# Annex 6: Literature study report

ANNEX 6: LITERATURE STUDY REPORT 1

**Hepatitis B virus** **2**

**Hepatitis C virus** **18**

**Human immunodeficiency virus** **38**

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**HTLV I/II** **76**

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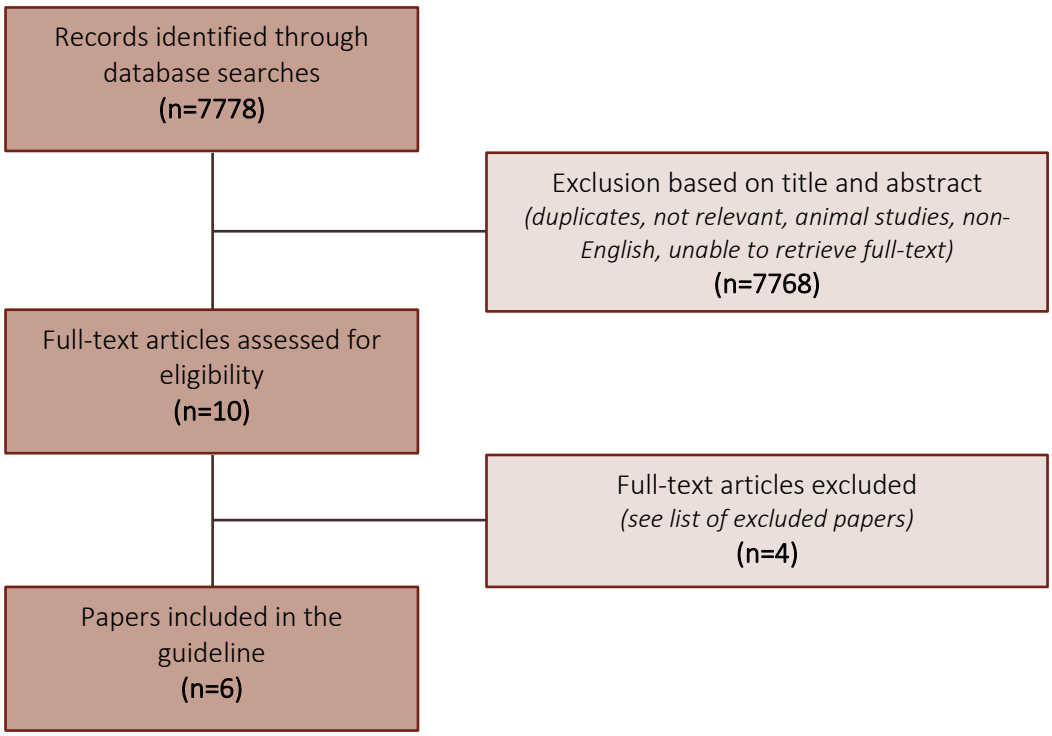
**Laboratory safety** **98**

# Hepatitis B virus

## WHAT ARE THE RISKS OF HEPATITIS B VIRUS TRANSMISSION THROUGH VAGINAL/ANAL INTERCOURSE?

### Flowchart

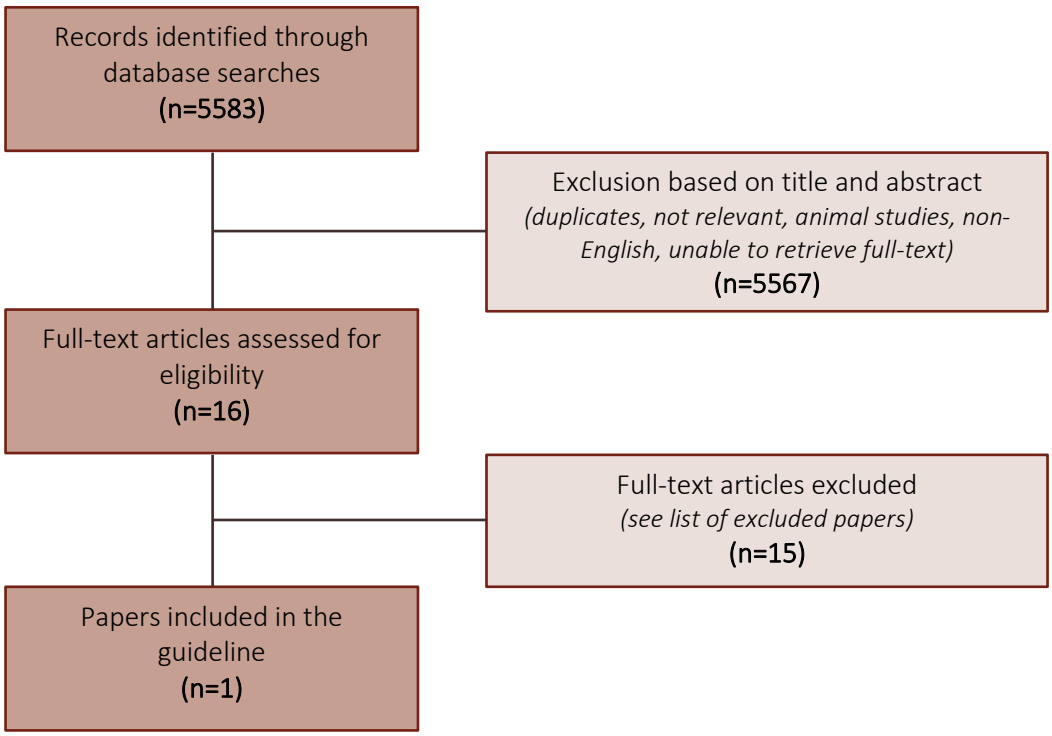



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Corona, R., Caprilli, F., Giglio, A., Stroffolini, T., Tosti, M. E., Gentili, G., Prignano, G., Pasquini, P. and Mele, A. Risk factors for hepatitis B virus infection among heterosexuals attending a sexually transmitted diseases clinic in Italy: role of genital ulcerative diseases. J Med Virol. 1996; 48 (3): 262-6. | Study population coinfected with several STDs |
| Lama, J. R., Agurto, H. S., Guanira, J. V., Ganoza, C., Casapia, M., Ojeda, N., Ortiz, A., Zamalloa, V., Suarez-Ognio, L., Cabezas, C., Sanchez, J. L. and Sanchez, J. Am J Trop Med Hyg. 2010; 83 (1): 194-200. | Men having sex with men |
| Luksamijarulkul, P., Piroonamornpun, P. and Triamchaisri, S. K. Hepatitis B seromarkers, hepatitis C antibody, and risk behaviors in married couples, a bordered province of western Thailand: Hepatitis B seromarkers, hepatitis C antibody, and risk behaviors. Hepat Mon. 2011; 11 (4): 273-7. | HCV coinfection in study population |
| Osella, A. R., Massa, M. A., Joekes, S., Blanch, N., Yacci, M. R., Centonze, S. and Sileoni, S. Hepatitis B and C virus sexual transmission among homosexual men. Am J Gastroenterol. 1998; 93 (1): 49-52. | Men having sex with men |

## IS THERE A THRESHOLD BELOW WHICH TRANSMISSION OF HEPATITIS B VIRUS IS UNLIKELY?

### Flowchart



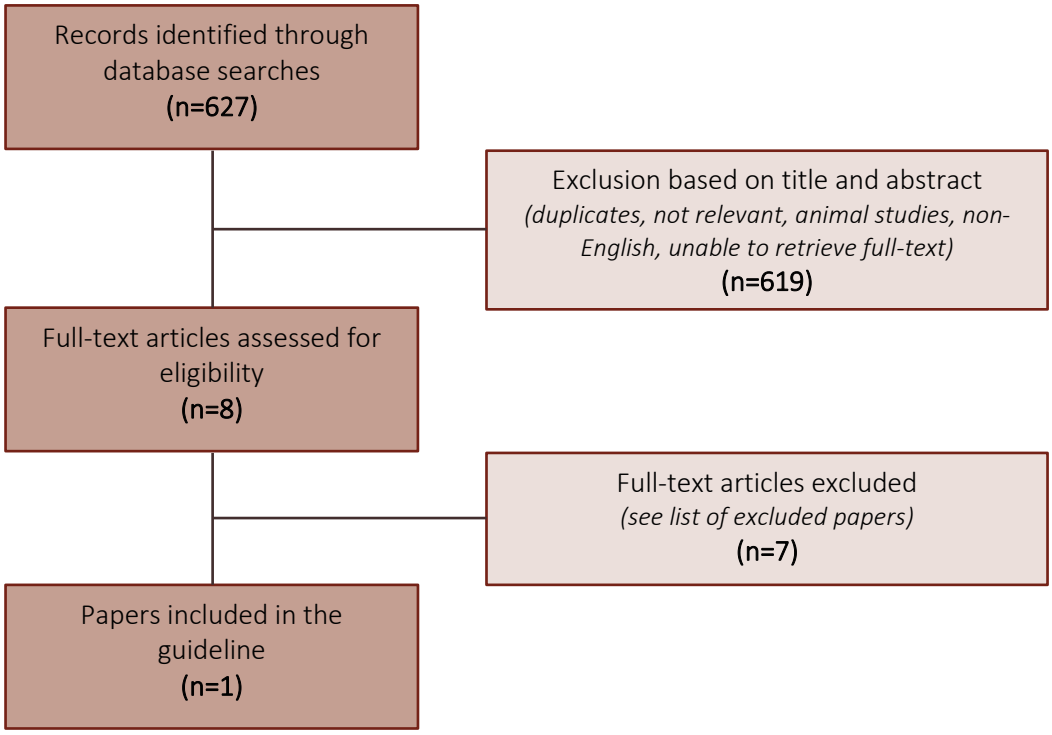

### List of excluded papers

| | Exclusion criterion |
|---|---|
| Boucheron, P., Lu, Y., Yoshida, K., Zhao, T., Funk, A. L., Lunel-Fabiani, F., Guingané, A., Tuaillon, E., van Holten, J., Chou, R., Bulterys, M. and Shimakawa, Y. Accuracy of HBeAg to identify pregnant women at risk of transmitting hepatitis B virus to their neonates: a systematic review and meta-analysis. Lancet Infect Dis. 2020; | HBV viral load was not determined before pregnancy |
| Burgis, J. C., Kong, D., Salibay, C., Zipprich, J., Harriman, K. and So, S. Perinatal transmission in infants of mothers with chronic hepatitis B in California. World J Gastroenterol. 2017; 23 (27): 4942-4949. | Severe risk of bias due to high dropout rate |
| Chang, K. C., Chang, M. H., Lee, C. N., Chang, C. H., Wu, J. F., Ni, Y. H., Wen, W. H., Shyu, M. K., Lai, M. W., Chen, S. M., Hu, J. J., Lin, H. H., Hsu, J. J., Mu, S. C., Lin, Y. C., Liu, C. J., Chen, D. S., Lin, L. H. and Chen, H. L. Decreased neonatal hepatitis B virus (HBV) viremia by maternal tenofovir treatment predicts reduced chronic HBV infection in children born to highly viremic mothers. Aliment Pharmacol Ther. 2019; 50 (3): 306-316. | Maternal VL testing during pregnancy, after conception |
| Chang, M. H., Hsu, H. Y., Huang, L. M., Lee, P. I., Lin, H. H. and Lee, C. Y. The role of transplacental hepatitis B core antibody in the mother-to-infant transmission of hepatitis B virus. J Hepatol. 1996; 24 (6): 674-9 | No measurement of HBV viral load |
| Geffert, K., Maponga, T. G., Henerico, S., Preiser, W., Mongella, S., Stich, A., Kalluvya, S., Mueller, A. and Kasang, C. Prevalence of chronic HBV infection in pregnant woman attending antenatal care in a tertiary hospital in Mwanza, Tanzania: a cross-sectional study. BMC Infect Dis. 2020; 20 (1): 395. | Does not actually answer to the question of MTCT |
| Liu, C. P., Zeng, Y. L., Zhou, M., Chen, L. L., Hu, R., Wang, L. and Tang, H. Factors associated with mother-to-child transmission of hepatitis B virus despite immunoprophylaxis. Intern Med. 2015; 54 (7): 711-6. | Viral load determined at birth, not before conception |
| Lu, Y., Zhu, F. C., Liu, J. X., Zhai, X. J., Chang, Z. J., Yan, L., Wei, K. P., Zhang, X., Zhuang, H. and Li, J. The maternal viral threshold for antiviral prophylaxis of perinatal hepatitis B | Viral load was measured at 36-40 weeks of gestation |

| | |
|---|---|
| virus transmission in settings with limited resources: A large prospective cohort study in China. Vaccine. 2017; 35 (48 Pt B): 6627-6633 | |
| Ngui, S. L., Andrews, N. J., Underhill, G. S., Heptonstall, J. and Teo, C. G. Failed postnatal immunoprophylaxis for hepatitis B: characteristics of maternal hepatitis B virus as risk factors. Clin Infect Dis. 1998; 27 (1): 100-6. | Bias selection, DNA sequence not examined in its totality, timing of viral load measurement not indicated |
| Oommen, P. T., Wirth, S., Wintermeyer, P. and Gerner, P. Relationship between viral load and genotypes of hepatitis B virus in children with chronic hepatitis B. J Pediatr Gastroenterol Nutr. 2006; 43 (3): 342-7. | HBV viral load determined after birth |
| Schillie, S., Walker, T., Veselsky, S., Crowley, S., Dusek, C., Lazaroff, J., Morris, S. A., Onye, K., Ko, S., Fenlon, N., Nelson, N. P. and Murphy, T. V. Outcomes of infants born to women infected with hepatitis B. Pediatrics. 2015; 135 (5): e1141-7. | Data collected from a paediatric programme, so multicentric, Not sure that the HVB load is measured in an identical manner according to the laboratories |
| Sellier, P., Maylin, S., Amarsy, R., Mazeron, M. C., Larrouy, L., Haim-Boukobza, S., Lopes, A., Moreno, M. D., Ricbourg, A., Simoneau, G., Magnier, J. D., Mercier-Delarue, S., Delcey, V., Evans, J., Cambau, E., Barranger, E., Simon, F. and Bergmann, J. F. Untreated highly viraemic pregnant women from Asia or sub-Saharan Africa often transmit hepatitis B virus despite serovaccination to newborns. Liver Int. 2015; 35 (2): 409-16. | HBV viral load determined during 3rd trimester of pregnancy |
| Singh, A. E., Plitt, S. S., Osiowy, C., Surynicz, K., Kouadjo, E., Preiksaitis, J. and Lee, B. Factors associated with vaccine failure and vertical transmission of hepatitis B among a cohort of Canadian mothers and infants. J Viral Hepat. 2011; 18 (7): 468-73. | Too small numbers |
| Thilakanathan, C., Wark, G., Maley, M., Davison, S., Lawler, J., Lee, A., Shackel, N., Nguyen, V., Jackson, K., Glass, A., Locarnini, S. A. and Levy, M. T. Mother-to-child transmission of hepatitis B: Examining viral cut-offs, maternal HBsAg serology and infant testing. Liver Int. 2018; 38 (7): 1212-1219. | HBV viral load determined during 2nd trimester of pregnancy |
| Wen, W. H., Chang, M. H., Zhao, L. L., Ni, Y. H., Hsu, H. Y., Wu, J. F., Chen, P. J., Chen, D. S. and Chen, H. L. Mother-to-infant transmission of hepatitis B virus infection: significance of maternal viral load and strategies for intervention. J Hepatol. 2013; 59 (1): 24-30. | Testing for viral load in 3rd trimester – 2 months postpartum |
| Wiseman, E., Fraser, M. A., Holden, S., Glass, A., Kidson, B. L., Heron, L. G., Maley, M. W., Ayres, A., Locarnini, S. A. and Levy, M. T. Perinatal transmission of hepatitis B virus: an Australian experience. Med J Aust. 2009; 190 (9): 489-92. | Timing of viral load determination not specified in the study |

## WHICH TECHNIQUE (IUI/IVF/ICSI) FOR MEDICALLY ASSISTED REPRODUCTION SHOULD BE USED IN COUPLES WITH HEPATITIS B VIRUS?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Davison F, Alexander GJ, Trowbridge R, Fagan EA, Williams R. Detection of hepatitis B virus DNA in spermatozoa, urine, saliva and leucocytes, of chronic HBsAg carriers. A lack of relationship with serum markers of replication. J Hepatol. 1987 Feb;4(1):37-44. | Too old study; autoradiographic study with HBV DNA to evidence HBV in sperm samples |
| Lou H, Ding W, Dong M, Zhu Y, Zhou C, Wang Z, Yang X, Yao Q, Li D, Miao M. The presence of hepatitis B surface antigen in the ova of pregnant women and its relationship with intra-uterine infection by hepatitis B virus. J Int Med Res 2010; 38:214–9. | No pregnancy data<br>No transmission data<br>No safety data |
| Nie, R., Jin, L., Zhang, H., Xu, B., Chen, W., Zhu, G. Presence of hepatitis B virus in oocytes and embryos: a risk of hepatitis B virus transmission during in vitro fertilization. Fertil Steril 95(5): 1667-71 | No pregnancy data<br>No transmission data<br>No safety data |
| Pirwany, I. R., Phillips, S., Kelly, S., Buckett, W. and Tan, S. L. Reproductive performance of couples discordant for hepatitis B and C following IVF treatment. J Assist Reprod Genet. 2004; 21 (5): 157-61. | Study comparing IVF/ICSI pregnancy rates in HBV with HCV and controls, not different MAR techniques |
| Yang J., b, Luo Q., j, Zhang C. and Wang, H. Study on HBV Vertical Transmission via the in vitro Fertilization (IVF) Technique. Journal of Reproduction and Contraception. 2009; 20 (2): 73-79. | No pregnancy data<br>No transmission data<br>No safety data |
| Ye F, Yue Y, Li S, Chen T, Bai G, Liu M, Zhang S. Presence of HBsAg, HBcAg, and HBVDNA in ovary and ovum of the patients with chronic hepatitis B virus infection. Am J Obstet Gynecol 2006;194: 387–92. | No pregnancy data<br>No transmission data<br>No safety data |

