

2021

ESHRE Guideline Group for MAR in  
patients with viral infection/disease

# Medically assisted reproduction in patients with viral infection/disease

Guideline of the European Society of Human  
Reproduction and Embryology

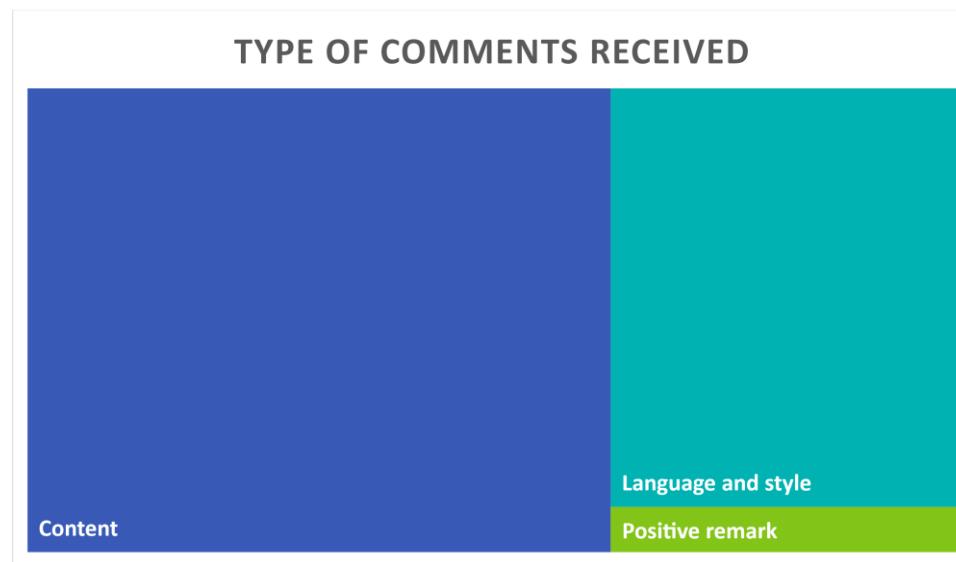
## REVIEW REPORT

The draft of the guideline on Medically assisted reproduction in patients with a viral infection/disease was published for stakeholder review for 6 weeks, between 18 February and 1 April 2021.

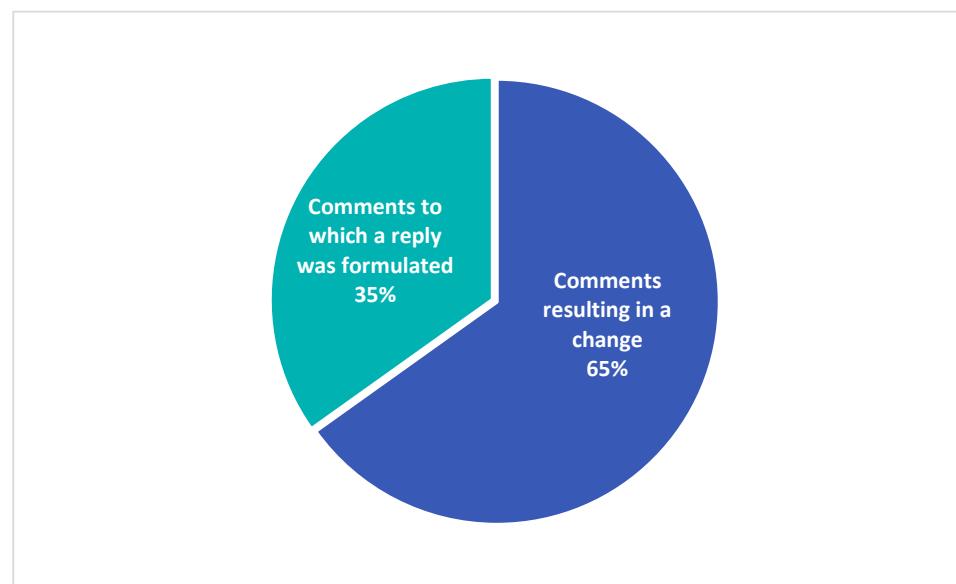
This report summarizes all reviewers, their comments and the reply of the guideline development group and is published on the ESHRE website as supporting documentation to the guideline.

During the stakeholder review, a total of 109 comments were received from 10 reviewers, including 1 representative of a professional organisation and 9 individual (or group of) experts.

The comments included 69 comments on the content of the guideline, 37 language and style corrections and 4 positive remarks that did not require a reply.



All comments were checked by the guideline development group and either addressed (in the guideline) or a reply was formulated. Most of the corrections for language and style (89%) were adapted in the guideline. Of the 69 comments to the content of the guideline and the recommendations, 38 (55%) resulted in an adaptation or correction in the guideline text.



# Experts that participated in the stakeholder review

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The list of representatives of professional organization, and of individual experts that provided comments to the guideline are summarized below.

