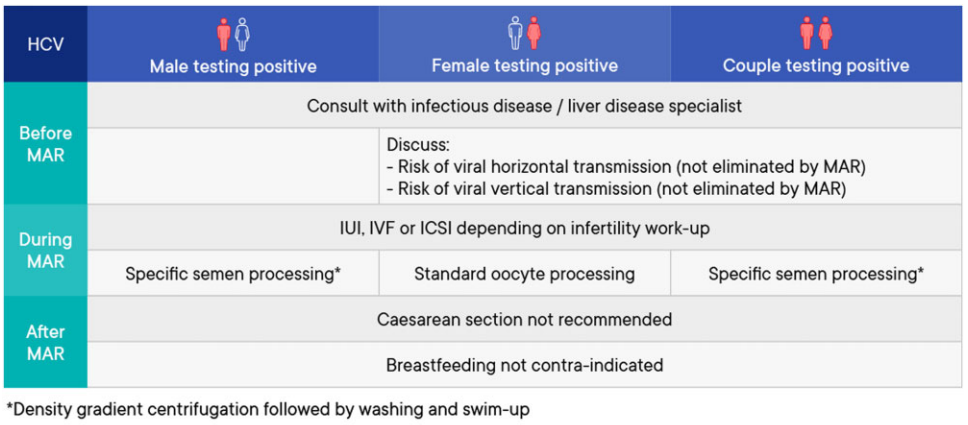

Figure 4. Summary of management of medically assisted reproduction in patients testing positive for hepatitis C virus. HCV, hepatitis C virus; MAR, medically assisted reproduction.

Prevention/reduction of transmission during assisted reproduction

There are no data regarding antiviral therapy in men or women with HCV without co-infections requiring MAR in order to reduce the risk of HCV transmission. None of the currently available HCV antiviral drugs are licensed for use in pregnancy.	*Conclusion*
A discontinuous gradient centrifugation, swim-up and washing is recommended for semen processing in patients testing positive for HCV (Bourlet *et al.*, 2002, 2009; Cassuto *et al.*, 2002; Meseguer *et al.*, 2002; Canto *et al.*, 2006; Garrido *et al.*, 2006; Savasi *et al.*, 2010; Leruez-Ville *et al.*, 2013; Savasi *et al.*, 2013; Molina *et al.*, 2014).	Strong ⊕○○○
After advanced semen processing, PCR testing for HCV is not necessary (Cassuto *et al.*, 2002; Canto *et al.*, 2006; Garrido *et al.*, 2006; Bourlet *et al.*, 2009; Savasi *et al.*, 2010; Leruez-Ville *et al.*, 2013; Molina *et al.*, 2014).	Strong ⊕○○○
Good laboratory practice regarding semen processing should be applied irrespective of whether only the male or both partners are testing positive for HCV.	GPP
High plasma HCV viral load is likely to be predictive of the presence of HCV RNA in semen. Strong evidence for the correlation of HCV viral load between serum and semen is currently lacking.	*Conclusion*

Reducing/avoiding vertical transmission

Cesarean delivery is not recommended on the basis of maternal HCV-positivity alone (Ghamar Chehreh *et al.*, 2011)	Strong ⊕○○○
Breastfeeding is not contra-indicated in HCV-positive women (Cottrell *et al.*, 2013)	Strong ⊕○○○

Human immunodeficiency virus

A summary of the management of medically assisted reproduction in patients testing positive for human immunodeficiency virus (HIV) can be found in Fig. 5.

Prevention of transmission before medically assisted reproduction

Human immunodeficiency virus (HIV)-1-serodiscordant couples should be informed that there is a risk of sexual transmission of the virus to the unaffected partner. To reduce this risk, couples must be advised to use barrier contraception and seek active therapy to reduce viral load (Baggaley *et al.*, 2010; LeMessurier *et al.*, 2018).	Strong ⊕⊕○○
Individuals testing positive for HIV-1, antiretroviral therapy can suppress viral replication. These patients should remain on antiretroviral therapy and providing undetectable viral loads in serum can be achieved and sustained, the risk of horizontal transmission through unprotected intercourse is minimal in the absence of other sexually transmitted diseases (Attia *et al.*, 2009).	Strong ⊕⊕○○
Commencing with medically assisted reproduction (MAR) treatments in patients positive for HIV-1 or 2 should be a joint decision between the patient, their partner, the fertility doctor and the infectious disease specialist.	Strong ⊕○○○
All patients testing positive for HIV, wishing to have a child should be counseled about the risk of horizontal and vertical transmission. In the case of the male testing positive for HIV, antiretroviral therapy can reduce the viral load in blood and semen to undetectable levels, allowing the possibility of natural conception. Reproductive counseling should include fertility and antiretroviral covariates.	GPP
In the case of the female testing positive for HIV-1 or 2, and even with undetectable viremia, the possibility of viral vertical transmission should be discussed prior to MAR treatment.	GPP