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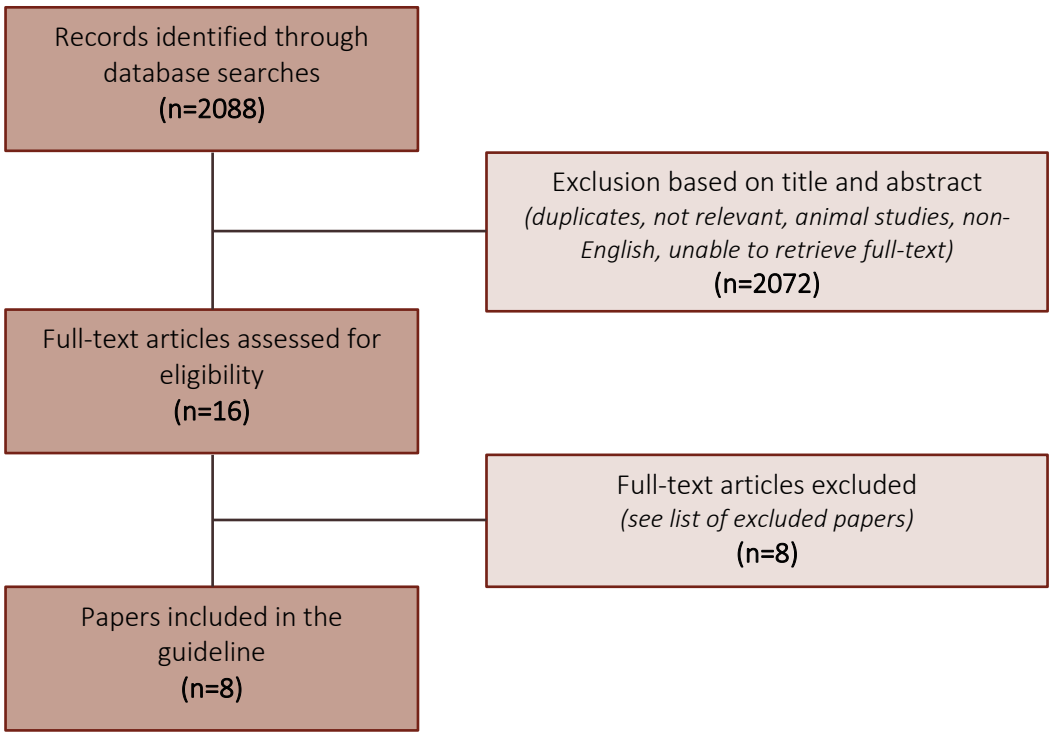
| Zheng, Z., Zhao, X., Hong, Y., Xu, B., Tong, J. and Xia, L. The safety of intracytoplasmic sperm injection in men with hepatitis B. Arch Med Sci. 2016; 12 (3): 587-91. | Small samples, does not allow true statistical analysis. Miscarriage rate does not reflect clinical reality |

## CAN HEPATITIS B VIRUS DNA BE DETECTED IN OOCYTES/ SPERM/ PLACENTA?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Goudeau, A., Yvonnet, B., Lesage, G., Barin, F., Denis, F., Coursaget, P., Chiron, J. P. and Diop Mar, I. Lack of anti-HBc IgM in neonates with HBsAg carrier mothers argues against transplacental transmission of hepatitis B virus infection. Lancet. 1983; 2 (8359): 1103-4 | No placental tissue was tested for HBV infection |
| Hadchouel, M., Scotto, J., Huret, J. L., Molinie, C., Villa, E., Degos, F. and Brechot, C. Presence of HBV DNA in spermatozoa: a possible vertical transmission of HBV via the germ line. J Med Virol. 1985; 16 (1): 61-6. | No details about the controls. Small number, old technology. |
| Lee, L. Y., Lee, G. H., Mattar, C., Saw, S. and Aw, M. Maternal HBeAg positivity and viremia associated with umbilical cord blood hepatitis B viremia. Pediatr Neonatol. 2019; 60 (5): 517-522. | No placental tissue was tested for HBV infection |
| Lou, H., Ding, W., Dong, M., Zhu, Y., Zhou, C., Wang, Z., Yang, X., Yao, Q., Li, D. and Miao, M. The presence of hepatitis B surface antigen in the ova of pregnant women and its relationship with intra-uterine infection by hepatitis B virus. J Int Med Res. 2010; 38 (1): 214-9. | Small sample: bias toward low positivity of ova for HBsAg and HbcAg |
| Nie, R., Jin, L., Zhang, H., Xu, B., Chen, W. and Zhu, G. Presence of hepatitis B virus in oocytes and embryos: a risk of hepatitis B virus transmission during in vitro fertilization. Fertil Steril. 2011; 95 (5): 1667-71. | This study is on reproductive material that is not used in MAR. DNA in follicular fluid could be contamination. |
| Shao, Q., Zhao, X. and Yao Li, M. D. Role of peripheral blood mononuclear cell transportation from mother to baby in HBV intrauterine infection. Arch Gynecol Obstet. 2013; 288 (6): 1257-61. | Poor methodology |

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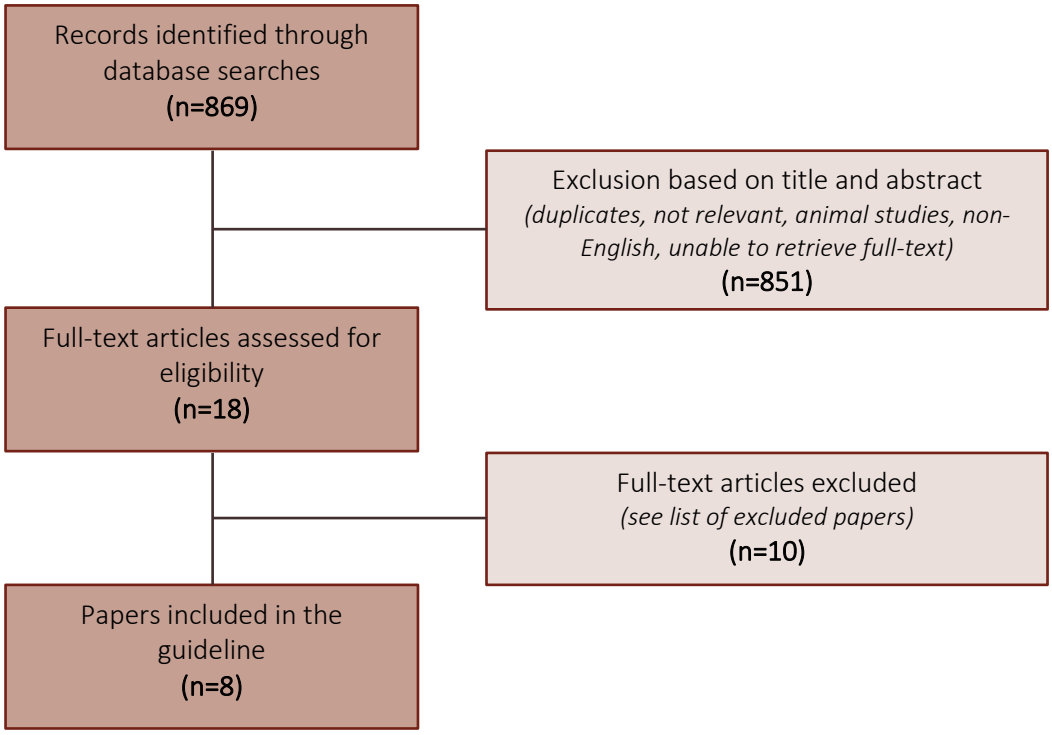
| Sirilert, S., Khamrin, P., Kumthip, K., Malasao, R., Maneekarn, N. and Tongsong, T. Placental infection of hepatitis B virus among Thai pregnant women: Clinical risk factors and its association with fetal infection. Prenat Diagn. 2020; 40 (3): 380-386. | The flow diagram and the text don't match numbers. |
| Ye F, Yue Y, Li S, Chen T, Bai G, Liu M, Zhang S. Presence of HBsAg, HBcAg, and HBVDNA in ovary and ovum of the patients with chronic hepatitis B virus infection. Am J Obstet Gynecol 2006;194: 387–92. | Bias toward low positivity of ova for HBsAg and HbcAg |

## DOES HEPATITIS B VIRUS/TREATMENT OF HEPATITIS B VIRUS BEFORE MEDICALLY ASSISTED REPRODUCTION IMPACT THE OUTCOME OF MEDICALLY ASSISTED REPRODUCTION?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Bu, Z., Kong, H., Li, J., Wang, F., Guo, Y., Su, Y., Zhai, J. and Sun, Y. Effect of male hepatitis B virus infection on outcomes of in vitro fertilization and embryo transfer treatment: insights from couples undergoing oocyte donation. Int J Clin Exp Med. 2014; 7 (7): 1860-6. | No information on any donor characteristics. Also very small study numbers (19 HBV+). |
| Jin, L., Nie, R., Li, Y., Xiao, N., Zhu, L. and Zhu, G. Hepatitis B surface antigen in oocytes and embryos may not result in vertical transmission to offspring of hepatitis B virus carriers. Fertil Steril. 2016; 105 (4): 1010-3. | Children were not tested before vaccination. . The testing on reproductive material was performed on unused material. |
| Kong, Y., Liu, Y., Liu, X., Li, N., Zhu, Z., Zhang, A., Liu, J., Ye, F. and Lin, S. Relationship between the mechanism of hepatitis B virus father-infant transmission and pregnancy outcome. Arch Gynecol Obstet. 2017; 295 (1): 253-257. | Severe risk of bias due to poor reporting of methodology |
| Lam, P. M., Suen, S. H., Lao, T. T., Cheung, L. P., Leung, T. Y. and Haines, C. Hepatitis B infection and outcomes of in vitro fertilization and embryo transfer treatment. Fertil Steril. 2010; 93 (2): 480-5. | Severe risk of bias due to incomplete reporting of results |
| Lin, S., Li, R., Zheng, X., Wang, L., Ren, X., Chen, L., Liu, Q., Liu, P. and Qiao, J. Impact of hepatitis B virus carrier serostatus on neonatal outcomes after IVF-ET. Int J Clin Exp Med. 2015; 8 (4): 6206-11. | Severe risk of bias due to poor reporting of methodology |
| Mak, J. S. M., Leung, M. B. W., Chung, C. H. S., Chung, J. P. W., Cheung, L. P., Lao, T. T. and Li, T. C. Presence of Hepatitis B virus DNA in follicular fluid in female Hepatitis B | Poor methodology (44% of women had |

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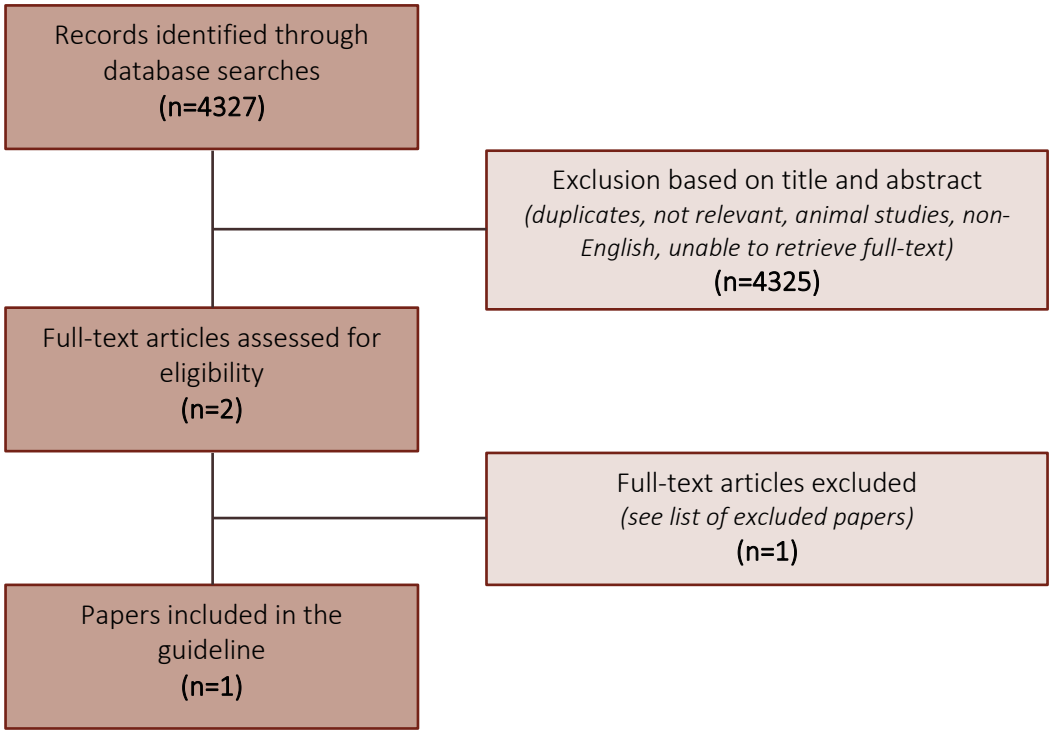
| carriers and outcome of IVF/ICSI treatment: A prospective observational study. Eur J Obstet Gynecol Reprod Biol. 2019; 239 11-15. | HBV infected oocytes) |
| Molina, I., Carmen Del Gonzalvo, M., Clavero, A., Angel Lopez-Ruz, M., Mozas, J., Pasquau, J., Sampedro, A., Martinez, L. and Castilla, J. A. Assisted reproductive technology and obstetric outcome in couples when the male partner has a chronic viral disease. Int J Fertil Steril. 2014; 7 (4): 291-300. | Females were vaccinated |
| Nie, R., Wang, M., Liao, T., Qian, K., Zhu, G. and Jin, L. Assisted conception does not increase the risk for mother-to-child transmission of hepatitis B virus, compared with natural conception: a prospective cohort study. Fertil Steril. 2019; 111 (2): 348-356. | very high LSCS rates in both ART and natural conception patients |
| Shi, L., Liu, S., Zhao, W., Zhou, H., Ren, W. and Shi, J. Hepatitis B virus infection reduces fertilization ability during in vitro fertilization and embryo transfer.<br>J Med Virol. 2014; 86 (7): 1099-104. | Numbers in the paper and in the tables don't correspond |
| Ye, F., Liu, Y., Jin, Y., Shi, J., Yang, X., Liu, X., Zhang, X., Lin, S., Kong, Y. and Zhang, L. The effect of hepatitis B virus infected embryos on pregnancy outcome. Eur J Obstet Gynecol Reprod Biol. 2014; 172 10-4 | Small sample size, No clear study hypothesis. |

## WHICH TECHNIQUES CAN BE USED TO PREVENT/REDUCE HEPATITIS B TRANSMISSION DURING ASSISTED REPRODUCTION?

### Flowchart

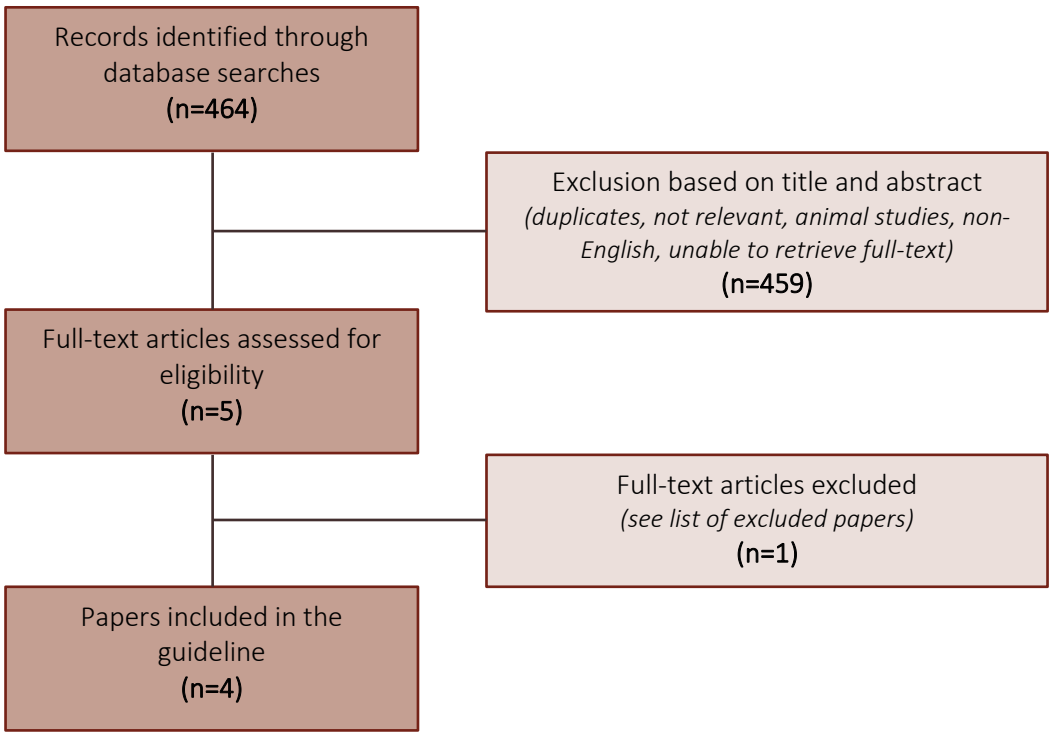



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Molina, I., Carmen Del Gonzalvo, M., Clavero, A., Angel Lopez-Ruz, M., Mozas, J., Pasquau, J., Sampedro, A., Martinez, L. and Castilla, J. A. Assisted reproductive technology and obstetric outcome in couples when the male partner has a chronic viral disease. Int J Fertil Steril. 2014; 7 (4): 291-300. | No sperm washing as all women were vaccinated and immune |