## Representatives of professional organizations

Organization	Country	Representative
British Fertility Society	UK	Harish M Bhandari

## Individual experts

Reviewer	Country
<b>Thomas Mitchell, James Duffy, Anastasia Mania, Niki Konsta, Ippokratis Sarris</b>	UK
<b>Pierre Boyer</b>	France
<b>Carlos Calhaz-Jorge</b>	Portugal
<b>Stefan Matik</b>	North Macedonia
<b>Qianhong Ma, Fang Ma</b>	China
<b>Charalampos Siristatidis</b>	Greece
<b>Liana Bosco</b>	Italy
<b>Kimball O. Pomeroy</b>	USA
<b>Janek von Byern</b>	Austria

# Reviewer comments and replies

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Name	Page	Line	Comment	Reply
<b>Introduction, scope and general comments</b>				
British Fertility Society			Extremely well written document which covers an important subject in reproductive medicine. The British Fertility Society would like to congratulate all the authors and thank them for their hard work.	Thank you.
British Fertility Society	Page 13	B5 rec 23	Typo – should say advanced (not advances)	This was adjusted.
British Fertility Society	Page 16	C6	CNP is not in list of abbreviations on page 163	This was adjusted.
British Fertility Society	Page 21	H 74	Typo – delete “of” or change hermetically to hermetic	This was adjusted.
British Fertility Society	Page 28	379	Typo – change “was” to “were”	This was adjusted.
British Fertility Society	Page 29	412	Add “is completed” after successful vaccination course	A successfull vaccination course implicates that the vaccination course was completed.
British Fertility Society	Page 29	420	Typo - delete “to”	This was adjusted.
British Fertility Society	Page 29	426	Suggest changing “including” to “of”	This was adjusted.
British Fertility Society	Page 33	523	Typo – “investigate” not “investigated”	This was adjusted.
British Fertility Society	Page 34	575	Typo – change “were” to “where”	This was adjusted.
British Fertility Society	Page 35	607	Typo – delete “and”	This was adjusted.
British Fertility Society	Page 35	608	Typo – delete “in”	This was adjusted.
British Fertility Society	Page 35	615	Typo – delete “and”	This was adjusted.
British Fertility Society	Page 41	779	Typo – delete “in”	This was adjusted.

<b>British Fertility Society</b>	Page 42	836	Add "1214 infants at more than 12 months of age"	This was adjusted.
<b>British Fertility Society</b>	Page 52	1148	Add "of these" after "positive and"	Thank you for the suggestion, this was amended as suggested by the reviewer.
<b>British Fertility Society</b>	Page 52	1163	Typo - change "was" to "were" (2 occurrences on this line)	This was adjusted.
<b>British Fertility Society</b>	Page 53	1170	"of which 19.8% had a relationship" might be better structured starting as new sentence "Prevalence was 19.8% for those with a relationship >20 years.."	Thank you for the suggestion, this was amended as suggested by the reviewer.
<b>British Fertility Society</b>	Page 53	1177	Typo - change "was" to "were"	This was adjusted.
<b>British Fertility Society</b>	Page 56	1257	Typo - delete "and"	This was adjusted.
<b>British Fertility Society</b>	Page 63	1469	Change "semen" to "prepared sperm samples" or "sperm preparations"	The GDG has discussed which term preferentially to use, and they decided on semen.
<b>British Fertility Society</b>	Page 64	1491	Typo – "O" missing from "One"	This was adjusted.
<b>British Fertility Society</b>	Page 65	1527	Typo – change "HcV" to "HCV"	This was adjusted.
<b>British Fertility Society</b>	Page 88	2247	Should "access" be "excess"?	This was adjusted.
<b>British Fertility Society</b>	Page 90	2323	Typo – delete "you"	This was adjusted.
<b>British Fertility Society</b>	Page 139	3928	Typo – change "can" to "be"	This was adjusted.
<b>British Fertility Society</b>	Page 156	4377	Typo – add "is" after "frozen sperm"	This was adjusted.
<b>British Fertility Society</b>	Page 157	4397	Typo – delete "of" or change hermetically to hermetic	This was adjusted.
<b>Carlos Calhaz-Jorge</b>			Warm congratulations to the GDG for the high quality of the guideline	Thank you.
<b>Carlos Calhaz-Jorge</b>			There are some inconsistency on the terminology – sometimes MAR others ART. Of course MAR is a much broader concept than just ART+IUI but I guess a consistent use along the text should be better	The abbreviation ART was not used in the guideline tekst.
<b>Carlos Calhaz-Jorge</b>			The inclusion of "Conclusions" in the "List of all recommendations" is disputable. I would support their removal.	The GDG did not formulate a recommendation for each PICO question. The conclusions provide an answer to the PICO question in the absence of a recommendation.

<b>Carlos Calhaz-Jorge</b>			Conditional recommendations don't follow the pattern "we recommend" and "we probably recommend" described in the guide for guidelines construction	All recommendations have been checked and the wording has been adjusted where necessary.
<b>Carlos Calhaz-Jorge</b>	13	B3 - last conclusion	"reduced implantation rate" is repeated	Thank you, this was adjusted.
<b>Carlos Calhaz-Jorge</b>		Rec 23	I guess it should be "advanced" instead of "advances"	We agree with this comment, this sentence has been deleted.
<b>Carlos Calhaz-Jorge</b>		Rec 45	Meaning of CNP? (not in abbreviations)	This has been adjusted.
<b>Stefan Matik</b>			Excellent and thorough work, a very detailed and comprehensive guideline.	Thank you.
<b>Stefan Matik</b>	Page 105	2873	'acquires' should be replaced with 'acquire'	This has been adjusted.
<b>Stefan Matik</b>	Page 105	2879	'cervix, oropharynx, penis, vulva, vagina and anus cancers.' should be replaced with 'cervical, oropharyngeal, vulvar, vaginal and anal cancers.' A causal role for HPVs in prostate cancer is highly likely. Reference: Lawson, J.S., Glenn, W.K. Evidence for a causal role by human papillomaviruses in prostate cancer – a systematic review. Infect Agents Cancer 15, 41 (2020). <a href="https://doi.org/10.1186/s13027-020-00305-8">https://doi.org/10.1186/s13027-020-00305-8</a>	This has been adjusted.
<b>Stefan Matik</b>	Page 105	2880	'cancer' should be replaced with 'cancers'	This has been adjusted.
<b>Stefan Matik</b>	Page 105	2889	'increase' should be replaced with 'increases'	This has been adjusted.
<b>Charalampos Siristatidis</b>			Comprehensive search, high level work, some points to be revised	Thank you.
<b>Hepatitis B virus (HBV)</b>				
<b>Carlos Calhaz-Jorge</b>	10		Both Rec 3 and 4 refer to "All patients ...". However the justification presented is restricted to vertical transmission. Maybe not the right justification.	The justification has been elaborated as suggested by the reviewer.
<b>Carlos Calhaz-Jorge</b>	12	rec 4/18	Why are not the patients participating in the joint decision?	Patients of course are participating to the decision and are informed of their infectious status and infertility tests. With this sentence, we just wanted to highlight that the decision to start MAR for these patients should not be the single decision from the fertility doctor but a joint one, together with the infectious disease specialist. We have amended the