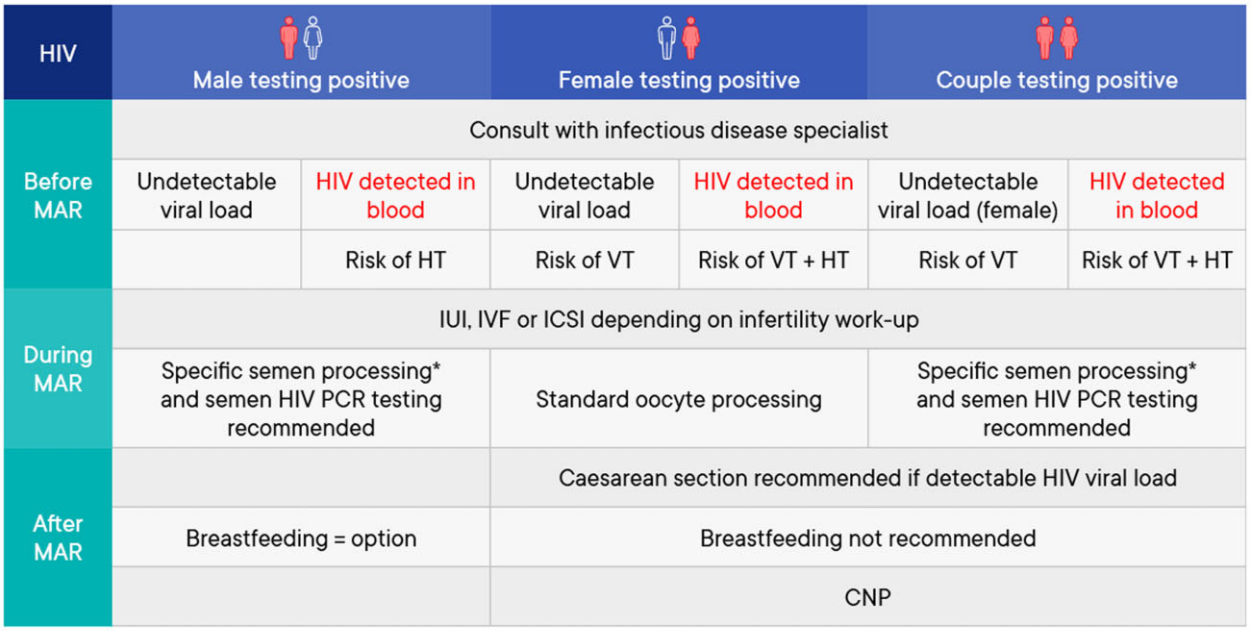

Figure 5. Summary of management of medically assisted reproduction in patients testing positive for human immunodeficiency virus. CNP, combined neonatal prophylaxis; HIV, human immunodeficiency virus; HT, horizontal transmission; MAR, medically assisted reproduction; VT, vertical transmission.

Assisted reproduction techniques and impact on outcomes

HIV infection status is not a reason to deny MAR treatment.	Strong ⊕◯◯◯
The cause of infertility should dictate the specific technique (IUI/IVF/ICSI) used for MAR in couples where one or both partners test positive for HIV (Vitorino *et al.*, 2011; Barnes *et al.*, 2014).	Strong ⊕⊕◯◯
Advanced semen processing should be used for male patients testing positive for HIV-1 to reduce the likelihood of viral presence (Dussaix *et al.*, 1993; Baccetti *et al.*, 1994; Quayle *et al.*, 1997; Deleage *et al.*, 2011; Miller *et al.*, 2019; Young *et al.*, 2019).	Strong ⊕◯◯◯
No special laboratory techniques are needed for processing of oocytes from female patients testing positive for HIV.	Strong ⊕◯◯◯
Serodiscordant couples with a male partner testing positive for HIV-1 should be informed that the efficacy of MAR is not impacted compared to HIV seronegative couples (Bujan *et al.*, 2007; Prisant *et al.*, 2010; Sauer and Chang, 2002; Cito *et al.*, 2019).	Strong ⊕◯◯◯
Serodiscordant couples with a female partner testing positive for HIV should be informed that the efficacy of IVF/ICSI could be reduced compared to HIV seronegative couples (Marques *et al.*, 2015).	Conditional ⊕◯◯◯