## DOES THE PLASMATIC VIRAL LOAD CORRELATE WITH HEPATITIS B VIRUS IN SEMEN?

### Flowchart

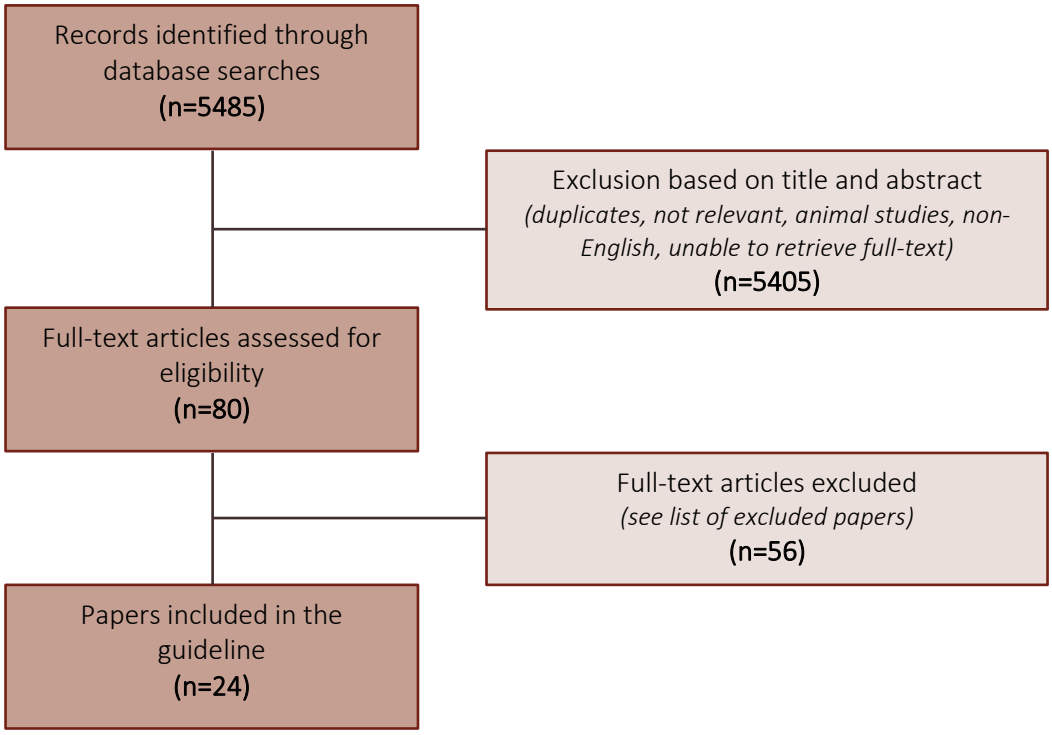



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Davison, F., Alexander, G. J., Trowbridge, R., Fagan, E. A. and Williams, R. Detection of hepatitis B virus DNA in spermatozoa, urine, saliva and leucocytes, of chronic HBsAg carriers. A lack of relationship with serum markers of replication. J Hepatol. 1987; 4 (1): 37-44. | HIV coinfection in part of the study population |

## WHICH INTERVENTIONS CAN BE USED TO REDUCE/AVOID VERTICAL TRANSMISSION OF HEPAPTITIS B VIRUS TO THE NEW-BORN?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Beasley, R. P., Stevens, C. E., Shiao, I. S. and Meng, H. C. Evidence against breast-feeding as a mechanism for vertical transmission of hepatitis B. Lancet. 1975; 2 (7938): 740-1. | Too old |
| Boot, H. J., Hahne, S., Cremer, J., Wong, A., Boland, G. and van Loon, A. M. Persistent and transient hepatitis B virus (HBV) infections in children born to HBV-infected mothers despite active and passive vaccination. J Viral Hepat. 2010; 17 (12): 872-8. | No treatment comparison group |
| Chakvetadze, C., Roussin, C., Roux, J., Mallet, V., Petinelli, M. E. and Pol, S. Efficacy of hepatitis B sero-vaccination in newborns of African HBsAg positive mothers. Vaccine. 2011; 29 (16): 2846-9. | No treatment comparison group |
| Chang, M. S., Gavini, S., Andrade, P. C. and McNabb-Baltar, J. Caesarean section to prevent transmission of hepatitis B: a meta-analysis. Can J Gastroenterol Hepatol. 2014; 28 (8): 439-44. | A more recent systematic review is available |
| Chen, H. L., Lin, L. H., Hu, F. C., Lee, J. T., Lin, W. T., Yang, Y. J., Huang, F. C., Wu, S. F., Chen, S. C., Wen, W. H., Chu, C. H., Ni, Y. H., Hsu, H. Y., Tsai, P. L., Chiang, C. L., Shyu, M. K., Lee, P. I., Chang, F. Y. and Chang, M. H. Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV. Gastroenterology. 2012; 142 (4): 773-781.e2. | Included in Machaira et al., 2015 |
| Delage, G., Remy-Prince, S. and Montplaisir, S. Combined active-passive immunization against the hepatitis B virus: five-year follow-up of children born to hepatitis B surface antigen-positive mothers. Pediatr Infect Dis J. 1993; 12 (2): 126-30. | Results were not analysed per treatment group |
| Goudeau, A., Lo, K. J., Coursaget, P., Tong, M. J., Yeh, C. L., Tsai, Y. T., Lee, J. K., Wu, T. C., Yeh, S. H. and Lee, S. D. Prevention of hepatitis B virus infection in children born to HBsAg positive/HBeAg positive mothers. Preliminary results of active and passive-active immunization. Dev Biol Stand. 1983; 54 399-404. | Included in SR Lee et al., 2006 |

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| Guo, Z., Shi, X. H., Feng, Y. L., Wang, B., Feng, L. P., Wang, S. P. and Zhang, Y. W. Risk factors of HBV intrauterine transmission among HBsAg-positive pregnant women. J Viral Hepat. 2013; 20 (5): 317-21. | Less than 50% of patients agreed to participate. This is a significant bias. |
| Hill, J. B., Sheffield, J. S., Kim, M. J., Alexander, J. M., Sercely, B. and Wendel, G. D. Risk of hepatitis B transmission in breast-fed infants of chronic hepatitis B carriers. Obstet Gynecol. 2002; 99 (6): 1049-52. | Included in SR Zheng et al., 2011 |
| Hu, Y., Chen, J., Wen, J., Xu, C., Zhang, S., Xu, B. and Zhou, Y. H. Effect of elective cesarean section on the risk of mother-to-child transmission of hepatitis B virus. BMC Pregnancy Childbirth. 2013; 13 119 | Included in SR Chen et al., 2019 |
| Hu, Y., Wu, Q., Xu, B., Zhou, Z., Wang, Z. and Zhou, Y. H. Influence of maternal antibody against hepatitis B surface antigen on active immune response to hepatitis B vaccine in infants. Vaccine. 2008; 26 (48): 6064-7. | No treatment comparison group |
| Huang, H., Xu, C., Liu, L., Chen, L., Zhu, X., Chen, J., Feng, J., Chen, T., Xu, B., Yang, J., Xu, B., Pan, M., Dai, Y., Hu, Y. and Zhou, Y. H. Increased protection of earlier use of immunoprophylaxis in preventing perinatal transmission of hepatitis B virus. Clin Infect Dis. 2020; | No treatment comparison group |
| Insulander, M., Lindh, G., Stenkvist, J., Samuelson, A. and Fischler, B. Long-term follow-up of a vaccination program for infants born to HBsAg-positive mothers in Stockholm County, Sweden. Vaccine. 2020; 38 (4): 790-793. | Follow-up study |
| Ip, H. M., Lelie, P. N., Wong, V. C., Kuhns, M. C. and Reesink, H. W. Prevention of hepatitis B virus carrier state in infants according to maternal serum levels of HBV DNA. Lancet. 1989; 1 (8635): 406-10. | Included in SR Lee et al., 2006 |
| Iwasawa, K., Inui, A., Tsunoda, T., Kondo, T., Kawamoto, M., Sogo, T., Komatsu, H. and Fujisawa, T. Hepatitis B (HB) immunoglobulin plus HB vaccine for intrauterine HB virus infection. Pediatr Int. 2015; 57 (3): 401-5. | No treatment comparison group |
| Jin, H., Zhao, Y., Tan, Z., Zhang, X., Zhao, Y., Wang, B. and Liu, P. Immunization interventions to interrupt hepatitis B virus mother-to-child transmission: a meta-analysis of randomized controlled trials. BMC Pediatr. 2014; 14 307. | Replaced by a more recent systematic review |
| Kanai, K., Takehiro, A., Noto, H., Nishida, M., Takahashi, K., Kawashima, Y., Igarashi, Y., Matsushita, K. and Shimizu, M. Prevention of perinatal transmission of hepatitis B virus (HBV) to children of e antigen-positive HBV carrier mothers by hepatitis B immune globulin and HBV vaccine. J Infect Dis. 1985; 151 (2): 287-90. | Very old study, small number of infants |
| Kang, W., Ding, Z., Shen, L., Zhao, Z., Huang, G., Zhang, J., Xiong, Q., Zhang, S., Zhang, S. and Wang, F. Risk factors associated with immunoprophylaxis failure against mother to child transmission of hepatitis B virus and hepatitis B vaccination status in Yunnan province, China. Vaccine. 2014; 32 (27): 3362-6. | No treatment comparison group |
| Kar, P. and Mishra, S. Management of hepatitis B during pregnancy. Expert Opin Pharmacother. 2016; 17 (3): 301-10. | Systematic review without meta-analysis |
| Keeble, S., Quested, J., Barker, D., Varadarajan, A. and Shankar, A. G. Immunization of babies born to HBsAg positive mothers: An audit on the delivery and completeness of follow up in Norfolk and Suffolk, United Kingdom. Hum Vaccin Immunother. 2015; 11 (5): 1153-6. | No treatment comparison group |
| Lee, L. Y., Aw, M. M., Saw, S., Rauff, M., Tong, P. Y. and Lee, G. H. Limited benefit of hepatitis B immunoglobulin prophylaxis in children of hepatitis B e antigen-negative mothers. Singapore Med J. 2016; 57 (10): 566-569. | No treatment comparison group |
| Lee, L. Y., Chan, S. M., Ong, C., M, M. Aw, Wong, F., Saw, S., Lee, G. H., Thoon, K. C. and Phua, K. B. Comparing monovalent and combination hepatitis B vaccine outcomes in children delivered by mothers with chronic hepatitis B. J Paediatr Child Health. 2019; 55 (3): 327-332. | This study compared effectiveness between 2 vaccines |
| Lee, C., Gong, Y., Brok, J., Boxall, E. H. and Gluud, C. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis. Bmj. 2006; 332 (7537): 328-36. | Replaced by a more recent systematic review |
| Lee, C. Y., Huang, L. M., Chang, M. H., Hsu, C. Y., Wu, S. J., Sung, J. L. and Safary, A. The protective efficacy of recombinant hepatitis B vaccine in newborn infants of hepatitis B | Included in SR Lee et al., 2006 |

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| e antigen-positive-hepatitis B surface antigen carrier mothers. Pediatr Infect Dis J. 1991; 10 (4): 299-303. | |
| Lee, Le Ye, Aw, Marion, Rauff, Mary, Loh, Kah-Sin, Lim, Seng Gee and Lee, Guan Huei. Hepatitis B immunoprophylaxis failure and the presence of hepatitis B surface gene mutants in the affected children. J Med Virol. 2015; 87 (8): 1344-50. | No treatment comparison group |
| Liu, C. P., Zeng, Y. L., Zhou, M., Chen, L. L., Hu, R., Wang, L. and Tang, H. Factors associated with mother-to-child transmission of hepatitis B virus despite immunoprophylaxis. Intern Med. 2015; 54 (7): 711-6. | No treatment comparison group |
| Lo, K. J., Tsai, Y. T., Lee, S. D., Yeh, C. L., Wang, J. Y., Chiang, B. N., Wu, T. C., Yeh, P. S., Goudeau, A., Coursaget, P. and et al. Combined passive and active immunization for interruption of perinatal transmission of hepatitis B virus in Taiwan. Hepatogastroenterology. 1985; 32 (2): 65-8. | Included in SR Lee et al., 2006 |
| Lu, Y., Liang, X. F., Wang, F. Z., Yan, L., Li, R. C., Li, Y. P., Zhu, F. C., Zhai, X. J., Li, J. and Zhuang, H. Hepatitis B vaccine alone may be enough for preventing hepatitis B virus transmission in neonates of HBsAg (+)/HBeAg (-) mothers. Vaccine. 2017; 35 (1): 40-45. | No treatment comparison group |
| Lu, Y., Liu, Y. L., Nie, J. J., Liang, X. F., Yan, L., Wang, F. Z., Zhai, X. J., Liu, J. X., Zhu, F. C., Chang, Z. J. and Li, J. Occult HBV Infection in Immunized Neonates Born to HBsAg-Positive Mothers: A Prospective and Follow-Up Study. PLoS One. 2016; 11 (11): e0166317. | No treatment comparison group |
| Matsumoto, T., Nakata, K., Hamasaki, K., Daikokoku, M., Nakao, K., Yamashita, Y., Shirahama, S. and Kato, Y. Efficacy of immunization of high-risk infants against hepatitis B virus evaluated by polymerase chain reaction. J Med Virol. 1997; 53 (3): 255-60. | No treatment comparison group |
| Noto, Hiroshi, Terao, Toshihiko, Ryou, Shigeo, Hirose, Yasuyuki, Yoshida, Takami, Ookubo, Hideo, Mito, Hidetoshi and Yoshizawa, Hiroshi. Combined passive and active immunoprophylaxis for preventing perinatal transmission of the hepatitis B virus carrier state in Shizuoka, Japan during 1980-1994. J Gastroenterol Hepatol. 2003; 18 (8): 943-9. | No treatment comparison group |
| Pan, Y. C., Jia, Z. F., Wang, Y. Q., Yang, N., Liu, J. X., Zhai, X. J., Song, Y., Wang, C., Li, J. and Jiang, J. The role of caesarean section and nonbreastfeeding in preventing mother-to-child transmission of hepatitis B virus in HBsAg-and HBeAg-positive mothers: results from a prospective cohort study and a meta-analysis. J Viral Hepat. 2020; | Systematic review without meta-analysis |
| Pan, C. Q., Zou, H. B., Chen, Y., Zhang, X., Zhang, H., Li, J. and Duan, Z. Cesarean section reduces perinatal transmission of hepatitis B virus infection from hepatitis B surface antigen-positive women to their infants. Clin Gastroenterol Hepatol. 2013; 11 (10): 1349-55. | Included in SR Chen et al., 2019 |
| Pande, C., Sarin, S. K., Patra, S., Kumar, A., Mishra, S., Srivastava, S., Bhutia, K., Gupta, E., Mukhopadhyay, C. K., Dutta, A. K. and Trivedi, S. S. Hepatitis B vaccination with or without hepatitis B immunoglobulin at birth to babies born of HBsAg-positive mothers prevents overt HBV transmission but may not prevent occult HBV infection in babies: a randomized controlled trial. J Viral Hepat. 2013; 20 (11): 801-10. | Included in SR Machaira et al., 2015 |
| Pongpipat, D., Suvatte, V. and Assateerawatts, A. Efficacy of hepatitis-B immunoglobulin and hepatitis-B vaccine in prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg. Asian Pac J Allergy Immunol. 1986; 4 (1): 33-6. | Included in SR Lee et al., 2006 |
| Poovorawan, Y., Chongsrisawat, V., Theamboonlers, A., Srinivasa, K., Hutagalung, Y., Bock, H. L. and Hoet, B. Long-term benefit of hepatitis B vaccination among children in Thailand with transient hepatitis B virus infection who were born to hepatitis B surface antigen-positive mothers. J Infect Dis. 2009; 200 (1): 33-8. | Study not powered in function of the primary vaccination schedules |
| Sasagawa, Y., Yamada, H., Morizane, M., Deguchi, M., Shirakawa, T., Morioka, I. and Tanimura, K. Hepatitis B virus infection: Prevention of mother-to-child transmission and exacerbation during pregnancy. J Infect Chemother. 2019; 25 (8): 621-625. | No treatment comparison group |
| Sehgal, A., Sehgal, R., Gupta, I., Bhakoo, O. N. and Ganguly, N. K. Use of hepatitis B vaccine alone or in combination with hepatitis B immunoglobulin for immunoprophylaxis of perinatal hepatitis B infection. J Trop Pediatr. 1992; 38 (5): 247-51. | Included in SR Machaira et al., 2015 |