				recommendation to make this more clear.
<b>Carlos Calhaz-Jorge</b>	Page 23	Table	Prevention of vertical transmission by CS – “probably not” However, most recommendations about avoiding CS are labeled “strong”. It looks somehow inconsistent	Recommendations are the result of balancing the evidence with benefits/harms, acceptability to patients and stakeholders, costs, etc. The table on page 23 is a summary of the evidence, which explains why this seems inconsistent. An introductory sentence has been added to the table to clarify this.
<b>Carlos Calhaz-Jorge</b>	Page 25	327-328	Not clear which European regions you are referring to	In the WHO hepatitis report, vaccination coverage has been reported by region, not by country.
<b>Stefan Matik</b>	Page 37	684	Although the scope of this section of the guideline is prevention/reduction of transmission during assisted reproduction, i.e. more specifically in this part – vaccination of serodiscordant couples; and good laboratory practices in the IVF laboratory are addressed in the ESHRE guideline on good practice in the IVF laboratory, it might be reasonable to highlight in this section that ‘vaccination against hepatitis B in unvaccinated IVF personnel is highly recommended to reduce the risk of viral transmission through contaminated biological material. Also, local and institutional guidelines should be strictly followed in the event of prick incidents with hepatitis B contaminated materials, as effective hepatitis B post-exposure prophylaxis is available.’	The Guideline is about patients with viral disease. Yet, this is a valid comment. A GPP has been added to the guideline.
<b>Qianhong Ma, Fang Ma</b>			It is suggested that there should be multicenter large sample data on the correlation between viral load in the body and replication rate at different stages of HBV infection status (when different antigens and antibodies are positive); it is also suggested that there should be a chain of convincing evidence for viral transmission(including mammalian and other animal studies) in the female, from the viral load of serum to the follicular fluid cumulus cell complex (or cumulus cells), the zona pellucida on the oocyte surface, and the surface of the ovum membrane; it is suggested that we should continue to study whether there are HBV related fragments integrated into the organelles and nuclei of human and animal germ cells infected with HBV; it is suggested that when women need emergency ART treatments should be further clarify , such as when HBV copy amount> 105~7and there are indications for antiviral therapy, the shortest effective time for antiviral therapy to control viral replication; it is suggested to continue the clinical and basic research on the influence of virus on sperm quality in HBV infected men, and to clarify the way of influence; it is suggested to explore the different proportion of reagents that can be used to remove virus adhesion on	It was not clear what the reviewer was referring to with this comment, so the GDG was unable to formulate a reply to this comment.

			sperm surface in men infected with HBV with different amount of virus replication; it is suggested that clinical detection methods (such as the detection of embryo culture medium) should be found to determine whether the embryo is infected with HBV. If the embryo is infected with HBV and the virus replication rate is high, whether there is an effective method to remove it. In embryo cryopreservation, it is suggested that gametes and embryos from the source of virus replication rate should be cryopreserved separately.	
<b>Hepatitis C virus (HCV)</b>				
Carlos Calhaz-Jorge	12	rec 4/18	Why are not the patients participating in the joint decision?	Patients of course are participating to the decision and are informed of their infectious status and infertility tests. With this sentence, we just wanted to highlight that the decision to start MAR for these patients should not be the single decision from the fertility doctor but a joint one, together with the infectious disease specialist. We have amended the recommendation to make this more clear.
Carlos Calhaz-Jorge		B4	Last sentence completely repeats Rec 18	We agree with this comment, this sentence has been deleted.
Carlos Calhaz-Jorge		Rec 24	Please consider "...of whether only the male or both partners..."	Thank you for this suggestion, this has been adjusted as suggested by the reviewer.
Carlos Calhaz-Jorge	Page 23	Table	Prevention of vertical transmission by CS – “probably not” However, most recommendations about avoiding CS are labeled “strong”. It looks somehow inconsistent	Recommendations are the result of balancing the evidence with benefits/harms, acceptability to patients and stakeholders, costs, etc. The table on page 23 is a summary of the evidence, which explains why this seems inconsistent. An introductory sentence has been added to the table to clarify this.
<b>Human Immunodeficiency virus (HIV)</b>				
Thomas Mitchell, James Duffy, Anastasia Mania, Niki Konsta, Ippokratis Sarris			Would the guideline committee please consider making the recommendations for horizontal transmission clearer with a specific recommendation that serodiscordant partners be counselled of effectively no risk of HIV transmission when compliant on cART with a sustained undetectable viral load.	The recommendation has been adjusted as suggested by the reviewers.