Prevention/reduction of transmission during assisted reproduction

The technique recommended for processing ejaculated semen for males testing positive for HIV is to perform a discontinuous density gradient centrifugation followed by 2 semen washing steps, followed by swim-up (Zafer *et al.*, 2016).	Strong ⊕⊕◯◯
Regardless of the semen processing technique used, the post-preparation sample that is going to be used in MAR from males tested positive for HIV should be HIV PCR tested (Zafer *et al.*, 2016).	Strong ⊕⊕◯◯
In serodiscordant couples with the male testing positive for HIV, only a HIV-negative tested sperm sample should be used for MAR (Zafer *et al.*, 2016).	Strong ⊕⊕◯◯
Good laboratory practice regarding semen processing should be applied irrespective of whether only the male or both partners are testing positive for HIV.	GPP
Advanced semen processing is recommended for male patients testing positive for HIV, regardless of the viral load in the serum and therapy status (Kalichman *et al.*, 2008).	Strong ⊕◯◯◯

Reducing/avoiding vertical transmission

Caesarean section is recommended in women with detectable HIV viral loads (Kennedy et al., 2017).	Strong ⊕⊕◯◯
A female testing positive for HIV should refrain from breastfeeding when and where she has safe nutritional alternatives (De Martino et al., 1992; Tess et al., 1998; Coutsoudis, 2000; Olayinka et al., 2000; Mbori-Ngacha et al., 2002; Magoni et al., 2005; Kagaayi et al., 2008; Peltier et al., 2009; Imade et al., 2010; Assefa et al., 2017; Njom Nlend et al., 2018).	Strong ⊕⊕◯◯
Combined neonatal prophylaxis (CNP) is recommended for neonates born to mothers testing positive for HIV.	Strong ⊕⊕⊕◯

Human papilloma virus

A summary of the management of medically assisted reproduction in patients testing positive for human papilloma virus (HPV) can be found in Fig. 6.

Prevention of transmission before medically assisted reproduction

The use of barrier contraception during sexual intercourse is advised to lower the risk of human papilloma virus (HPV) transmission (Dillner et al., 1996; Kjaer et al., 2001; Hernandez et al., 2008; Burchell et al., 2010; Widdice et al., 2013).	GPP
All women starting medically assisted reproduction (MAR) should undergo testing to detect HPV-related cervical lesions.	GPP

Assisted reproduction techniques and impact on outcomes

The cause of infertility should dictate the specific technique (IUI/IVF/ICSI) used for MAR in couples where one or both partners test positive for HPV.	Strong ⊕◯◯◯
Women infected with HPV should be informed that MAR does not eliminate the risk of vertical transmission.	GPP
The possibility of HPV testing could be discussed with couples undergoing IUI.	Research only
Couples with a known positive HPV test should be advised that HPV is a transient infection, and postponing MAR treatment is an option depending on the individual circumstances.	GPP

Prevention/reduction of transmission during assisted reproduction

There is weak evidence that therapeutic HPV vaccination in HPV-positive men may increase pregnancy rates in natural conception and reduce miscarriage rates. However, more studies are necessary.	*Conclusion*
HPV-positive males should be informed that no current semen preparation technique can eliminate the virus from the infected semen sample.	GPP

Reducing/avoiding vertical transmission

Caesarean delivery is not recommended on the basis of maternal HPV-positivity alone (Chatzistamatiou et al., 2016; Zouridis et al., 2018).	Strong ⊕⊕◯◯
Breastfeeding is not contra-indicated in HPV-positive women (Yoshida et al., 2011; Glenn et al., 2012; Louvanto et al., 2017).	Conditional ⊕◯◯◯

Human T-lymphotropic virus I/II

A summary of the management of medically assisted reproduction in patients testing positive for human T-lymphotropic virus (HTLV) I/II can be found in Fig. 7.