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| Sellier, P., Maylin, S., Amarsy, R., Mazeron, M. C., Larrouy, L., Haim-Boukobza, S., Lopes, A., Moreno, M. D., Ricbourg, A., Simoneau, G., Magnier, J. D., Mercier-Delarue, S., Delcey, V., Evans, J., Cambau, E., Barranger, E., Simon, F. and Bergmann, J. F. Untreated highly viraemic pregnant women from Asia or sub-Saharan Africa often transmit hepatitis B virus despite serovaccination to newborns. Liver Int. 2015; 35 (2): 409-16. | Focus on viral load and geography, not on prophylaxis regimen |
| Shao, Z. J., Zhang, L., Xu, J. Q., Xu, D. Z., Men, K., Zhang, J. X., Cui, H. C. and Yan, Y. P. Mother-to-infant transmission of hepatitis B virus: a Chinese experience. J Med Virol. 2011; 83 (5): 791-5. | No treatment comparison group |
| Shi, Z., Yang, Y., Wang, H., Ma, L., Schreiber, A., Li, X., Sun, W., Zhao, X., Yang, X., Zhang, L., Lu, W., Teng, J. and An, Y. Breastfeeding of newborns by mothers carrying hepatitis B virus: a meta-analysis and systematic review. Arch Pediatr Adolesc Med. 2011; 165 (9): 837-46. | Replaced by a more comprehensive systematic review |
| Soleimani Amiri, M. J., Hasanjani Roushan, M. R., Baiany, M., Taheri, H. and Hasanjani Roushan, M. Outcomes of passive-active immunoprophylaxis given to infants of mothers infected with hepatitis B virus in Babol, Iran. J Clin Virol. 2010; 49 (4): 283-5. | No treatment comparison group |
| Song, Y. M., Sung, J., Yang, S., Choe, Y. H., Chang, Y. S. and Park, W. S. Factors associated with immunoprophylaxis failure against vertical transmission of hepatitis B virus. Eur J Pediatr. 2007; 166 (8): 813-8. | No treatment comparison group |
| Tang, J. R., Hsu, H. Y., Lin, H. H., Ni, Y. H. and Chang, M. H. Hepatitis B surface antigenemia at birth: a long-term follow-up study. J Pediatr. 1998; 133 (3): 374-7. | No treatment comparison group |
| Tong, C. Y., Robson, C., Wu, Y., Issa, R., Watts, T., Wilkinson, M., Wong, T. and Lorek, A. Post-vaccination serological test results of infants at risk of perinatal transmission of hepatitis B using an intensified follow-up programme in a London centre. Vaccine. 2013; 31 (31): 3174-8. | HIV coinfected women included in the study group |
| van Steenbergen, J. E., Leentvaar-Kuijpers, A., Baayen, D., Dukers, H. T., van Doornum, G. J., van den Hoek, J. A. and Coutinho, R. A. Evaluation of the hepatitis B antenatal screening and neonatal immunization program in Amsterdam, 1993-1998. Vaccine. 2001; 20 (1-2): 7-11. | No treatment comparison group |
| Wang, J., Zhu, Q. and Zhang, X. Effect of delivery mode on maternal-infant transmission of hepatitis B virus by immunoprophylaxis. Chin Med J (Engl). 2002; 115 (10): 1510-2. | Included in SR Chen et al., 2019 |
| Wong, V. C., Ip, H. M., Reesink, H. W., Lelie, P. N., Reerink-Brongers, E. E., Yeung, C. Y. and Ma, H. K. Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis-B vaccine and hepatitis-B immunoglobulin. Double-blind randomised placebo-controlled study. Lancet. 1984; 1 (8383): 921-6. | Included in SR Lee et al., 2006 |
| Xu, H., Zeng, T., Liu, J. Y., Lei, Y., Zhong, S., Sheng, Y. J., Zhou, Z. and Ren, H. Measures to reduce mother-to-child transmission of Hepatitis B virus in China: a meta-analysis. Dig Dis Sci. 2014; 59 (2): 242-58. | A more recent systematic review is available |
| Yang, M., Qin, Q., Fang, Q., Jiang, L. and Nie, S. Cesarean section to prevent mother-to-child transmission of hepatitis B virus in China: A meta-analysis. BMC Pregnancy Childbirth. 2017; 17 (1): 303. | A more recent systematic review is available |
| Yang, J., Zeng, X. M., Men, Y. L. and Zhao, L. S. Elective caesarean section versus vaginal delivery for preventing mother to child transmission of hepatitis B virus--a systematic review. Virol J. 2008; 5 100. | A more recent systematic review is available |
| Yin, Y., Wu, L., Zhang, J., Zhou, J., Zhang, P. and Hou, H. Identification of risk factors associated with immunoprophylaxis failure to prevent the vertical transmission of hepatitis B virus. J Infect. 2013; 66 (5): 447-52. | No treatment comparison group |
| Zanetti, A. R., Dentico, P., Del Vecchio Blanco, C., Sagnelli, E., Villa, E., Ferroni, P. and Bergamini, F. Multicenter trial on the efficacy of HBIG and vaccine in preventing perinatal hepatitis B. Final report. J Med Virol. 1986; 18 (4): 327-34. | No treatment comparison group |
| Zhang, L., Gui, X. E., Teter, C., Zhong, H., Pang, Z., Ding, L., Li, F., Zhou, Y. and Zhang, L. Effects of hepatitis B immunization on prevention of mother-to-infant transmission of hepatitis B virus and on the immune response of infants towards hepatitis B vaccine. Vaccine. 2014; 32 (46): 6091-7. | Same study population as Zhang et al., 2014 |

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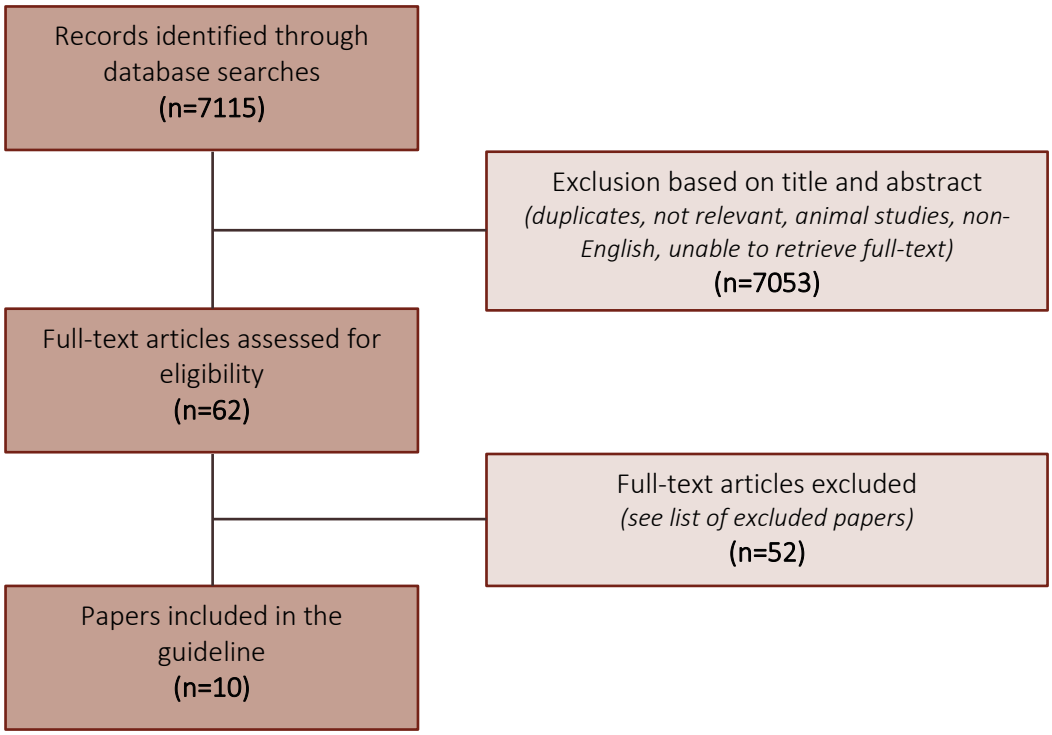
| Zou, H., Chen, Y., Duan, Z., Zhang, H. and Pan, C. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. J Viral Hepat. 2012; 19 (2): e18-25. | No treatment comparison group |
| Zou, H., Chen, Y., Duan, Z. and Zhang, H. Protective effect of hepatitis B vaccine combined with two-dose hepatitis B immunoglobulin on infants born to HBsAg-positive mothers. PLoS One. 2011; 6 (10): e26748. | No treatment comparison group |

# Hepatitis C virus

## WHAT ARE THE RISKS OF HEPATITIS C VIRUS TRANSMISSION THROUGH VAGINAL/ANAL INTERCOURSE?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
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| Akahane, Y., Kojima, M., Sugai, Y., Sakamoto, M., Miyazaki, Y., Tanaka, T., Tsuda, F., Mishiro, S., Okamoto, H., Miyakawa, Y. and Mayumi, M. Hepatitis C virus infection in spouses of patients with type C chronic liver disease. Ann Intern Med. 1994; 120 (9): 748-52. | Included in SR Ackerman et al., 2000 |
| Bessa, M., Rodart, I. F., Menezes, G. B., Carmo, T. M., Athanazio, D. A. and Reis, M. G. Limited evidence of HCV transmission in stable heterosexual couples from Bahia, Brazil. Braz J Infect Dis. 2009; 13 (4): 262-5. | No data on coinfections. Small group and included partners with risk of parenteral HCV infection |
| Bresters, D., Mauser-Bunschoten, E. P., Reesink, H. W., Roosendaal, G., van der Poel, C. L., Chamuleau, R. A., Jansen, P. L., Weegink, C. J., Cuypers, H. T., Lelie, P. N. and et al. Sexual transmission of hepatitis C virus. Lancet. 1993; 342 (8865): 210-1. | Included in SR Ackerman et al., 2000 |
| Brettler, D. B., Mannucci, P. M., Gringeri, A., Rasko, J. E., Forsberg, A. D., Rumi, M. G., Garsia, R. J., Rickard, K. A. and Colombo, M. The low risk of hepatitis C virus transmission among sexual partners of hepatitis C-infected hemophilic males: an international, multicenter study. Blood. 1992; 80 (2): 540-3. | Included women coinfected with HBV and HIV |
| Caporaso, N., Ascione, A., D'Antonio, M., Di Costanzo, G. G., Galeota Lanza, A., Tremolada, F., Diodati, G., Rumi, M. G., Parravicini, M. L., Pastore, G. and et al. | Included in SR Ackerman et al., 2000 |

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| Prevalence of anti-HCV among spouses and offspring of anti-HCV positive subjects: an Italian multicentre study. Ital J Gastroenterol. 1995; 27 (1): 5-7. | |
| Cavalheiro Nde, P., La Rosa, Ad, Elagin, S., Tengan, F. M. and Barone, A. A. Hepatitis C virus: molecular and epidemiological evidence of male-to-female transmission. Braz J Infect Dis. 2010; 14 (5): 427-32. | Aim was to establish evidence of heterosexual transmission. Too small group size (n=9) and included HCV concordant couples |
| Daikos, G. L., Lai, S. and Fischl, M. A. Hepatitis C virus infection in a sexually active inner city population. The potential for heterosexual transmission. Infection. 1994; 22 (2): 72-6. | Included patients coinfected with HIV and HBV |
| Demelia, L., Vallebona, E., Poma, R., Sanna, G., Masia, G. and Coppola, R. C. HCV transmission in family members of subjects with HCV related chronic liver disease. Eur J Epidemiol. 1996; 12 (1): 45-50. | Included in SR Ackerman et al., 2000 |
| Diago, M., Zapater, R., Tuset, C., Carbonell, P., Gonzalez, C., Cors, R. and Casas, E. Intrafamily transmission of hepatitis C virus: sexual and non-sexual contacts. J Hepatol. 1996; 25 (2): 125-8. | Included in SR Ackerman et al., 2000 |
| Fani, A., Sofian, M., Fathollahi, M., Adeli, P. and Fani, P. Intra familial transmission of hepatitis C virus infection in Iran. Iranian Journal of Clinical Infectious Diseases. 2009; 4 (3): 157-161. | Significant risk of bias due to methodology |
| Garcia-Bengoechea, M., Cortes, A., Lopez, P., Vega, J. L., Emparanza, J. I., Sarriugarte, A., Santos, E. and Arenas, J. I. Intrafamilial spread of hepatitis C virus infection. Scand J Infect Dis. 1994; 26 (1): 15-8. | Included in SR Ackerman et al., 2000 |
| Gordon, S. C., Patel, A. H., Kulesza, G. W., Barnes, R. E. and Silverman, A. L. Lack of evidence for the heterosexual transmission of hepatitis C. Am J Gastroenterol. 1992; 87 (12): 1849-51. | Included in SR Ackerman et al., 2000 |
| Goto, M., Fujiyama, S., Kawano, S., Taura, Y., Sato, S., Sato, T. and Akahoshi, M. Intrafamilial transmission of hepatitis C virus. J Gastroenterol Hepatol. 1994; 9 (1): 13-8. | Included in SR Ackerman et al., 2000 |
| Hallam, N. F., Fletcher, M. L., Read, S. J., Majid, A. M., Kurtz, J. B. and Rizza, C. R. Low risk of sexual transmission of hepatitis C virus. J Med Virol. 1993; 40 (3): 251-3. | Include HIV coinfected patients (56%) |
| Hou, C. H., Chen, W. Y., Kao, J. H., Chen, D. S., Yang, Y., Chen, J. J., Lee, S. H., Wu, D. J. and Yang, S. C. Intrafamilial transmission of hepatitis C virus in hemodialysis patients. J Med Virol. 1995; 45 (4): 381-5. | Included patients coinfected with HBV |
| Humayun, M., Haider, I. and Khan, W. M. Sexual transmission of Hepatitis C virus in monogamous married couples. Journal of Medical Sciences (Peshawar). 2012; 20 (2): 78-81. | Case report in the presence of higher quality evidence |
| Indolfi, G., Bartolini, E., Azzari, C., Becciolini, L., Moriondo, M., De Martino, M. and Resti, M. Intrafamilial transmission of hepatitis C virus: Infection of the father predicts the risk of perinatal transmission. Journal of Medical Virology. 2008; 80 (11): 1907-1911. | Multivariate analysis for risk factors in HCV seroconcordant couples |
| Kao, J. H., Chen, P. J., Yang, P. M., Lai, M. Y., Sheu, J. C., Wang, T. H. and Chen, D. S. Intrafamilial transmission of hepatitis C virus: the important role of infections between spouses. J Infect Dis. 1992; 166 (4): 900-3. | Included in SR Ackerman et al., 2000 |
| Kao, J. H., Hwang, Y. T., Chen, P. J., Yang, P. M., Lai, M. Y., Wang, T. H. and Chen, D. S. Transmission of hepatitis C virus between spouses: the important role of exposure duration. Am J Gastroenterol. 1996; 91 (10): 2087-90. | Included in SR Ackerman et al., 2000 |
| Karaca, C., Cakaloğlu, Y., Demir, K., Ozdil, S., Kaymakoğlu, S., Badur, S. and Okten, A. Risk factors for the transmission of hepatitis C virus infection in the Turkish population. Dig Dis Sci. 2006; 51 (2): 365-9. | Included patients coinfected with HBV |
| Kolho, E., Naukkarinen, R., Ebeling, F., Rasi, V., Ikkala, E. and Krusius, T. Transmission of hepatitis C virus to sexual partners of seropositive patients with bleeding disorders: a rare event. Scand J Infect Dis. 1991; 23 (6): 667-70. | Included bleeding disorders |
| Kumar, R. M. Interspousal and intrafamilial transmission of hepatitis C virus: a myth or a concern? Obstet Gynecol. 1998; 91 (3): 426-31. | Included only pregnant women in 3rd trimester. |