<b>Thomas Mitchell, James Duffy, Anastasia Mania, Niki Konsta, Ippokratis Sarris</b>			In our view the guideline could be strengthened by emphasising the importance of engaging with a HIV specialist when planning fertility treatment.	The GDG stands by the recommendation as it was formulated originally and does not need further elaboration.
<b>Thomas Mitchell, James Duffy, Anastasia Mania, Niki Konsta, Ippokratis Sarris</b>			Reflecting upon the guideline we believe the guideline requires further emphasis upon a patient centered approach to care. Explicitly states regarding personalisation of treatment including a specific commitment to shared decision making which incorporates and considers a patient's values, circumstances, and preferences would be helpful. Such an approach has particular emphasis within this patient population.	This holds true for all patients in general care, no specifically for patients with viral diseases. Patient perspective is an important factor that is always taken into account when formulating recommendations in the ESHRE guidelines in line with the GRADE methodology.
<b>Thomas Mitchell, James Duffy, Anastasia Mania, Niki Konsta, Ippokratis Sarris</b>			Please consider strengthening your recommendations when considering the proven benefits of commencing cART treatment in all patients with a new diagnosis of HIV before medically assisted reproduction. Such an approach would serve to reinforce the benefit of starting cART, within the context of transmission and improved longer term outcome. CD4 cell count should not be used as a criterion for starting cART.	Starting patients on antiretroviral therapy before initiating MAR is a decision to be made by the infectious disease specialist, not the fertility doctor. This is explained in the justification below the recommendation that commencing MAR should be a joined decision between the patient, the fertility doctor and the infectious disease specialist.
<b>Thomas Mitchell, James Duffy, Anastasia Mania, Niki Konsta, Ippokratis Sarris</b>			Please consider reviewing your recommendations pertaining to the use of barrier contraception. It is our view that making these recommendations clear with specific circumstances for which barrier contraception is needed would provide greater clarity to colleagues and patients.	The GDG finds that the advise for use of barrier conception or the possibility to use unprotected intercourse is clearly indicated for each virus in the guideline.
<b>Thomas Mitchell, James Duffy, Anastasia Mania, Niki Konsta, Ippokratis Sarris</b>			In our view the guideline could be strengthened by emphasising the need for a multi-disciplinary approach to pre-conception counselling which includes the optimization of health status, including reviewing their antiretroviral agents.	The GDG stands by the recommendation as it was formulated originally and does not need further elaboration.
<b>Thomas Mitchell, James Duffy, Anastasia Mania, Niki Konsta, Ippokratis Sarris</b>			In our view the guideline could be strengthened by emphasising the pivotal role of cART in reducing vertical transmission.	One recommendation has been adjusted as suggested by the reviewers. The other recommendations on vertical transmission already implicate the importance of undetectable serum HIV loads and don't require further elaboration in our opinion.
<b>British Fertility Society</b>	Page 90	2312	Use of fresh semen samples may be difficult due to need coordinate with rapid PCR testing – should cryopreservation be mentioned?	The reviewer made a valid remark. The guideline recommends PCR testing, however, how testing should be organized in practice is not within scope of the guideline.

<b>Carlos Calhaz-Jorge</b>	Page 14	Rec 29	Again patients excluded from a joint decision... The justification is the same text of the recommendation. Needed?	Patients of course are participating to the decision. They have already expressed their intention to do MAR. and are informed of their infectious statut and infertility test. At that point, it is the obligation of the physicians to evaluate the biological safety of the procedure and, of course, inform the patients and explain why this is possible or not. The justification has been altered.
<b>Carlos Calhaz-Jorge</b>	Page 15	Rec 34	It looks a scientific statement and not at all a recommendation	The recommendation has been adjusted.
<b>Carlos Calhaz-Jorge</b>	Page 16	Rec38	In the justification it seems that some word is missing after "the most"	Thank you, the justification has been adjusted.
<b>Carlos Calhaz-Jorge</b>		Rec39, 40 and 41	I suggest stating that we are talking of men tested positive for HIV. Just for the sake of correctness	Thank you, these recommendations have been adjusted as suggested.
<b>Carlos Calhaz-Jorge</b>	Page 24	Table	HIV – virus detected in the sperm "No". Is it correct?	Indeed, there is no evidence of infectious HIV virions in sperm, only HIV-like viral particles. A remark has been added to the table to clarify this.
<b>Qianhong Ma, Fang Ma</b>			it is suggested to first improve the effectiveness of antiviral treatment and the effectiveness of blocking mother to child transmission; it is suggested that women infected with HIV (including type I and type II) should take contraceptives in the acute attack period, and avoid other sexual intercourse routes (including oral and anal sex); it is suggested that art treatment should be avoided for women infected with HIV without more medical evidence of blocking mother to child transmission; for men with HIV infection, it is suggested to find more effective methods of semen treatment to remove virus from seminal plasma and sperm surface. For the couples infected with HIV who have acquired gametes or embryos, we should find a method to detect the amount of virus replication in gametes and embryos, and determine the fate of gametes and embryos.	It was not clear what the reviewer was referring to with this comment, so the GDG was unable to formulate a reply to this comment.
<b>Charalampos Siristatidis</b>	P 16 table	C6 ln 43	"Caesarean section is recommended in women with detectable HIV viral load.": it would be preferable and practical to indicate the load in numerical data.	Thank you for this comment. However, we have not looked into the evidence regarding HIV viral threshold before delivery for vertical transmission.
<b>Charalampos Siristatidis</b>		C6 ln 44	As the evidence is strong, the sentence " and where safe nutritional alternatives exist ' can be removed.	The evidence is indeed strong, however, even within Europe, not every woman testing positive for HIV has the option to use safe nutritional alternatives for breastfeeding.