Prevention of transmission before medically assisted reproduction

It is suggested human T-cell lymphotropic virus (HTLV I/II)-serodiscordant couples should be informed that there is a risk of sexual transmission of the virus to the unaffected partner. To reduce this risk, couples could be advised to use barrier contraception and receive reproductive counseling if they want to conceive (Roucoux et al., 2005; Stuver et al., 1993).	Conditional ⊕◯◯◯

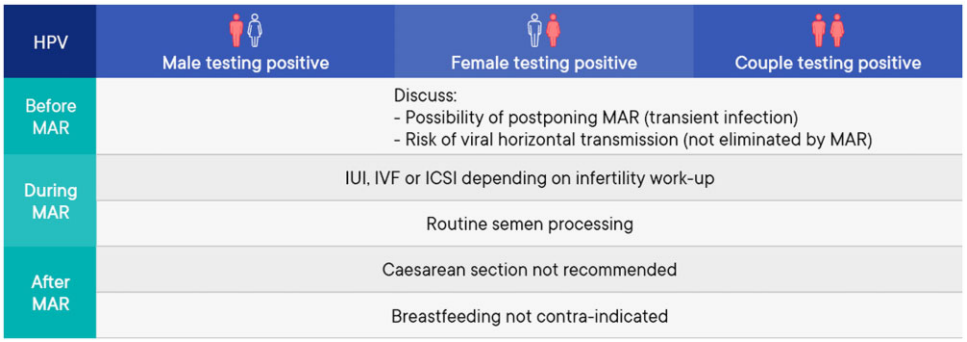

Figure 6. Summary of management of medically assisted reproduction in patients testing positive for human papilloma virus. HPV, human papilloma virus; MAR, medically assisted reproduction.

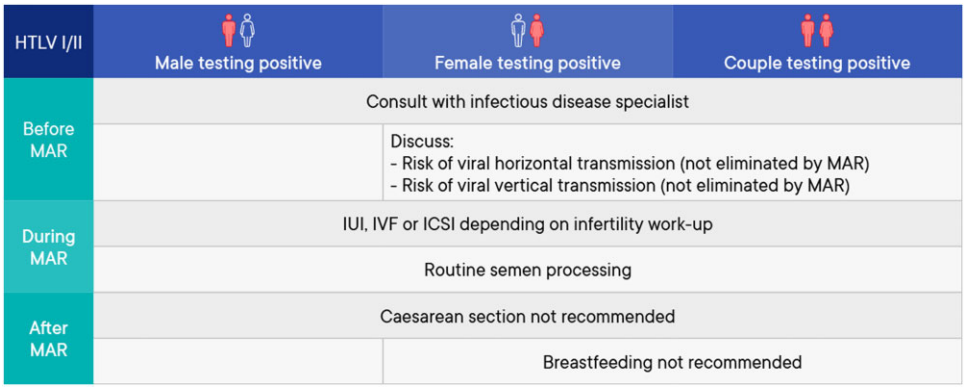

Figure 7. Summary of management of medically assisted reproduction in patients testing positive for human T-lymphotropic virus I/II. HTLV, human T-lymphotropic virus; MAR, medically assisted reproduction.

Assisted reproduction techniques and impact on outcomes

The cause of infertility should dictate the specific technique (IUI/IVF/ICSI) used for medically assisted reproduction (MAR) in couples where one or both partners test positive for HTLV I/II (Stuver *et al.*, 1993; Kaplan *et al.*, 1996; Paiva *et al.*, 2017).	Strong ⊕○○○
Women testing positive for HTLV I/II should be informed that MAR does not eliminate the risk of vertical transmission.	GPP
Studies on HTLV I/II viruses are dated and the technology to detect these viruses has changed a lot since. Therefore, the possibility of HTLV I/II presence in gametes or placenta cannot be confirmed or excluded. To date, the risk of HTLV I/II transmission through the use of infected semen or oocytes remains to be proven.	*Conclusion*
The impact of female HTLV I infection on MAR outcomes remains unknown.	*Conclusion*

Prevention/reduction of transmission during assisted reproduction

No studies were identified comparing routine semen preparation with advanced semen processing in males testing positive for HTLV I/II. Similarly, no studies were identified investigating the correlation between viral load in semen and serum in HTLV I/II infected patients.