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| | No data on sexual behaviour |
| Lei, J. H., Liang, J., Gong, X., Xiao, X. Q., Chen, Z. and Peng, F. Analysis of Transmission Routes of Hepatitis C Virus Based on Virus Genotyping in 341 Cases with Different Suspected Initial Infection Time Points in Hunan Province, China. Med Sci Monit. 2018; 24 5232-5241. | Multinomial logistic regression analysis on HCV transmission routes |
| Magder, L. S., Fix, A. D., Mikhail, N. N., Mohamed, M. K., Abdel-Hamid, M., Abdel-Aziz, F., Medhat, A. and Strickland, G. T. Estimation of the risk of transmission of hepatitis C between spouses in Egypt based on seroprevalence data. Int J Epidemiol. 2005; 34 (1): 160-5. | Model generated to estimate risk of HCV transmission between spouses |
| Marino, N., Di Pietro, M., Moschitta, P., Balocchini, E., Chionne, P., Spada, E., Rapicetta, M., Stroffolini, T. and Mazzotta, F. Intrafamily spread of hepatitis C virus infection. New Microbiol. 1994; 17 (2): 147-50. | Included in SR Ackerman et al., 2000 |
| Meisel, H., Reip, A., Faltus, B., Lu, M., Porst, H., Wiese, M., Roggendorf, M. and Kruger, D. H. Transmission of hepatitis C virus to children and husbands by women infected with contaminated anti-D immunoglobulin. Lancet. 1995; 345 (8959): 1209-11. | Included in SR Ackerman et al., 2000 |
| Mele, A., Stroffolini, T., Tosti, M. E., Corona, R., Santonastasi, F., Gallo, G., Ragni, P., Balocchini, E., Bernacchia, R. and Moiraghi, A. Heterosexual transmission of hepatitis C in Italy. J Med Virol. 1999; 57 (2): 111-3. | Association between HCV transmission and sexual activity with multiple partners |
| Ndong-Atome, G. R., Njouom, R., Padilla, C., Bisvigou, U., Makuwa, M. and Kazanji, M. Absence of intrafamilial transmission of hepatitis C virus and low risk for sexual transmission in rural central Africa indicate a cohort effect. J Clin Virol. 2009; 45 (4): 349-53. | Very small sample size (14), no data on sexual intercourse, no data on coinfections |
| Neumayr, G., Propst, A., Schwaighofer, H., Judmaier, G. and Vogel, W. Lack of evidence for the heterosexual transmission of hepatitis C. Qjm. 1999; 92 (9): 505-8. | Spouses included with increased risk of parenteral HCV infection. |
| Njouom, R., Lavoie, M., Foupouapouognigni, Y., Frost, E., Deslandes, S., Mamadou-Yaya, F., Mbelesso, P., Mbadingai, S. and Pepin, J. Transmission of hepatitis C virus among spouses in Cameroon and the Central African Republic. J Med Virol. 2011; 83 (12): 2113-8. | Significant risk of bias due to methodology |
| Omar, M. Z., Metwally, M. A., El-Feky, H. M., Ahmed, I. A., Ismail, M. A. and Idris, A. Role of intrafamilial transmission in high prevalence of hepatitis C virus in Egypt. Hepat Med. 2017; 9 27-33. | Data on infected spouses not documented. Data on sexual practices not registered |
| Osmond, D. H., Padian, N. S., Sheppard, H. W., Glass, S., Shiboski, S. C. and Reingold, A. Risk factors for hepatitis C virus seropositivity in heterosexual couples. Jama. 1993; 269 (3): 361-5. | Included in SR Ackerman et al., 2000 |
| Pramoolsinsap, C., Kurathong, S. and Lerdverasirikul, P. Prevalence of anti-HCV antibody in family members of anti-HCV-positive patients with acute and chronic liver disease. Southeast Asian J Trop Med Public Health. 1992; 23 (1): 12-6. | Included in SR Ackerman et al., 2000 |
| Qureshi, H., Arif, A., Ahmed, W. and Alam, S. E. HCV exposure in spouses of the index cases. J Pak Med Assoc. 2007; 57 (4): 175-7. | Significant risk of selection bias |
| Rafik, M. M., El Shazly, Y., Abbas, A. A., Abd Elhady, W., Ragab, D. and AlShennawy, D. Sexual Transmission of HCV in Heterologous Monogamous Spouses. J Sex Transm Dis. 2014; 2014 140640. | No data presented on patient selection, characteristics or methodology |
| Riestra Menendez, S., Rodriguez Garcia, M., Sanchez San Roman, F., Menendez Tevar, F., Suarez Gonzalez, A., Alvarez Navascues, C., Perez Alvarez, R. and Rodrigo Saez, L. Intrafamilial spread of hepatitis C virus. Infection. 1991; 19 (6): 431-3. | Included subjects coinfected with HBV |
| Sachithanandan, S. and Fielding, J. F. Low rate of HCV transmission from women infected with contaminated anti-D immunoglobulin to their family contacts. Ital J Gastroenterol Hepatol. 1997; 29 (1): 47-50. | Included in SR Ackerman et al., 2000 |

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| Sagnelli, E., Gaeta, G. B., Felaco, F. M., Stroffolini, T., Conti, S., Glielmo, A., Piccinino, F. and Giusti, G. Hepatitis C virus infection in households of anti-HCV chronic carriers in Italy: a multicentre case-control study. Infection. 1997; 25 (6): 346-9. | No data on infected spouses. No data on sexual behaviour. No data on coinfections. |
| Saltoglu, N., Tasova, Y., Burgut, R. and Dundar, I. H. Sexual and non-sexual intrafamilial spread of hepatitis C virus: intrafamilial transmission of HCV. Eur J Epidemiol. 1998; 14 (3): 225-8. | Significant risk of bias due to poor reporting of methodology |
| Schoub, B. D., Johnson, S., McAnerney, J. M. and Blackburn, N. K. The role of sexual transmission in the epidemiology of hepatitis C virus in black South Africans. Trans R Soc Trop Med Hyg. 1992; 86 (4): 431-3. | Selected patients were HIV coinfected and comprised prostitutes |
| Scotto, G., Savastano, A. M., Fazio, V., Conte, P. E., Ferrara, S., Mangano, A. and Tantimonaco, G. Sexual transmission of hepatitis C virus infection. Eur J Epidemiol. 1996; 12 (3): 241-4. | No data on viral load/HCV pcr documented. Possible selection bias. No control group. Very old study |
| Setoguchi, Y., Kajihara, S., Hara, T., Motomura, M., Mizuta, T., Wada, I., Yamamoto, K. and Sakai, T. Analysis of nucleotide sequences of hepatitis C virus isolates from husband-wife pairs. J Gastroenterol Hepatol. 1994; 9 (5): 468-71. | Included in SR Ackerman et al., 2000 |
| Stroffolini, T., Lorenzoni, U., Menniti-Ippolito, F., Infantolino, D. and Chiaramonte, M. Hepatitis C virus infection in spouses: sexual transmission or common exposure to the same risk factors? Am J Gastroenterol. 2001; 96 (11): 3138-41. | Significant risk of bias due to methodology |
| Takahashi, M., Yamada, G., Doi, T., Takatani, M., Kishi, F., Miyamoto, R., Yoshizawa, H., Okamoto, H. and Tsuji, T. Intrafamilial clustering of genotypes of hepatitis C virus RNA. Acta Med Okayama. 1994; 48 (6): 293-7. | Included in SR Ackerman et al., 2000 |
| Takahashi, M., Yamada, G. and Tsuji, T. Intrafamilial transmission of hepatitis C. Gastroenterol Jpn. 1991; 26 (4): 483-8. | Aim was to evaluate HCV genotype within families with at least 2 members HCV positive |
| Tanaka, K., Stuver, S. O., Ikematsu, H., Okayama, A., Tachibana, N., Hirohata, T., Kashiwagi, S., Tsubouchi, H. and Mueller, N. E. Heterosexual transmission of hepatitis C virus among married couples in southwestern Japan. Int J Cancer. 1997; 72 (1): 50-5. | Included patients coinfected with HTLV-1 |
| Tedder, R. S., Gilson, R. J., Briggs, M., Loveday, C., Cameron, C. H., Garson, J. A., Kelly, G. E. and Weller, I. V. Hepatitis C virus: evidence for sexual transmission. Bmj. 1991; 302 (6788): 1299-302. | Included patients coinfected with HIV and HBV |
| Tengan, F. M., Eluf-Neto, J., Cavalheiro, N. P. and Barone, A. A. Sexual transmission of hepatitis C virus. Rev Inst Med Trop Sao Paulo. 2001; 43 (3): 133-7. | Includes patients with a history of STD without further details on current or past infections and what type of STD |
| Thomas, D. L., Zenilman, J. M., Alter, H. J., Shih, J. W., Galai, N., Carella, A. V. and Quinn, T. C. Sexual transmission of hepatitis C virus among patients attending sexually transmitted diseases clinics in Baltimore--an analysis of 309 sex partnerships. J Infect Dis. 1995; 171 (4): 768-75. | Study group comprised patients coinfected with HIV. |
| Utsumi, T., Hashimoto, E., Okumura, Y., Takayanagi, M., Nishikawa, H., Kigawa, M., Kumakura, N. and Toyokawa, H. Heterosexual activity as a risk factor for the transmission of hepatitis C virus. J Med Virol. 1995; 46 (2): 122-5. | Multivariate analyse for risk factors for HCV transmission in male prisoners including IV drug users |
| Watts, D. M., Corwin, A. L., Omar, M. A. and Hyams, K. C. Low risk of sexual transmission of hepatitis C virus in Somalia. Trans R Soc Trop Med Hyg. 1994; 88 (1): 55-6. | Selected patients were HIV coinfected and comprised prostitutes |
| Wuytack, F., Lutje, V., Jakobsen, J. C., Weiss, K. H., Flanagan, P., Gethin, G., Murphy, L., Smyth, S., Devane, D. and Smith, V. Sexual transmission of Hepatitis C Virus | Aim is determining risk factors for HCV transmission, including |

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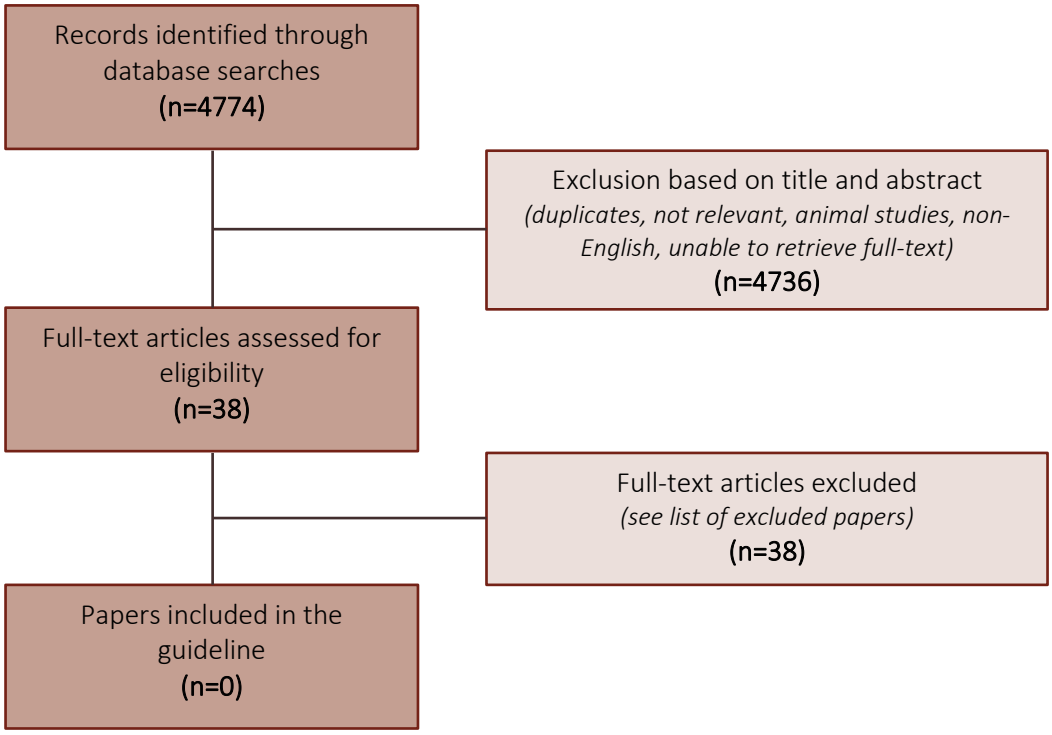
| infection in a heterosexual population: A systematic review. HRB Open Res. 2018; 1 10. | patients with STI and excluding papers from high prevalence countries |

## IS THERE A PRE-TREATMENT (BEFORE MAR) THRESHOLD BELOW WHICH TRANSMISSION OF HEPATITIS C VIRUS IS UNLIKELY?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Aslam, N., Ghaffar, A., Khurshid, M., Hussain, S. M. and Afzal, M. Diagnosis of hepatitis C in pregnant mothers and its transfer pattern in neonates. Pak J Pharm Sci. 2017; 30 (6): 2253-2257. | Poor design and low number of participants |
| Attallah, A. M., Abdallah, S. O., El-Far, M., Omran, M. M., Tabll, A. A., Ghaly, M. F., Ezzat, S. M., Elhamshary, M. O., El-Gohary, Z. M., Mohamedin, A. H., El-Morsi, A. A., Askora, A. A., Abdelrazek, M. A., El-Kafrawy, H. M., Keneber, M. H., Khalil, M. R., Aggag, M. M., Elbendary, M. S., El-Deeb, M. M., Abuzaid, M. S., Mansour, A. T. and Attallah, A. A. Perinatal transmission of hepatitis C antigens: envelope 1, envelope 2 and non-structural 4. Infect Dis (Lond). 2015; 47 (8): 568-74. | Focus on Ag detection |
| Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. Clin Infect Dis. 2014 Sep 15;59(6):765-73. | Included studies measured maternal HCV antibody and viremia during pregnancy or at delivery |
| Ceci O, Margiotta M, Marello F, et al. Vertical transmission of hepatitis C virus in a cohort of 2,447 HIV-seronegative pregnant women: a 24-month prospective study. J Pediatr Gastroenterol Nutr. 2001;33(5):570-575. | Maternal viral load determined during pregnancy (not specified) |
| Conte D, Fraquelli M, Prati D, Colucci A, Minola E. Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women. Hepatology. 2000;31(3):751-755. | Maternal viral load determined during pregnancy (1st trimester) |

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| Dal Molin, G., D'Agaro, P., Ansaldi, F., Ciana, G., Fertz, C., Alberico, S. and Campello, C. Mother-to-infant transmission of hepatitis C virus: rate of infection and assessment of viral load and IgM anti-HCV as risk factors. J Med Virol. 2002; 67 (2): 137-42. | HIV coinfected patients. Viral load determined at delivery |
| Delotte, J., Barjoan, E. M., Berrebi, A., Laffont, C., Benos, P., Pradier, C. and Bongain, A. Obstetric management does not influence vertical transmission of HCV infection: results of the ALHICE group study. J Matern Fetal Neonatal Med. 2014; 27 (7): 664-70. | Maternal viral load determined during pregnancy (probably 1st trimester) |
| Elrazek, A., Amer, M., El-Hawary, B., Salah, A., Bhagavathula, A. S., Alboraie, M. and Saab, S. Prediction of HCV vertical transmission: what factors should be optimized using data mining computational analysis. Liver Int. 2017; 37 (4): 529-533. | Maternal viral load determined during pregnancy (probably 1st trimester) |
| Ferrero, S., Lungaro, P., Bruzzone, B. M., Gotta, C., Bentivoglio, G. and Ragni, N. Prospective study of mother-to-infant transmission of hepatitis C virus: a 10-year survey (1990-2000). Acta Obstet Gynecol Scand. 2003; 82 (3): 229-34. | No viral load values references |
| Garcia-Tejedor, A., Maiques-Montesinos, V., Diago-Almela, V. J., Pereda-Perez, A., Alberola-Cunat, V., Lopez-Hontangas, J. L., Perales-Puchalt, A. and Perales, A. Risk factors for vertical transmission of hepatitis C virus: a single center experience with 710 HCV-infected mothers. Eur J Obstet Gynecol Reprod Biol. 2015; 194 173-7. | The threshold of 650 copies/ml is actually the cut-off for detectable or undetectable viral load |
| Garland, S. M., Tabrizi, S., Robinson, P., Hughes, C., Markman, L., Devenish, W. and Kliman, L. Hepatitis C - Role of perinatal transmission. Australian and New Zealand Journal of Obstetrics and Gynaecology. 1998; 38 (4): 424-427. | Maternal viral load determined after birth. Possible HIV and HBV coinfections in study population |
| Granovsky, M. O., Minkoff, H. L., Tess, B. H., Waters, D., Hatzakis, A., Devoid, D. E., Landesman, S. H., Rubinstein, A., Di Bisceglie, A. M. and Goedert, J. J. Hepatitis C virus infection in the mothers and infants cohort study. Pediatrics. 1998; 102 (2 Pt 1): 355-9. | No threshold value reported |
| Hayashida, A., Inaba, N., Oshima, K., Nishikawa, M., Shoda, A., Hayashida, S., Negishi, M., Inaba, F., Inaba, M., Fukasawa, I., Watanabe, H. and Takamizawa, H. Re-evaluation of the true rate of hepatitis C virus mother-to-child transmission and its novel risk factors based on our two prospective studies. J Obstet Gynaecol Res. 2007; 33 (4): 417-22. | Maternal viral load determined during pregnancy (at delivery) |
| Hillemanns, P., Dannecker, C., Kimmig, R. and Hasbargen, U. Obstetric risks and vertical transmission of hepatitis C virus infection in pregnancy. Acta Obstet Gynecol Scand. 2000; 79 (7): 543-7. | No threshold value reported |
| Hisada, M., O'Brien, T. R., Rosenberg, P. S. and Goedert, J. J. Virus load and risk of heterosexual transmission of human immunodeficiency virus and hepatitis C virus by men with hemophilia. The Multicenter Hemophilia Cohort Study. J Infect Dis. 2000; 181 (4): 1475-8. | Nice paper studying horizontal transmission although no threshold is established. |
| Jhaveri, R., Hashem, M., El-Kamary, S. S., Saleh, D. A., Sharaf, S. A., El-Mougy, F., Abdelsalam, L., Ehab, M. and El-Ghazaly, H. Hepatitis C Virus (HCV) Vertical Transmission in 12-Month-Old Infants Born to HCV-Infected Women and Assessment of Maternal Risk Factors. Open Forum Infect Dis. 2015; 2 (2): ofv089. | Maternal viral load determined during pregnancy (probably 1st trimester) |
| Lima, M. P., Pedro, R. J. and Rocha, M. D. Mother-to-Infant transmission of hepatitis C virus (HCV) in Brazil. J Trop Pediatr. 2004; 50 (4): 236-8. | No threshold value reported |
| Marine-Barjoan, E., Berrebi, A., Giordanengo, V., Favre, S. F., Haas, H., Moreigne, M., Izopet, J., Tricoire, J., Tran, A., Pradier, C. and Bongain, A. HCV/HIV co-infection, HCV viral load and mode of delivery: risk factors for mother-to-child transmission of hepatitis C virus? Aids. 2007; 21 (13): 1811-5. | Focused on HCV/HIV coinfection |
| Mast EE, Hwang LY, Seto DS, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. J Infect Dis. 2005;192(11):1880-1889. | No threshold values reported. |
| Mok J, Pembrey L, Tovo PA, Newell ML; European Paediatric Hepatitis C Virus Network. When does mother to child transmission of hepatitis C virus occur? Arch Dis Child Fetal Neonatal Ed. 2005 Mar;90(2):F156-60. | Focused on timing of infection |