Charalampos Siristatidis	VI Annex 7 lit	446	The study of Giles 2011 was excluded, because of the small study cohort (39 HIV-positive clients): I am not sure if this stands correctly, unless the number of included patients was a priori determined and decided to be excluded. The same observation stands for Wu, 2011. Also, in "Coinfections in the study population": was there an intention to pool data? To make the final conclusion more robust?	As part of the guideline development process, a risk of bias analysis was performed for all studies considered for inclusion in the guideline. These studies were redeemed high risk of bias and the presence of higher quality evidence resulted in their exclusion from the body of evidence of the guideline. The exclusion of studies including co-infected patients was a decision that was made by the GDG at the start of the evidence synthesis, because coinfections might influence the outcomes of the studies.
Charalampos Siristatidis		540	"Significant risk of bias due to poor methodology": I totally agree (that one study with poor methodology would affect our final effect estimate), but this belongs to a sensitivity analysis.	As part of the guideline development process, a risk of bias analysis was performed for all studies considered for inclusion in the guideline. These studies were redeemed high risk of bias and the presence of higher quality evidence resulted in their exclusion from the body of evidence of the guideline.
<b>Human Papilloma virus (HPV)</b>				
Thomas Mitchell, James Duffy, Anastasia Mania, Niki Konsta, Ippokratis Sarris			In our view the guideline recommendation regarding the routine HPV vaccination should be reviewed.	The recommendation has been taken out of the guideline.
Thomas Mitchell, James Duffy, Anastasia Mania, Niki Konsta, Ippokratis Sarris			In our view the guideline recommendation regarding the postponement of MAR to allow for HPV clearance should be reviewed.	The GDG stands by this recommendation.
Carlos Calhaz-Jorge	Page 17	Rec 47	This recommendation sounds strange in the context of MAR	This is a recommendation in the section "prevention of viral transmission before MAR".
Carlos Calhaz-Jorge		Rec 48	Justification doesn't seem consistent with "strong" recommendation	Since current evidence does not show that one technique is safer in terms of viral transmission, it is important that the MAR technique is used that is most suited for the cause of infertility.
Carlos Calhaz-Jorge	Page 23	Table	Prevention of vertical transmission by CS – "probably not" However, most recommendations about avoiding CS are labeled "strong". It looks somehow inconsistent	Recommendations are the result of balancing the evidence with benefits/harms, acceptability to patients and stakeholders, costs, etc. The table on

				page 23 is a summary of the evidence, which explains why this seems inconsistent. An introductory sentence has been added to the table to clarify this.
<b>Stefan Matik</b>	Page 105	2892	'rate is highest at the penis and lowest at the urethra' could be explained more specifically - 'rate is highest at the penis (penile shaft, followed by the glans penis/coronal sulcus) and lowest at the urethra'. Reference: Giuliano, A. R., Nielson, C. M., Flores, R., Dunne, E. F., Abrahamsen, M., Papenfuss, M. R., Markowitz, L. E., Smith, D., & Harris, R. B. (2007). The optimal anatomic sites for sampling heterosexual men for human papillomavirus (HPV) detection: the HPV detection in men study. <i>The Journal of infectious diseases</i> , 196(8), 1146–1152. <a href="https://doi.org/10.1086/521629">https://doi.org/10.1086/521629</a> .	Thank you for this information. However, this anatomical detail does not add significant clue to the guideline.
<b>Stefan Matik</b>	Page 106	2916	Could be added at the end of the sentence: 'and moreover the presence of HPV DNA on the sperm surface may represent an antigenic stimulus for antisperm antibodies (ASA) formation'. Reference: Garolla, A., Pizzol, D., Bertoldo, A., De Toni, L., Barzon, L., & Foresta, C. (2013). Association, prevalence, and clearance of human papillomavirus and antisperm antibodies in infected semen samples from infertile patients. <i>Fertility and Sterility</i> , 99(1), 125–131.e2. doi:10.1016/j.fertnstert.2012.09.006	Thank you for this comment, this has been added to the guideline text.
<b>Stefan Matik</b>	Page 106	2923	It should be added: 'because none of the current HPV tests takes into consideration the origin of the detected HPV DNA' Reference: from the same reference source.	Thank you for your comment. This depends on the sample and its anatomical site.
<b>Stefan Matik</b>	Page 106	2929-2930	'Human papillomaviruses (HPVs) are small DNA tumour viruses that mainly infect mucosal epithelia of' to be replaced with "Human papillomaviruses (HPVs) are small, non-enveloped, icosahedral viruses with double stranded circular DNA that mainly infect skin or mucosal epithelia of" Reference: Gheit T. (2019). Mucosal and Cutaneous Human Papillomavirus Infections and Cancer Biology. <i>Frontiers in oncology</i> , 9, 355. <a href="https://doi.org/10.3389/fonc.2019.00355">https://doi.org/10.3389/fonc.2019.00355</a>	Thank you for this information. However, it is a virological detail that does not add significant informations in this context.
<b>Stefan Matik</b>	Page 107	2966-2697	In the conclusion it could be added that HPV testing of sperm donors prior to enrollment/freezing might be considered in the future. Reference: Depuydt CE, Donders G, Verstraete L, Vanden Broeck D, Beert J, Salembier G, Bosmans E, Dhont TN, 3217 Van Der Auwera I, Vandeborne K et al. Time has come to include Human Papillomavirus (HPV) 3218 testing in sperm donor banks. Facts, views & vision in ObGyn 2018;10: 201-205.	Thank you for the suggestion. However, there is still too much unknown about the types of HPV involved in infertility.
<b>Stefan Matik</b>	Page 110	3068-3069	It could be added in the sentence that some of the currently available vaccines also protect against low-risk HPV types (6, 11). HPV 6 and 11 are responsible for 90 % of the cases of genital warts. Reference: Yanofsky VR, Patel RV, Goldenberg G. Genital warts: a comprehensive review. <i>J Clin Aesthet Dermatol</i> . 2012 Jun;5(6):25-36. PMID: 22768354; PMCID: PMC3390234.	Thank you for this suggestion, this was added to the justification.