Reducing/avoiding vertical transmission

Caesarean delivery is not recommended on the basis of maternal HTLV I/II positivity alone (Paiva *et al.*, 2018).	Strong ⊕○○○
A female testing positive for HTLV I/II should refrain from breastfeeding when and where she has safe nutritional alternatives (Boostani *et al.*, 2018)	Strong ⊕○○○

Zika virus

A summary of the management of medically assisted reproduction in patients testing positive for Zika virus (ZIKV) can be found in Fig. 8.

Prevention of transmission before medically assisted reproduction

A male diagnosed with ZIKV-infection or returning from a ZIKV endemic region should use barrier contraception with any partner, for 3 months.	GPP
A female diagnosed with ZIKV-infection or returning from a ZIKV endemic region should use barrier contraception and avoid pregnancy for 2 months.	GPP

Assisted reproduction techniques and impact on outcomes

If a patient or partner has been diagnosed with ZIKV-infection or returning from a ZIKV endemic region in the last 3 months, medically assisted reproduction (MAR) treatment should be postponed.	GPP
In case of fertility preservation, the approach should be tailored to the individual situation	GPP
In the case of fertility preservation, there is insufficient data on the risk of viral transmission using gametes potentially infected with Zika virus. An individual risk assessment is advised before using these gametes.	GPP
If ZIKV-infection is diagnosed in male or female during MAR treatment, the cycle should be stopped, and the couple should be advised to use barrier contraception for 3 months.	GPP

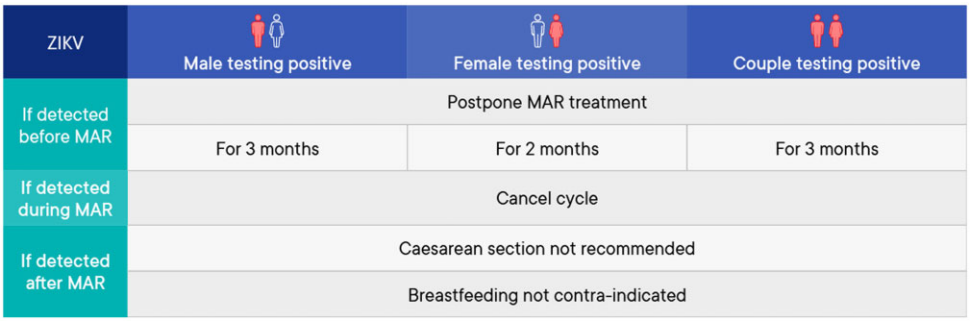

Figure 8. Summary of management of medically assisted reproduction in patients testing positive for Zika virus. MAR, medically assisted reproduction; ZIKV, Zika virus.

Prevention/reduction of transmission during assisted reproduction

There are currently no semen processing techniques available that can completely remove Zika virus from semen.	*Conclusion*
MAR is not advised even if serum is free of Zika virus because of poor correlation between serum and semen viral load (Joguet *et al.*, 2017; Musso *et al.*, 2017; Barzon *et al.*, 2018; Mead *et al.*, 2018; Paz-Bailey *et al.*, 2018).	Strong ⊕○○○

Reducing/avoiding vertical transmission

The possibility of transmission of Zika virus through breastfeeding has only been assessed in 12 mother-child pairs. This provides insufficient evidence to establish a recommendation.	*Conclusion*

Laboratory safety

Can separate cryo tank storage prevent cross contamination of stored material?

Since viruses can survive and be transmitted via liquid nitrogen (LN2), separate storage of reproductive cells according to viral positive and viral negative status is recommended.	GPP
Emptied and dried cryo tanks and transport shippers should be disinfected according to local standard operating procedures to reduce the potential of cross-contamination.	GPP
Individual clinics must risk assess to decide the number of cryo tanks needed.	GPP
Separate cryopreservation dewars should be used to quarantine gametes and embryos from patients with unknown infectious status.	GPP

Can the type of cryostorage environment (liquid versus vapor/open versus closed systems) prevent cross contamination of stored material?

Vapor phase cryopreservation could be considered over liquid nitrogen in terms of safety to reduce the risk of cross-contamination (Bielanski, 2005; Grout and Morris, 2009; Mirabet *et al.*, 2012; Molina *et al.*, 2016)	Conditional ⊕○○○
Provided the cryomaterial is not compromised, cryodevices, such as sealed semen straws/vials, should be cleaned with a disinfectant wipe after removal from LN2 storage to mitigate risk of transmission of pathogens from the cryodevice surface.	GPP

Can the type of vials prevent cross-contamination of stored material?