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| Moriya, T., Sasaki, F., Mizui, M., Ohno, N., Mohri, H., Mishiro, S. and Yoshizawa, H. Transmission of hepatitis C virus from mothers to infants: its frequency and risk factors revisited. Biomed Pharmacother. 1995; 49 (2): 59-64. | Too old study |
| Murakami, J., Nagata, I., Iitsuka, T., Okamoto, M., Kaji, S., Hoshika, T., Matsuda, R., Kanzaki, S., Shiraki, K., Suyama, A. and Hino, S. Risk factors for mother-to-child transmission of hepatitis C virus: Maternal high viral load and fetal exposure in the birth canal. Hepatol Res. 2012; 42 (7): 648-57. | Maternal viral load determined during pregnancy (probably 1st trimester) |
| Ohto, H., Terazawa, S., Sasaki, N., Sasaki, N., Hino, K., Ishiwata, C., Kako, M., Ujiie, N., Endo, C., Matsui, A. and et al. Transmission of hepatitis C virus from mothers to infants. The Vertical Transmission of Hepatitis C Virus Collaborative Study Group. N Engl J Med. 1994; 330 (11): 744-50. | Too old study |
| Okamoto, M., Nagata, I., Murakami, J., Kaji, S., Iitsuka, T., Hoshika, T., Matsuda, R., Tazawa, Y., Shiraki, K. and Hino, S. Prospective reevaluation of risk factors in mother-to-child transmission of hepatitis C virus: high virus load, vaginal delivery, and negative anti-NS4 antibody. J Infect Dis. 2000; 182 (5): 1511-4. | Maternal viral load determined during pregnancy (probably 1st trimester) |
| Psaros Einberg, A., Brenndorfer, E. D., Frelin, L., Hallberg, L., Sallberg, M. and Fischler, B. Neonatal Exposure to Hepatitis C Virus Antigens in Uninfected Children Born to Infected Mothers. J Pediatr Gastroenterol Nutr. 2018; 66 (1): 106-111. | Focused on HCV T cell response. |
| Ragonnet-Cronin, M., Hostager, R., Hedskog, C., Osinusi, A., Svarovskaia, E. and Wertheim, J. O. HIV co-infection is associated with increased transmission risk in patients with chronic hepatitis C virus. J Viral Hepat. 2019; 26 (11): 1351-1354. | Focussed on HCV genotype |
| Resti M, Azzari C, Mannelli F, et al. Mother to child transmission of hepatitis C virus: prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1. Tuscany Study Group on Hepatitis C Virus Infection. BMJ. 1998;317(7156):437-441. | No threshold data reported |
| Sabatino, G., Ramenghi, L. A., di Marzio, M. and Pizzigallo, E. Vertical transmission of hepatitis C virus: an epidemiological study on 2,980 pregnant women in Italy. Eur J Epidemiol. 1996; 12 (5): 443-7. | No threshold value reported. |
| Saez, A., Losa, M., Lo Iacono, O., Lozano, C., Alvarez, E., Pita, L. and Garcia-Monzon, C. Diagnostic and prognostic value of virologic tests in vertical transmission of hepatitis C virus infection: results of a large prospective study in pregnant women. Hepatogastroenterology. 2004; 51 (58): 1104-8. | No threshold value reported. |
| Shebl, F. M., El-Kamary, S. S., Saleh, D. A., Abdel-Hamid, M., Mikhail, N., Allam, A., El-Arabi, H., Elhenawy, I., El-Kafrawy, S., El-Daly, M., Selim, S., El-Wahab, A. A., Mostafa, M., Sharaf, S., Hashem, M., Heyward, S., Stine, O. C., Magder, L. S., Stoszek, S. and Strickland, G. T. Prospective cohort study of mother-to-infant infection and clearance of hepatitis C in rural Egyptian villages. J Med Virol. 2009; 81 (6): 1024-31. | Maternal viral load determined during pregnancy (probably 3rd trimester) |
| Spencer, J. D., Latt, N., Beeby, P. J., Collins, E., Saunders, J. B., McCaughan, G. W. and Cossart, Y. E. Transmission of hepatitis C virus to infants of human immunodeficiency virus-negative intravenous drug-using mothers: rate of infection and assessment of risk factors for transmission. J Viral Hepat. 1997; 4 (6): 395-409. | Coinfected patients included in the study group |
| Steininger, C., Kundi, M., Jatzko, G., Kiss, H., Lischka, A. and Holzmann, H. Increased risk of mother-to-infant transmission of hepatitis C virus by intrapartum infantile exposure to maternal blood. J Infect Dis. 2003; 187 (3): 345-51. | Maternal viral load was determined 150 days before or after delivery |
| Syriopoulou, V., Nikolopoulou, G., Daikos, G. L., Theodoridou, M., Pavlopoulou, I., Nicolaidou, P. and Manolaki, N. Mother to child transmission of hepatitis C virus: rate of infection and risk factors. Scand J Infect Dis. 2005; 37 (5): 350-3. | Viral titers non-significant |
| Tajiri, H., Miyoshi, Y., Funada, S., Etani, Y., Abe, J., Onodera, T., Goto, M., Funato, M., Ida, S., Noda, C., Nakayama, M. and Okada, S. Prospective study of mother-to-infant transmission of hepatitis C virus. Pediatr Infect Dis J. 2001; 20 (1): 10-4. | Maternal viral load determined during pregnancy (not specified) |
| Thomas, S. L., Newell, M. L., Peckham, C. S., Ades, A. E. and Hall, A. J. A review of hepatitis C virus (HCV) vertical transmission: risks of transmission to infants born to mothers with and without HCV viraemia or human immunodeficiency virus infection. Int J Epidemiol. 1998; 27 (1): 108-17. | Maternal viraemic status was assessed at delivery in most studies which reported timing of tests. |

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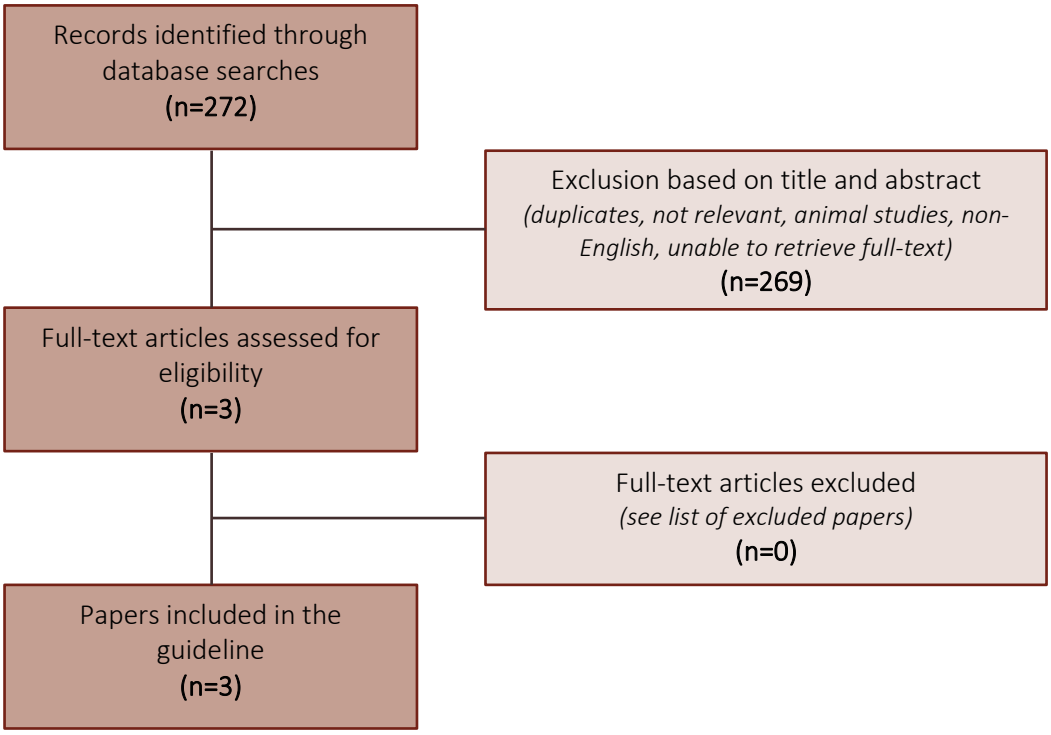
| Towers, C. V. and Fortner, K. B. Infant follow-up postdelivery from a hepatitis C viral load positive mother. J Matern Fetal Neonatal Med. 2018; 1-3. | Focused on follow-up |
| Veronesi, L., Verrotti Di Pianella, C., Benassi, L., Benaglia, G., Affanni, P. and Tanzi, M. L. Mother to child transmission of hepatitis C virus in a province of northern Italy. J Prev Med Hyg. 2007; 48 (2): 47-9. | Maternal viral load determined during pregnancy (at delivery) |
| Zanetti, A. R., Tanzi, E., Romano, L., Zuin, G., Minola, E., Vecchi, L. and Principi, N. A prospective study on mother-to-infant transmission of hepatitis C virus. Intervirology. 1998; 41 (4-5): 208-12. | Ranges of viral load overlapped |

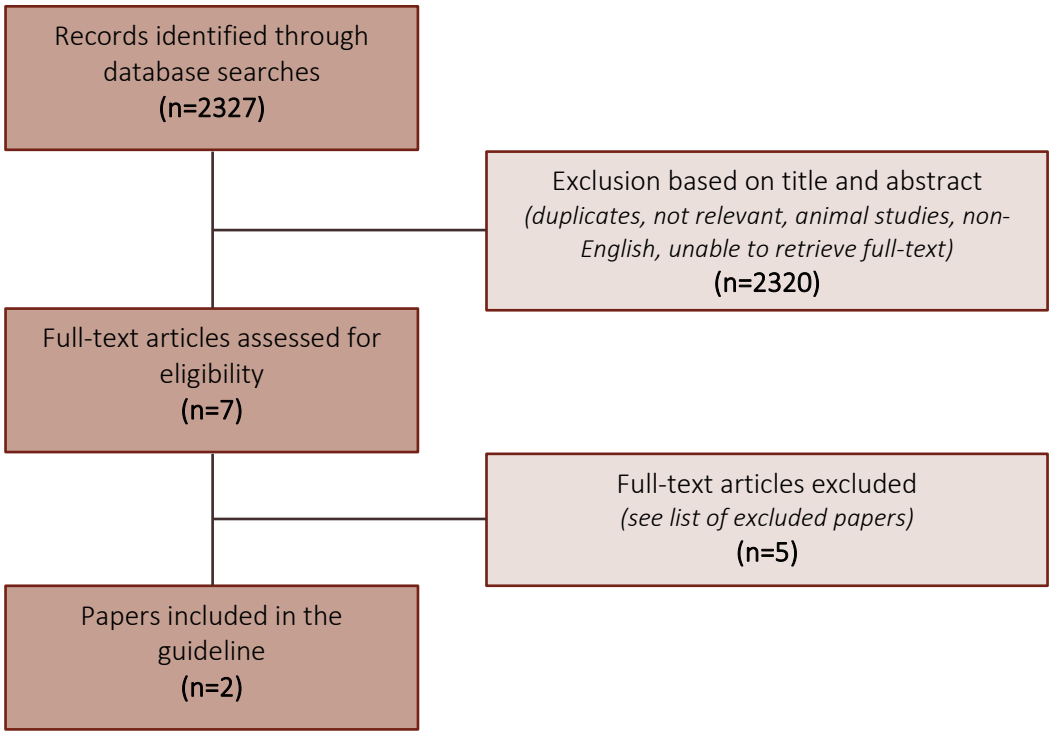
## SHOULD IUI, IVF OR ICSI BE PREFERENTIALLY USED FOR MEDICALLY ASSISTED REPRODUCTION IN HEPATITIS C INFECTED COUPLES?

Flowchart



## CAN HEPATITIS C VIRAL RNA BE DETECTED IN OOCYTES/ SPERM/ PLACENTA?

### Flowchart

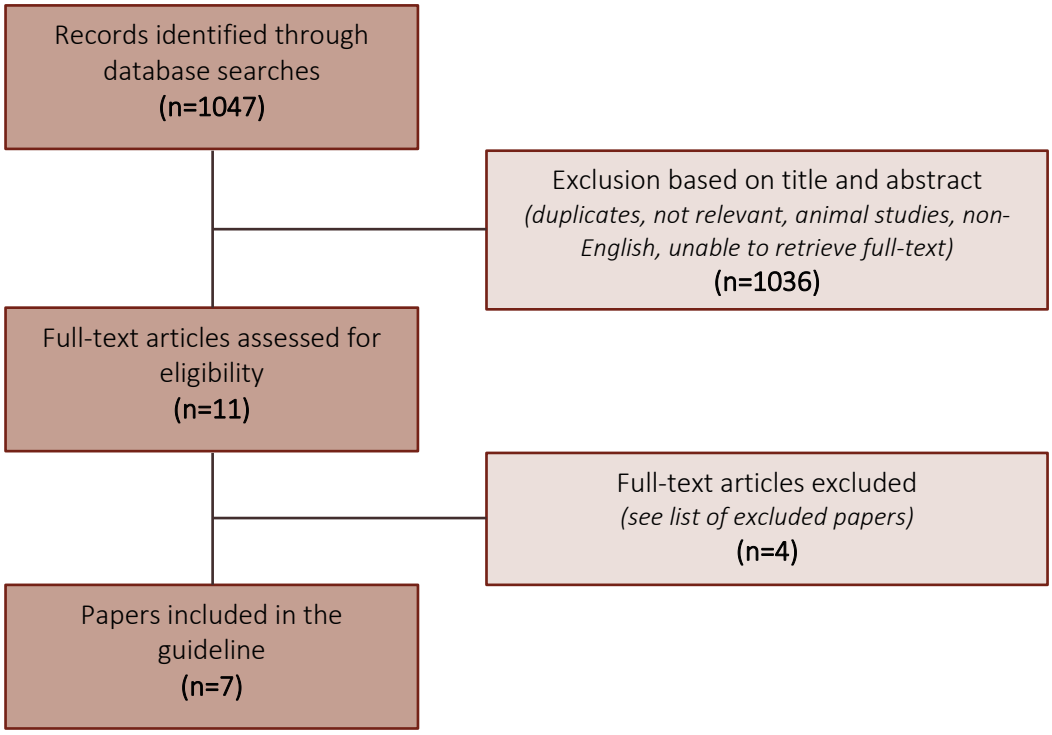



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Agha, S., Sherif, L. S., Allam, M. A. and Fawzy, M. Transplacental transmission of hepatitis C virus in HIV-negative mothers. Res Virol. 1998; 149 (4): 229-34. | Old study, small numbers |
| Cavalheiro Nde, P., Santos, A. C., Melo, C. E., Morimitsu, S. R. and Barone, A. A. Hepatitis C virus detection in the semen of infected patients. Braz J Infect Dis. 2008; 12 (5): 358-61. | Limitation old fashion technique. |
| Mok, J., Pembrey, L., Tovo, P. A. and Newell, M. L. When does mother to child transmission of hepatitis C virus occur? Arch Dis Child Fetal Neonatal Ed. 2005; 90 (2): F156-60. | HIV coinfection in the study population |
| Savasi, V., Parrilla, B., Ratti, M., Oneta, M., Clerici, M. and Ferrazzi, E. Hepatitis C virus RNA detection in different semen fractions of HCV/HIV-1 co-infected men by nested PCR. Eur J Obstet Gynecol Reprod Biol. 2010; 151 (1): 52-5. | HIV coinfection in the study population |
| Takase, S., Sato, I., Sawada, M. and Takada, A. Studies on intra-familial transmission of hepatitis C virus: An evidence for transplacental vertical transmission from mother to baby. International Hepatology Communications. 1993; 1 (4): 204-208. | Old study, not enough evidence |