<b>Stefan Matik</b>	Page 115	3212-3213	'Emerging evidence indicates that HPV infection in males affects sperm parameters and may cause reduced pregnancy and increase miscarriage rates.' could be replaced with 'Emerging evidence indicates that HPV semen infection in males affects sperm parameters and may cause reduced pregnancy and increased miscarriage rates, and thus it could be considered a possible risk factor for male infertility'	Thank you for this suggestion. However, the message is the same and in addition, sperm parameters is not an outcome in this guideline.
<b>Stefan Matik</b>	Page 116	3276	'spontaneous' to be added before pregnancies in this sentence: '(vaccine group) whilst 72 did not (control group). Forty-one spontaneous pregnancies, 11 in the control group and'	This was added to the text as suggested by the reviewer.
<b>Charalampos Siristatidis</b>		D3 In 48	Instead of "The cause of infertility should dictate the specific technique" should be rephrased, as there is "there is currently not enough evidence to recommend one".	Thank you for the suggestion, however, the GDG prefers the original formulation of the sentence.
<b>Charalampos Siristatidis</b>		D3 In 51	"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." Clinically HPV when present, will not disappear, so the recommendation should be expressed differently, e.g. according to grade?, macroscopic lesions? HPV testing?	The GDG does not agree with this comment. In approximately one year the 90% of HPV individuals are able to clear the virus (Baseman and Koutsky, 2005).
<b>Charalampos Siristatidis</b>		D4 In 52	The sentence "However, more studies are necessary." can be removed.	This sentence indicates that at present our knowledge in this topic is poor.
<b>Charalampos Siristatidis</b>		D4 In 53	maternal HPV positivity alone : I agree, what about the partners status?	This question is only relevant in the situation of maternal infection.
<b>Liana Bosco</b>			Please consider this paper and include it in your references as it pertains to a very important aspect of the association between HPV and infertility. Capra, G., Schillaci, R., Bosco, L., Roccheri, M.C., Perino, A., Ragusa, M.A. HPV infection in semen: Results from a new molecular approach. <i>Epidemiology and Infection</i> 2019; 147, e177, 1–8. DOI.org/10.1017/S0950268819000621	After careful reconsideration, the GDG decided to include this study.
<b>Liana Bosco</b>			Please consider this paper and include it in your references as topic in "prevention through vaccination is recommended for both partners". Bosco L., Serra N., Fasciana T., Pistoia D., Vella M., Di Gregorio L., Schillaci R., Perino A., Calagna G., Firenze A & Capra G. Potential impact of a nonavalent anti HPV vaccine in Italian men with and without clinical manifestations. <i>Scientific Reports</i> 2021, 11:4096; <a href="https://doi.org/10.1038/s41598-021-83639-6">https://doi.org/10.1038/s41598-021-83639-6</a>	This study does not fit in the scope of the guideline. The GDG also decided to take out the recommendation regarding HPV vaccination out of the guideline.
<b>Liana Bosco</b>	107	2965	Capra et al. (2019) reported that has been developed a new approach to evaluate virus localisation in the different semen components. Has been analysed also the specific genotype localisation and viral DNA quantity by qPCR. Results show that HPV DNA can be identified in every fraction of semen: spermatozoa, somatic cells and seminal plasma. Different samples can contain the HPV DNA in different fractions and several HPV genotypes can be found in the same fraction. Additionally, different fractions may contain multiple HPV genotypes in different relative quantity. Has been analysed the wholeness of HPV DNA in sperm cells by	This recent investigation adds some details on HPV localization in the semen components, but we already reported the significant role of HPV in the decreased male fertility.