Hermetical sealing of cryovials with additional covers could reduce the risk of cross-contamination of stored material (Chen *et al.*, 2006)	Conditional ⊕○○○

Can high security straws prevent cross-contamination of stored material?

The use of high security straws in combination with thermal sealing is the preferred approach as it minimizes the risk of cross-contamination (Maertens *et al.*, 2004).	Strong ⊕○○○
At the time of thawing, decontamination of the exterior of the straw and the single use of sterile scissors will reduce the risk of contaminating the stored contents with potential pathogens.	GPP

Can the use of separate labs prevent cross contamination?

Given that personal protective equipment (PPE), laboratory equipment and exposed surfaces can be contaminated even after good laboratory practice, disinfection and changing PPE between cases can reduce the risk of cross-contamination.	GPP
The recommended procurement, processing, release and storage procedures should be used for all samples, not only virally positive samples.	GPP

Discussion

The current paper summarizes the 78 recommendations on prevention of viral transmission before and during MAR, preferred MAR techniques, their effect on outcomes, and interventions to reduce/avoid vertical transmission to the newborn collated from the ESHRE guideline on 'Medically assisted reproduction in patients with a viral infection/disease'. This guideline covers all aspects of the management of MAR in patients with a viral infection/disease, and was written by a multidisciplinary group of gynecologists and fertility specialists, embryologists and a virologist. It offers a broad scope for investigating, counseling and treating couples and individuals with a viral condition, be it transitory or chronic. As a basis for the current guideline, a broad and formal literature review was conducted. We identified very few randomized controlled trials with evidence for most interventions deriving from case series.

Considering the importance and clinical relevance of the topic, it was surprising to find that research data on many aspects, for example gamete–embryo–viral interaction in the MAR laboratory, are scarce. Even though the viruses discussed in the current guideline are of the most prevalent and/or 'understood' viruses at the present time, the current studies are limited in size and quality owing to the reduced number of patients with viral infection/disease presenting at fertility clinics or having access to MAR treatment. Furthermore, some viruses cause a transient event (i.e. ZIKA, HPV), many times asymptomatic, and the window of opportunity for long-term research is not present. A second deterrent for establishing robust research projects in the case of ZIKA, for example, is the current accepted guideline that pregnancy should be avoided, making any research proposal ethically questionable. The group reviewed the data on HPV infection and male and female infertility and even though this research is novel, this is a virus that deserves the attention of practitioners and patients alike.

In the case of HTLV I/II, its limited geographical prevalence means that even though the effects of the infection are significant for the affected individuals, the relevance to the global medical community remains low. In consequence, studies on the impact of HTLV I/II infection on MAR are lacking.

Research gaps were detected in several areas, and these are documented in a list of recommendations for further research (Supplementary Data II). As a matter of focus for the future, national data collection on outcomes of MAR treatment in patients with viral disease and the development of national centers of excellence where a larger cohort of affected patients can be offered therapy might help create the opportunity to find answers to questions that remain unanswered after this review, protected by an ethical and legal framework that could allow the opportunity to conduct high quality research on the topic.

Despite the limitations of guidelines in general, and the limitations in the evidence supporting the current guideline, the guideline group is confident that this document will help best practice in the management of MAR in patients with a viral infection/disease.

Supplementary data

Supplementary data are available at *Human Reproduction Open* online.

Data availability

The full guideline document, the literature study and evidence tables can be found on the ESHRE website (www.eshre.eu/virusguideline).

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Authors' roles

E.M. chaired the GDG and hence fulfilled a leading role in collecting the evidence, writing the manuscript and dealing with reviewer comments. N.L.C. as methodological expert, performed all literature searches for the guideline, provided methodological support and coordinated the guideline development. All other authors, listed in alphabetical order, as GDG members, contributed equally to the manuscript, by drafting key questions, synthesizing evidence, writing the different parts of the guideline and discussing recommendations until consensus within the group was reached.

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Conflict of interest

A.D. reports research fees from Ferring and Merck, consulting fees from Ferring, outside the submitted work. C.P. reports speakers fees from Merck and MSD outside the submitted work. K.T. reports speakers fees from Cooper Surgical and Ferring and consultancy fees as member of the advisory board BioTeam of Ferring, outside the submitted work. The other authors have no conflicts of interest to declare.

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