## DOES HEPATITIS C VIRUS/TREATMENT OF HEPATITIS C VIRUS BEFORE MEDICALLY ASSISTED REPRODUCTION IMPACT THE OUTCOME OF MEDICALLY ASSISTED REPRODUCTION?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Bourlet, T., Lornage, J., Maertens, A., Garret, A. S., Saoudin, H., Tardy, J. C., Jimenez, C., Guerin, J. F., Pozzetto, B. and Levy, R. Prospective evaluation of the threat related to the use of seminal fractions from hepatitis C virus-infected men in assisted reproductive techniques. Hum Reprod. 2009; 24 (3): 530-5. | Coinfection with HIV in study population |
| Mencaglia, L., Falcone, P., Lentini, G. M., Consigli, S., Pisoni, M., Lofiego, V., Guidetti, R., Piomboni, P. and De Leo, V. ICSI for treatment of human immunodeficiency virus and hepatitis C virus-serodiscordant couples with infected male partner. Hum Reprod. 2005; 20 (8): 2242-6. | Patients recovered from or with no HCV-infection |
| Molina, I., Carmen Del Gonzalvo, M., Clavero, A., Angel Lopez-Ruz, M., Mozas, J., Pasquau, J., Sampedro, A., Martinez, L. and Castilla, J. A. Assisted reproductive technology and obstetric outcome in couples when the male partner has a chronic viral disease. Int J Fertil Steril. 2014; 7 (4): 291-300. | Coinfections in study population |
| Savasi, V., Oneta, M., Parrilla, B. and Cetin, I. Should HCV discordant couples with a seropositive male partner be treated with assisted reproduction techniques (ART)? Eur J Obstet Gynecol Reprod Biol. 2013; 167 (2): 181-4. | No treatment comparison |

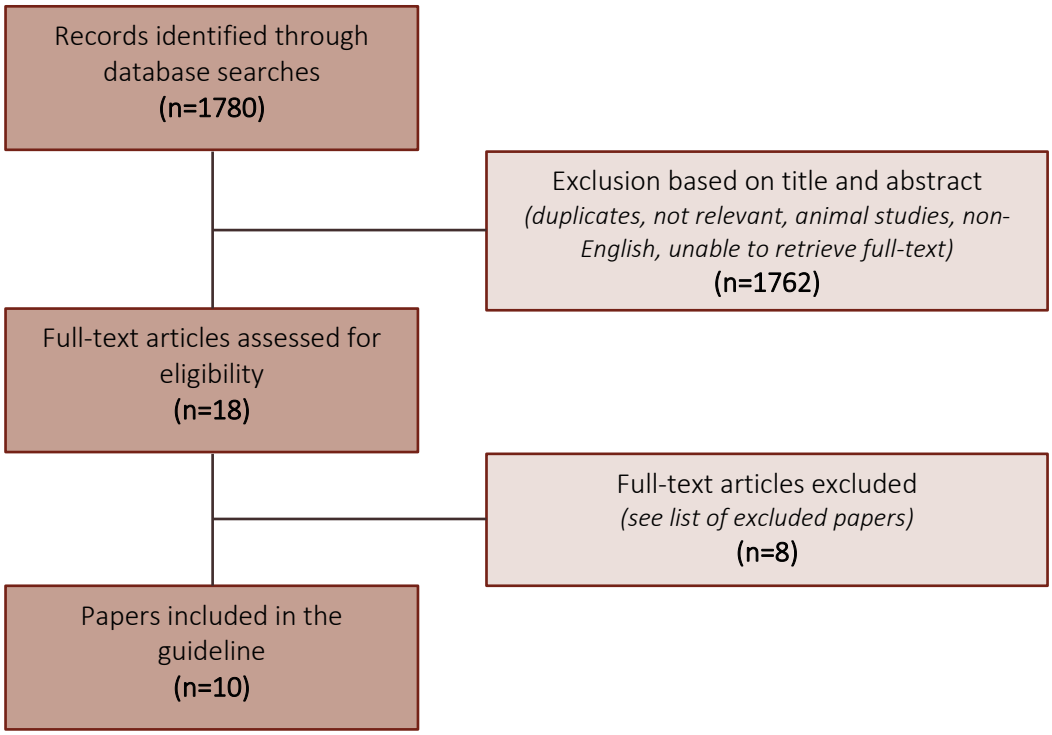
## WHICH TECHNIQUES CAN BE USED TO PREVENT/REDUCE HEPATITIS C VIRUS TRANSMISSION DURING MEDICALLY ASSISTED REPRODUCTION?

Semen processing

*The evidence on semen processing will be discussed in detail in the next section*

## WHAT IS THE BEST TECHNIQUE FOR SEMEN PROCESSING TO REDUCE HEPATITIS C VIRAL LOAD?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Cito, G., Coccia, M. E., Fucci, R., Picone, R., Cocci, A., Russo, G. I., Rizzello, F., Trotta, M., Badolato, L., Basile, V., Criscuoli, L., Serni, S., Carini, M. and Natali, A. Influence of male human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection on the reproductive outcomes in serodiscordant couples: a case-control study. Andrology. 2019; 7 (6): 852-858. | Data on semen testing not documented. |
| Garrido, N., Gil-Salom, M., Martinez-Jabaloyas, J. M. and Meseguer, M. 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. | Study population |
| Garrido, N., Meseguer, M., Bellver, J., Remohi, J., Simon, C. and Pellicer, A. Report of the results of a 2 year programme of sperm wash and ICSI treatment for human immunodeficiency virus and hepatitis C virus serodiscordant couples. Hum Reprod. 2004; 19 (11): 2581-6. | Included men who received interferon treatment |
| Halfon, Philippe, Giorgetti, Claude, Bourlière, Marc, Chabert-Orsoni, Véronique, Khiri, Hacène, Pénaranda, Guillaume, Chincholle, Jean-Marc, Gallais, Hervé, Ravaux, Isabelle, Moreau, Jacques, Gastaud, Jean-Albert and Roulier, Roger. Medically assisted procreation and transmission of hepatitis C virus: absence of HCV RNA in purified sperm fraction in HIV co-infected patients. AIDS. 2006; 20 (2): 241-6. | Significant risk of bias due to incomplete reporting |
| Mencaglia, L., Falcone, P., Lentini, G. M., Consigli, S., Pisoni, M., Lofiego, V., Guidetti, R., Piomboni, P. and De Leo, V. ICSI for treatment of human immunodeficiency virus and hepatitis C virus-serodiscordant couples with infected male partner. Hum Reprod. 2005; 20 (8): 2242-6. | Population treated for or with no HCV |
| Levy, R., Bourlet, T., Maertens, A., Salle, B., Lornage, J., Laurent, J. L., Pozzetto, B. and Guerin, J. F. Pregnancy after safe IVF with hepatitis C virus RNA-positive sperm. Hum Reprod. 2002; 17 (10): 2650-3. | Case report in the presence of higher quality evidence |

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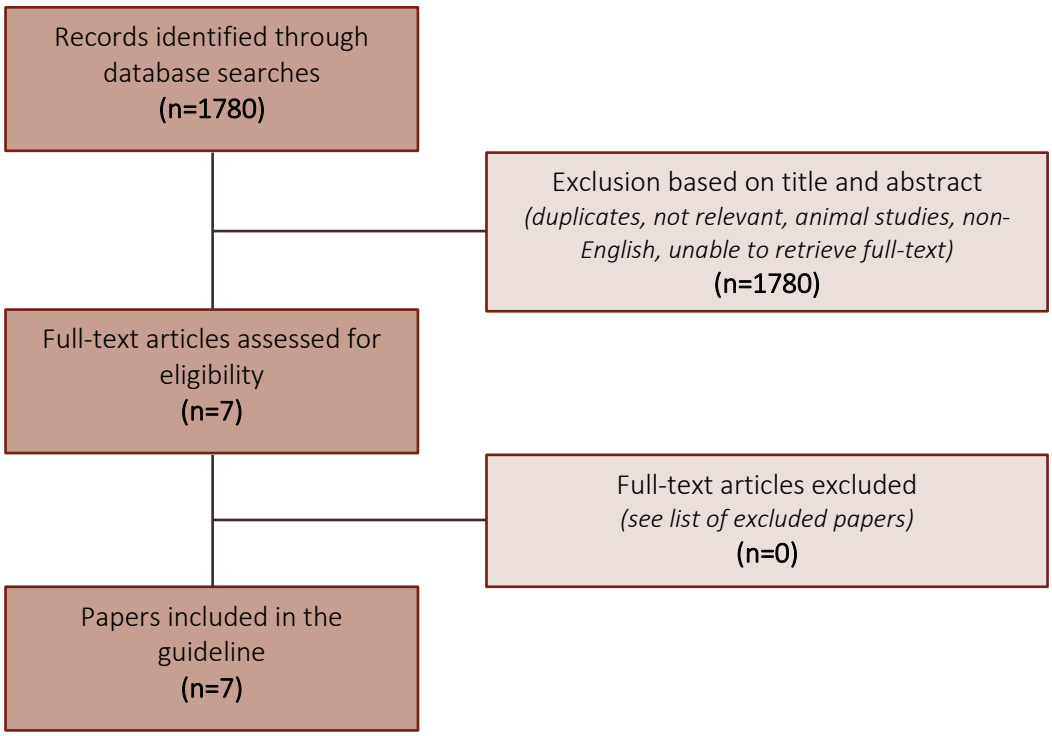
| Levy, R., Tardy, J. C., Bourlet, T., Cordonier, H., Mion, F., Lornage, J. and Guerin, J. F. Transmission risk of hepatitis C virus in assisted reproductive techniques. Hum Reprod. 2000; 15 (4): 810-6. | Significant risk of bias due to incomplete reporting |
| Pasquier, C., Daudin, M., Righi, L., Berges, L., Thauvin, L., Berrebi, A., Massip, P., Puel, J., Bujan, L. and Izopet, J. Sperm washing and virus nucleic acid detection to reduce HIV and hepatitis C virus transmission in serodiscordant couples wishing to have children. Aids. 2000; 14 (14): 2093-9. | Significant risk of bias due to poor methodology and incomplete reporting |

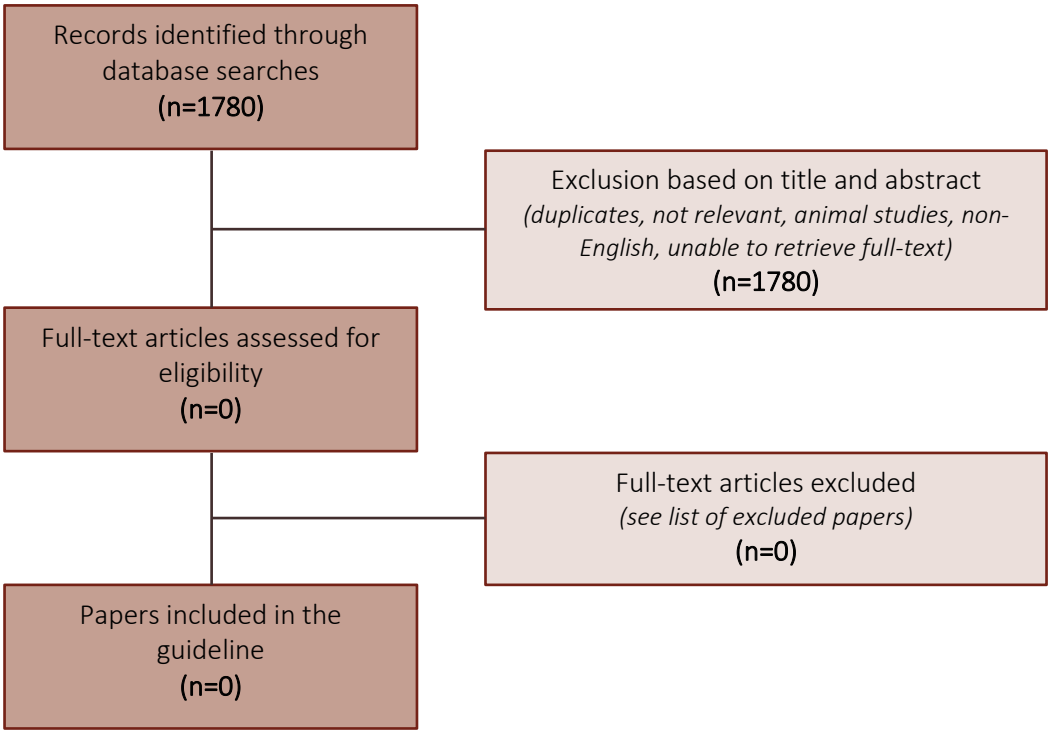
## IS THERE A NEED FOR PCR TESTING OF POST-WASHED SPERM?

Flowchart



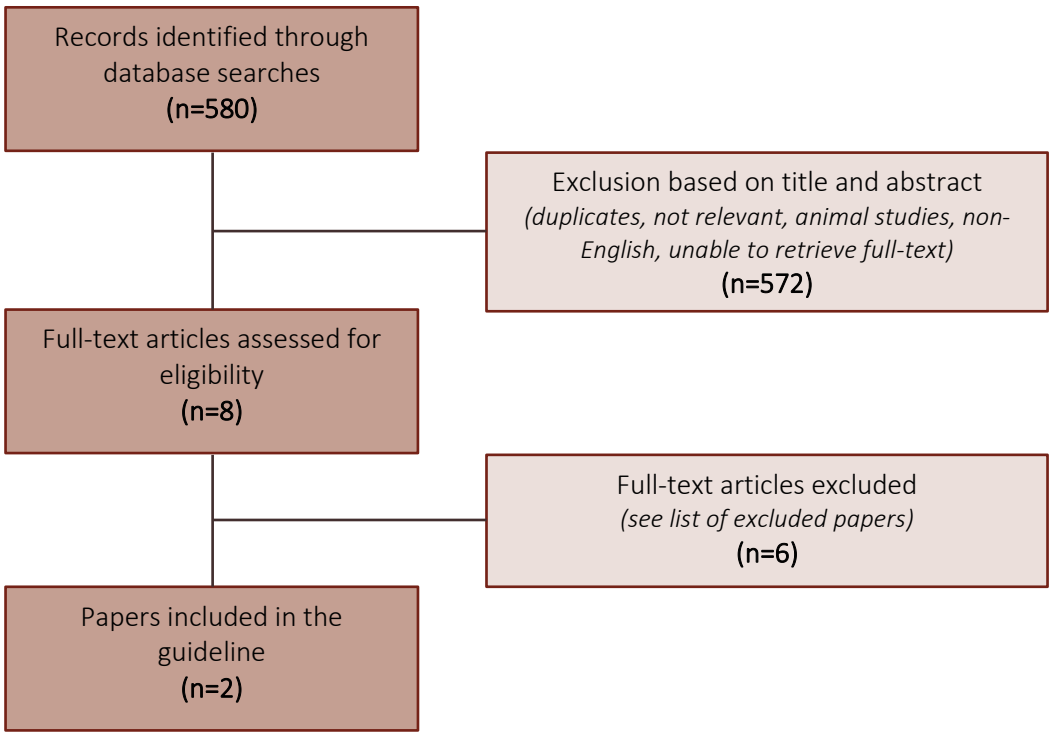
## IS THERE A NEED FOR SEMEN PROCESSING WHEN BOTH THE MALE AND FEMALE ARE INFECTED?