			qPCR. In one sample more than half of viral genomes were defective, suggesting a possible recombination event. The new method allows to easily distinguish different sperm infections and to observe the possible effects on semen. The data support the proposed role of HPV in decreased fertility and prompt new possible consequences of the infection in semen. (Capra, G., Schillaci, R., Bosco, L., Roccheri, M.C., Perino, A., Ragusa, M.A. HPV infection in semen: Results from a new molecular approach. <i>Epidemiology and Infection</i> 2019; 147, e177, 1–8. DOI.org/10.1017/S0950268819000621)	
Liana Bosco	110	3069	Bosco et al. (2021) reported that the potential impact of the nonavalent HPV vaccine vs quadrivalent was significant for low and high impact (29.7% > 18.8%; 34.6% > 26.6%, respectively). Particularly, in men with lesions and risky sexual contact was significant only for low impact (35.5% > 29.7%; 31.4% > 19.7%, respectively). In partners with positive females was significant for low impact (26.3% > 15.1%) and high impact (33.7% > 23.2%). Nonavalent vaccine offers broader protection in men with HPV positive partners, who would have a potential role in the transmission of the infection. (Bosco L., Serra N., Fasciana T., Pistoia D., Vella M., Di Gregorio L., Schillaci R., Perino A., Calagna G., Firenze A & Capra G. Potential impact of a nonavalent anti HPV vaccine in Italian men with and without clinical manifestations. <i>Scientific Reports</i> 2021, 11:4096; <a href="https://doi.org/10.1038/s41598-021-83639-6">https://doi.org/10.1038/s41598-021-83639-6</a> )	The GDG decided to take out the recommendation on vaccination for HPV.
<b>Human T-lymphotropic virus I/II (HTLV) I/II</b>				
Carlos Calhaz-Jorge	Page 18	Rec 55 and 56	Please see my general comment on the format of "conditional recommendations"	Valid point. The strength of the recommendation has been changed to 'strong'
Carlos Calhaz-Jorge	Page 19	Rec 58	Justification doesn't seem consistent with "strong" recommendation. And is it a strong rec?	The justification has been elaborated as suggested by the reviewer.
Charalampos Siristatidis		E3	"there is only 1 publication comparing HTLV I positive with HTLV I negative women that reported no difference in pregnancy rates after ICSI." This can be removed	This conclusion has been rewritten as suggested by the reviewer.
Charalampos Siristatidis		E4	"No studies were identified comparing routine semen preparation with advanced semen processing in male testing positive for HTLV I/II." as here this is a place for recommendations and to ensure the similarity in all these pages, I would recommend the reference to "no studies or few studies" or a sentence in a section below in parentheses to be added in the place in the right. This stands for the rest of the text and recommendations.	This conclusion has been rewritten as suggested by the reviewer.
<b>Zika virus</b>				
Carlos Calhaz-Jorge		F2	It is a repetition of Rec 60 and 61. And refers "chapter 4, above". Again, I suggest "conclusions" not to be included in the "List of all recommendations"	The reference to 'chapter 4' was removed and the text improved. Rec 60 refers to men and 61 to women.

<b>Carlos Calhaz-Jorge</b>	Page 20	Rec 63	I suggest to add "after returning from a risk area".	The recommendation was modified as suggested by the reviewer.
<b>Carlos Calhaz-Jorge</b>		Rec 65	Not easy to understand. If the topic is fertility preservation, is not obvious that gamete cryopreservation is needed? And the justification seems contradictory with the cautious recommendations of postponing 3 months when the male is infected	Thank you, the recommendation has been reformulated.
<b>Carlos Calhaz-Jorge</b>		Rec 67	"MAR should not proceed ..." in which situation(s)?	The recommendation was amended to 'MAR is not advised.'
<b>Carlos Calhaz-Jorge</b>	Page 23	Table	Prevention of vertical transmission by CS – "probably not" However, most recommendations about avoiding CS are labeled "strong". It looks somehow inconsistent	Recommendations are the result of balancing the evidence with benefits/harms, acceptability to patients and stakeholders, costs, etc. The table on page 23 is a summary of the evidence, which explains why this seems inconsistent. An introductory sentence has been added to the table to clarify this.
<b>Laboratory safety</b>				
Pierre Boyer			Vapour phase cryopreservation could be considered over liquid nitrogen in terms of safety to reduce the risk of cross-contamination. The reduced risk of contamination in the nitrogen vapor phase is not demonstrated neither by the work of Grout nor that of Mirabet. The risk of cross-contamination of liquid nitrogen (N2L) is due to handling for the supply or maintenance of containers without risk difference according to the liquid or vapor phase and is linked to the capture of contaminants with the freezing of water molecules from the atmosphere which fall to the bottom of the container by gravity. N2L has no wetting power and the calefaction does not allow contamination. The properties of the gas persist even in its liquefied phase; it does not ever become a liquid. Moreover, the slow and automated freezing in a small, closed chamber, described by Grout, has not been used today except in rare cases, since vitrification became widespread. As described, the contaminations found in the water trapped in the lower part of the container after thawing are generally environmental germs and exclusively contamination of water without cross-contamination of the samples themselves (Molina, I. Fertil Steril 2016 July 106, 127-32).	Thank you for your comment, which agrees with our statement that vapour phase could be considered over liquid nitrogen in terms of safety to reduce the risk of cross-contamination. We agree that the reduced risk of contamination in the nitrogen vapor phase is not demonstrated by the work of Grout or Mirabet. We are grateful for the reference of Molina and have added this into the text along with the statement "the contaminations found in the water trapped in the lower part of the container after thawing are generally environmental germs and exclusively contamination of water without cross-contamination of the samples themselves (Molina, I. Fertil Steril 2016 July 106, 127-32)"
Pierre Boyer	155	4367	The cleaning of transport containers due to the absorbent material which retains nitrogen as well as all containers with small diameter necks cannot be sterilized. This type of recommendation is irrelevant and should be removed	Thank you for your comment. We agree that we are unaware of any disinfection procedure for the absorbent material in
154	4338			

				dry transport shippers, and have adjusted the text accordingly.
<b>Carlos Calhaz-Jorge</b>		Rec 68	Justification is not consistent with "strong" recommendation. It is just a comment	The recommendation has been adjusted as a GPP.
<b>Carlos Calhaz-Jorge</b>	Page 21	Rec 71	Justification is not consistent with "strong" recommendation. It is just a comment	The recommendation has been adjusted as a GPP.
<b>Carlos Calhaz-Jorge</b>		Rec 75	Justification is not consistent with "strong" recommendation. It is just a comment	Disagree. If cryostorage devices are not suitably sealed to provide closure integrity and sample stability, then the risk of infection from the cryo tank and other samples exists. Patient safety justifies this as a strong recommendation.
<b>Kimball O. Pomeroy</b>			The case of infection from a cross-contaminated tissue (see below) should also probably state that not only was this tissue not reproductive tissue but was a large blood source stored in liquid nitrogen in a device (ethyl vinyl bags) not comparable to the storage devices used in reproductive. These bags have been shown to have a 10% failure rate in liquid nitrogen (Khuu et. al. 2002).	Agree. The text has been adjusted to incorporate this comment.
<b>Kimball O. Pomeroy</b>			These two paragraphs present evidence of contamination and not cross-contamination. That external contaminants can enter a tank is not applicable to the discussion and could confuse the issue. I would remove these.	Agree. The text has been adjusted to add the statement "Contamination found in the lower part of the liquid nitrogen vessels after thawing are generally environmental germs and exclusively contamination of water without cross-contamination of the samples themselves (Molina et al, 2016)."
<b>Kimball O. Pomeroy</b>	p 154	4324	The case of infection from a cross-contaminated tissue (see below) should also probably state that not only was this tissue not reproductive tissue but was a large blood source stored in liquid nitrogen in a device (ethyl vinyl bags) not comparable to the storage devices used in reproductive. These bags have been shown to have a 10% failure rate in liquid nitrogen (Khuu et. al. 2002).	Agree. The text has been adjusted to incorporate this comment.
<b>Kimball O. Pomeroy</b>	p 155	4353-4364	These two paragraphs present evidence of contamination and not cross-contamination. That external contaminants can enter a tank is not applicable to the discussion and could confuse the issue.	Agree. The text has been adjusted to add the statement "Contamination found in the lower part of the liquid nitrogen vessels after thawing are generally environmental germs and exclusively contamination of water without cross-contamination of the samples themselves (Molina et al, 2016)."
<b>Kimball O. Pomeroy</b>			There is a section on "Can the Type of Storage Environment Prevent Cross-Contamination of Stored Material?" I believe the first part of this section confuses	We agree that the point about clarifying contamination vs. cross-contamination is

		<p>"contamination" with "cross-contamination" and does not really apply to the situation of potentially contaminated tissue. I would delete the following:</p> <p>"4353 Unlike LN2 vapour phase (LNVP) storage vessels, LN2 storage vessels will accumulate particulate matter</p> <p>4354 from the atmosphere with time. This includes pathogenic organisms which may remain viable by</p> <p>4355 immersion in LN2. Pathogens can accumulate on the surface of cryodevices placed into LN2 storage,</p> <p>4356 creating a contamination risk, particularly when removed from storage and warmed (Grout and Morris,</p> <p>4357 2009). Contamination of samples in LNVP also carries potential risk.</p> <p>4358 Mirabet et al. aimed to identify microbiological agent in the liquid nitrogen containers, while comparing</p> <p>4359 different types of tanks (liquid nitrogen vs gas phase vs half gas half liquid). The vapour phase tank</p> <p>4360 yielded less contamination than the liquid phase (Mirabet, et al., 2012). "</p>	<p>relevant. However, rather than deleting the text, we have added a sentence to state "Contamination found in the lower part of the liquid nitrogen vessels after thawing are generally environmental germs and exclusively contamination of water without cross-contamination of the samples themselves (Molina et al, 2016)." </p>
Kimball O. Pomeroy		<p>Also, it should be noted that the case of infection from a cross-contaminated tissue (see below) should also probably state that not only was this tissue not reproductive tissue, but was a large blood source stored in liquid nitrogen in a device (ethyl vinyl bags) not comparable to the storage devices used in reproductive. These bags have been shown to have a 10% failure rate in liquid nitrogen (Khuu et. al. 2002).</p>	The text has been adjusted
Kimball O. Pomeroy		<p>"4324 One study (Hawkins et al., 1996) showed viral transmission through LN2, both related to the risk of 4325 damage to stored material. In the study transmission of HBV via damage to infected stored bone 4326 marrow was shown, which led to six patients becoming infected with the virus (Hawkins et al, 1996); 4327 Whilst this study is dated and did not involve reproductive cells or tissue, viral transmission through 4328 LN2 is demonstrated."</p>	The text has been adjusted
Janek von Byern		<p>in Austria we had a big issue with the health agency concerning the cross-contamination through the usage of the ICSI system or pipettes. Although we use oil-filled systems for ICSI injection and holding pipettes we had to proof that a viral contamination from one patient though the other is not given, even when (surely) changing the pipettes between the patients. Their concern was, that the oil may content virus particles and infect the next patient during ICSI. Sorry it sounds stupid, but we had a year discussion concerning this point</p>	<p>Thank you for your comment. We have added the statement "Use of single use devices (e.g. ICSI pipettes) mitigates the risk of cross-contamination."</p>
Janek von Byern		<p>The same for the normal pipette or stripper system when handling the oocytes, semen or embryos. We use filtered tips and have specific stripper for Hep B and Hep C positive patients but still... It is a stupid issue by the agency but it would be great to discuss this in your guidelines.</p>	<p>Thank you for your comment. We have added the statement "Use of single use devices (e.g. ICSI pipettes) mitigates the risk of cross-contamination." We hope this helps to encourage good practice.</p>

Janek von Byern			<p>Another aspect is the cross-contamination in the incubator system either by the air-flow or during handling by the lab member. Here it would be great to mention that viral positive samples should be strictly in its own incubator and that the lab members should change their gloves after handling such samples before checking non-viral samples!! Maybe you mentioned it already in the guidelines, but I did not find it specifically in the content.</p>	Thank you for your comment. We have adjusted the recommendation to now state "Given that personal protective equipment (PPE), laboratory equipment and exposed surfaces can be contaminated even whenafter demonstrating good laboratory practice, disinfection and changing PPE between cases can reduce the risk of cross-contamination". We have not made a comment about separate incubators as there is no documented evidence of cross-contamination that we are aware of.
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