Flowchart



## DOES THE PLASMATIC VIRAL LOAD CORRELATE WITH HEPATITIS C VIRUS IN SEMEN?

### Flowchart

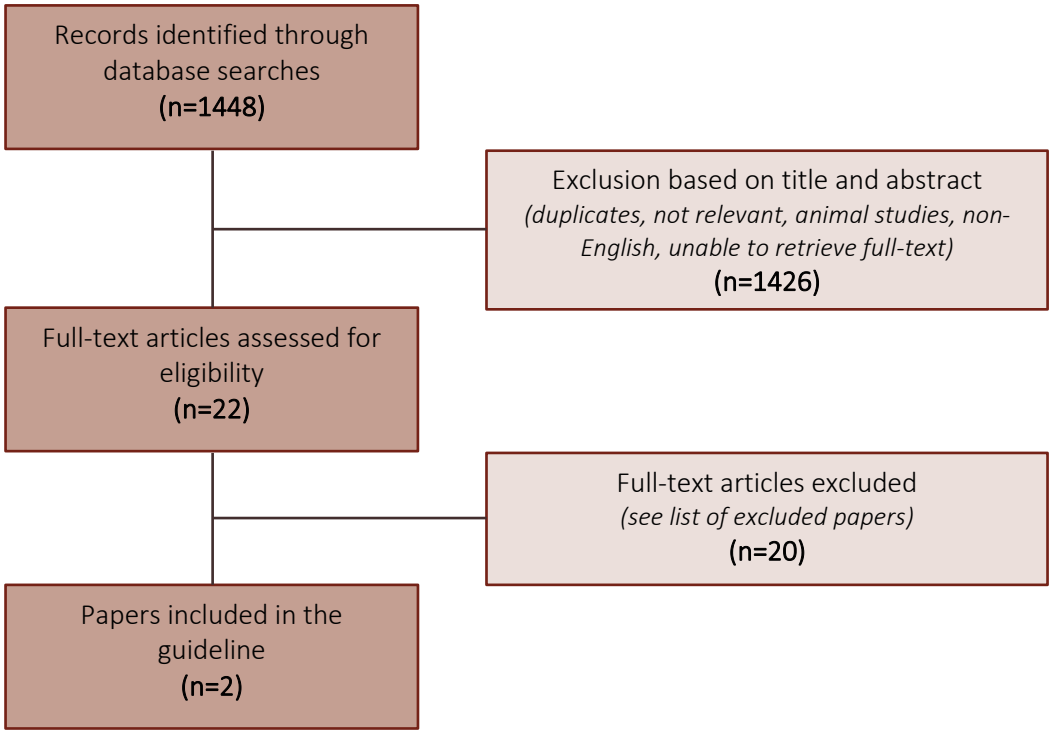



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Cavalheiro Nde, P., Santos, A. C., Melo, C. E., Morimitsu, S. R. and Barone, A. A. Hepatitis C virus detection in the semen of infected patients. Braz J Infect Dis. 2008; 12 (5): 358-61. | Comparing 2 PCR techniques |
| Debono, E., Halfon, P., Bourliere, M., Gerolami-Santandrea, V., Gastaldi, M., Castellani, P., Cartouzou, G., Botta-Fridlund, D., Cau, P. and Gauthier, A. Absence of hepatitis C genome in semen of infected men by polymerase chain reaction, branched DNA and in situ hybridization. Liver. 2000; 20 (3): 257-61. | Comparing 3 different techniques for qualitative and qualitative HCV detection to evaluate inhibition of HCV-pcr |
| Fried, M. W., Shindo, M., Fong, T. L., Fox, P. C., Hoofnagle, J. H. and Di Bisceglie, A. M. Absence of hepatitis C viral RNA from saliva and semen of patients with chronic hepatitis C. Gastroenterology. 1992; 102 (4 Pt 1): 1306-8. | Evaluate presence HCV in saliva and semen |
| Liou, T. C., Chang, T. T., Young, K. C., Lin, X. Z., Lin, C. Y. and Wu, H. L. Detection of HCV RNA in saliva, urine, seminal fluid, and ascites. J Med Virol. 1992; 37 (3): 197-202. | Old study, outcome measure was not quantitative |
| Pekler, V. A., Robbins, W. A., Nyamathi, A., Yashina, T. L., Leak, B. and Robins, T. A. Use of versant TMA and bDNA 3.0 assays to detect and quantify hepatitis C virus in semen. J Clin Lab Anal. 2003; 17 (6): 264-70. | Comparing 2 PCR techniques |
| Pfaender, S., Helfritz, F. A., Siddharta, A., Todt, D., Behrendt, P., Heyden, J., Riebesehl, N., Willmann, W., Steinmann, J., Munch, J., Ciesek, S. and Steinmann, E. Environmental Stability and Infectivity of Hepatitis C Virus (HCV) in Different Human Body Fluids. Front Microbiol. 2018; 9 504. | Evaluating stability HCV in spiked semen |

## WHICH INTERVENTIONS CAN BE USED TO REDUCE/AVOID VERTICAL TRANSMISSION OF HEPAPTITIS C VIRUS TO THE NEW-BORN?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. European Paediatric Hepatitis C Virus Network. Bjog. 2001; 108 (4): 371-7. | Included in SR Contrell et al., 2013 |
| A significant sex--but not elective cesarean section--effect on mother-to-child transmission of hepatitis C virus infection. J Infect Dis. 2005; 192 (11): 1872-9. | Included in SR Contrell et al., 2013 |
| Bhola, K. and McGuire, W. Does avoidance of breast feeding reduce mother-to-infant transmission of hepatitis C virus infection? Arch Dis Child. 2007; 92 (4): 365-6. | Replaced by a more recent systematic review |
| Dal Molin, G., D'Agaro, P., Ansaldi, F., Ciana, G., Fertz, C., Alberico, S. and Campello, C. Mother-to-infant transmission of hepatitis C virus: rate of infection and assessment of viral load and IgM anti-HCV as risk factors. J Med Virol. 2002; 67 (2): 137-42. | HIV coinfection in study population |
| Garcia-Tejedor, A., Maiques-Montesinos, V., Diago-Almela, V. J., Pereda-Perez, A., Alberola-Cunat, V., Lopez-Hontangas, J. L., Perales-Puchalt, A. and Perales, A. Risk factors for vertical transmission of hepatitis C virus: A single center experience with 710 HCV-infected mothers. European Journal of Obstetrics Gynecology and Reproductive Biology. 2015; 194 173-177. | HIV coinfection in study population |
| Gibb, D. M., Goodall, R. L., Dunn, D. T., Healy, M., Neave, P., Cafferkey, M. and Butler, K. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. Lancet. 2000; 356 (9233): 904-7. | Included in SR Contrell et al., 2013 |
| Hayashida, A., Inaba, N., Oshima, K., Nishikawa, M., Shoda, A., Hayashida, S., Negishi, M., Inaba, F., Inaba, M., Fukasawa, I., Watanabe, H. and Takamizawa, H. Re-evaluation of the true rate of hepatitis C virus mother-to-child transmission and its novel risk factors based on our two prospective studies. J Obstet Gynaecol Res. 2007; 33 (4): 417-22. | Included in SR Ghamar-Chehreh et al., 2011 |

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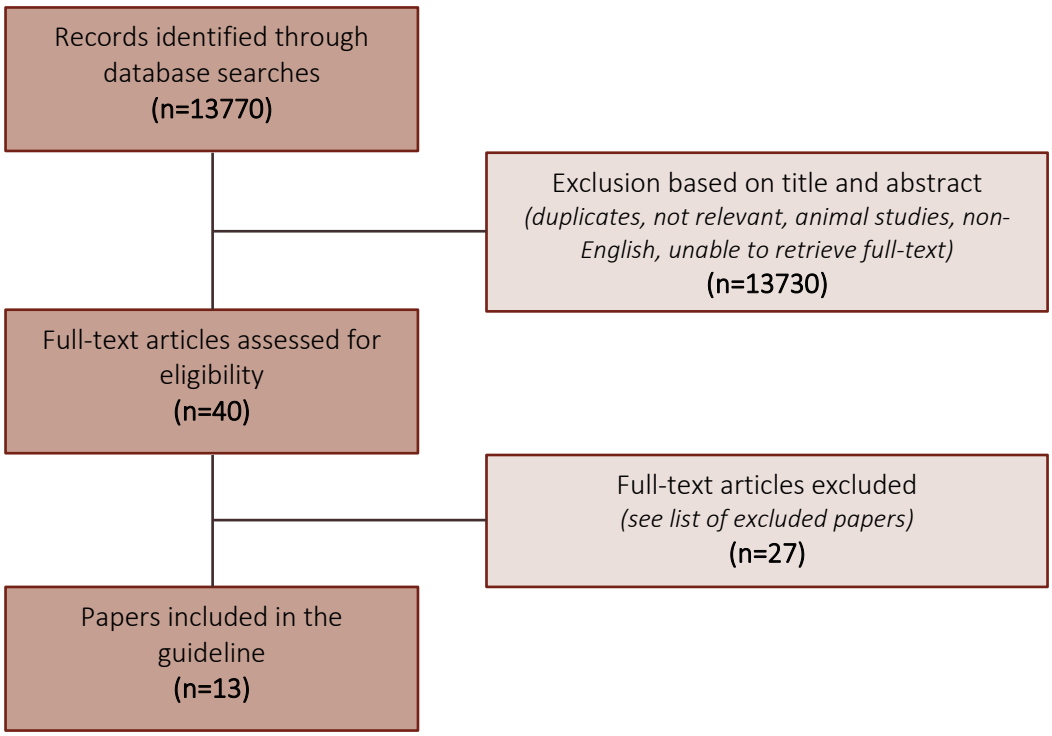
|---|---|
| Marine-Barjoan, E., Berrebi, A., Giordanengo, V., Favre, S. F., Haas, H., Moreigne, M., Izopet, J., Tricoire, J., Tran, A., Pradier, C. and Bongain, A. HCV/HIV co-infection, HCV viral load and mode of delivery: risk factors for mother-to-child transmission of hepatitis C virus? Aids. 2007; 21 (13): 1811-5. | HIV coinfection in study population |
| McIntyre, P. G., Tosh, K. and McGuire, W. Caesarean section versus vaginal delivery for preventing mother to infant hepatitis C virus transmission. Cochrane Database Syst Rev. 2006; (4): Cd005546. | No studies included in this systematic review |
| McMenamin, M. B., Jackson, A. D., Lambert, J., Hall, W., Butler, K., Coulter-Smith, S. and McAuliffe, F. M. Obstetric management of hepatitis C-positive mothers: analysis of vertical transmission in 559 mother-infant pairs. Am J Obstet Gynecol. 2008; 199 (3): 315.e1-5. | HIV coinfection in study population |
| Mok, J., Pembrey, L., Tovo, P. A. and Newell, M. L. When does mother to child transmission of hepatitis C virus occur? Arch Dis Child Fetal Neonatal Ed. 2005; 90 (2): F156-60. | Same study population as J Infect Dis. 2005; 192(11): 1872-9 |
| Murakami, J., Nagata, I., Iitsuka, T., Okamoto, M., Kaji, S., Hoshika, T., Matsuda, R., Kanzaki, S., Shiraki, K., Suyama, A. and Hino, S. Risk factors for mother-to-child transmission of hepatitis C virus: Maternal high viral load and fetal exposure in the birth canal. Hepatol Res. 2012; 42 (7): 648-57. | Significant risk of selection and performance bias |
| Pembrey, L., Newell, M. L. and Tovo, P. A. Hepatitis C virus infection in pregnant women and their children. Italian Journal of Gynaecology and Obstetrics. 2000; 12 (1): 21-28. | Included in SR Contrell et al., 2013 |
| Plunkett, B. A. and Grobman, W. A. Elective cesarean delivery to prevent perinatal transmission of hepatitis C virus: a cost-effectiveness analysis. Am J Obstet Gynecol. 2004; 191 (3): 998-1003. | Cost effectiveness analysis using Markov analysis |
| Schackman, B. R., Oneda, K. and Goldie, S. J. The cost-effectiveness of elective Cesarean delivery to prevent hepatitis C transmission in HIV-coinfected women. Aids. 2004; 18 (13): 1827-34. | Cost effectiveness analysis using Markov analysis |
| Steininger, C., Kundi, M., Jatzko, G., Kiss, H., Lischka, A. and Holzmann, H. Increased risk of mother-to-infant transmission of hepatitis C virus by intrapartum infantile exposure to maternal blood. J Infect Dis. 2003; 187 (3): 345-51. | Data on ECS not computable due to retrospective design |
| Tajiri, H., Miyoshi, Y., Funada, S., Etani, Y., Abe, J., Onodera, T., Goto, M., Funato, M., Ida, S., Noda, C., Nakayama, M. and Okada, S. Prospective study of mother-to-infant transmission of hepatitis C virus. Pediatr Infect Dis J. 2001; 20 (1): 10-4. | Included in SR Contrell et al., 2013 |
| Tanzi, M., Bellelli, E., Benaglia, G., Cavatorta, E., Merialdi, A., Mordacci, E., Ribero, M. L., Tagger, A., Verrotti, C. and Volpicelli, A. The prevalence of HCV infection in a cohort of pregnant women, the related risk factors and the possibility of vertical transmission. Eur J Epidemiol. 1997; 13 (5): 517-21. | Included in SR Contrell et al., 2013 |
| Zanetti, A. R., Tanzi, E., Romanó, L., Principi, N., Zuin, G., Minola, E., Zapparoli, B., Palmieri, M., Marini, A., Ghisotti, D., Friedman, P., Hunt, J. and Laffler, T. Multicenter trial on mother-to-infant transmission of GBV-C virus. The Lombardy Study Group on Vertical/Perinatal Hepatitis Viruses Transmission. J Med Virol. 1998; 54 (2): 107-12. | Included in SR Contrell et al., 2013 |
| Zanetti, A. R., Tanzi, E., Romanò, L., Zuin, G., Minola, E., Vecchi, L. and Principi, N. A prospective study on mother-to-infant transmission of hepatitis C virus. Intervirology. 1998; 41 (4-5): 208-12. | Included in SR Contrell et al., 2013 |

# Human immunodeficiency virus

## WHAT ARE THE RISKS OF HUMAN IMMUNODEFICIENCY VIRUS TRANSMISSION THROUGH VAGINAL/ANAL INTERCOURSE?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Andes, W. A., Rangan, S. R. and Wulff, K. M. Exposure of heterosexuals to human immunodeficiency virus and viremia: evidence for continuing risks in spouses of hemophiliacs. Sex Transm Dis. 1989; 16 (2): 68-73. | Very old study |
| Bavinton, B. R., Pinto, A. N., Phanuphak, N., Grinsztejn, B., Prestage, G. P., Zablotska-Manos, I. B., Jin, F., Fairley, C. K., Moore, R., Roth, N., Bloch, M., Pell, C., McNulty, A. M., Baker, D., Hoy, J., Tee, B. K., Templeton, D. J., Cooper, D. A., Emery, S., Kelleher, A. and Grulich, A. E. Viral suppression and HIV transmission in serodiscordant male couples: an international, prospective, observational, cohort study. Lancet HIV. 2018; 5 (8): e438-e447. | 64% of couples became ineligible before the end of the study |
| Combescure, C., Vallier, N., Ledergerber, B., Cavassini, M., Furrer, H., Rauch, A., Battegay, M., Bernasconi, E., Vernazza, P. and Hirschel, B. How reliable is an undetectable viral load? HIV Med. 2009; 10 (8): 470-6. | Study focusses on viral load, not on the risk of sexual transmission |
| Donnell, D., Baeten, J. M., Kiarie, J., Thomas, K. K., Stevens, W., Cohen, C. R., McIntyre, J., Lingappa, J. R. and Celum, C. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. Lancet. 2010; 375 (9731): 2092-8. | Included in SR LeMessurier et al., 2018 |
| Fielding, K. L., Brettle, R. P., Gore, S. M., O'Brien, F., Wyld, R., Robertson, J. R. and Weightman, R. Heterosexual transmission of HIV analysed by generalized estimating equations. Stat Med. 1995; 14 (12): 1365-78. | Focus on simulations and statistical models |

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| Jin, F., Prestage, G. P., Mao, L., Poynten, I. M., Templeton, D. J., Grulich, A. E. and Zablotska, I. Any Condomless Anal Intercourse is No Longer an Accurate Measure of HIV Sexual risk Behavior in Gay and Other Men Who have Sex with Men. Front Immunol. 2015; 6 86. | Study focusses on risk behaviour, not on the risk of sexual transmission |
| Knight, K. R., Shade, S. B., Purcell, D. W., Rose, C. D., Metsch, L. R., Latka, M. H., Latkin, C. A. and Gómez, C. A. Sexual transmission risk behavior reported among behaviorally bisexual HIV-positive injection drug-using men. J Acquir Immune Defic Syndr. 2007; 46 Suppl 2 S80-7. | Study focusses on risk behaviour, not on the risk of sexual transmission |
| Latif, A. S., Katzenstein, D. A., Bassett, M. T., Houston, S., Emmanuel, J. C. and Marowa, E. Genital ulcers and transmission of HIV among couples in Zimbabwe. Aids. 1989; 3 (8): 519-23. | Study focusses on risk behaviour, not on the risk of sexual transmission |
| Lingappa, J. R., Hughes, J. P., Wang, R. S., Baeten, J. M., Celum, C., Gray, G. E., Stevens, W. S., Donnell, D., Campbell, M. S., Farquhar, C., Essex, M., Mullins, J. I., Coombs, R. W., Rees, H., Corey, L. and Wald, A. Estimating the impact of plasma HIV-1 RNA reductions on heterosexual HIV-1 transmission risk. PLoS One. 2010; 5 (9): e12598. | HSV coinfection in the study population |
| Loutfy, M. R., Wu, W., Letchumanan, M., Bondy, L., Antoniou, T., Margolese, S., Zhang, Y., Rueda, S., McGee, F., Peck, R., Binder, L., Allard, P., Rourke, S. B. and Rochon, P. A. Systematic review of HIV transmission between heterosexual serodiscordant couples where the HIV-positive partner is fully suppressed on antiretroviral therapy. PLoS One. 2013; 8 (2): e55747. | Replaced by a more recent systematic review |
| Mackelprang, R. D., Baeten, J. M., Donnell, D., Celum, C., Farquhar, C., de Bruyn, G., Essex, M., McElrath, M. J., Nakku-Joloba, E. and Lingappa, J. R. Quantifying ongoing HIV-1 exposure in HIV-1-serodiscordant couples to identify individuals with potential host resistance to HIV-1. J Infect Dis. 2012; 206 (8): 1299-308. | HSV coinfection in the study population |
| Mastro, T. D., Satten, G. A., Nopkesorn, T., Sangkharomya, S. and Longini, I. M., Jr. Probability of female-to-male transmission of HIV-1 in Thailand. Lancet. 1994; 343 (8891): 204-7. | Mathematical model centred around estimates of the number of contacts |
| Melo, M. G., Santos, B. R., De Cassia Lira, R., Varella, I. S., Turella, M. L., Rocha, T. M. and Nielsen-Saines, K. Sexual transmission of HIV-1 among serodiscordant couples in Porto Alegre, southern Brazil. Sex Transm Dis. 2008; 35 (11): 912-5. | Included in SR LeMessurier et al., 2018 |
| Patel, P., Borkowf, C. B., Brooks, J. T., Lasry, A., Lansky, A. and Mermin, J. Estimating per-act HIV transmission risk: a systematic review. Aids. 2014; 28 (10): 1509-19. | Replaced by a more recent systematic review |
| Pedraza, M. A., del Romero, J., Roldan, F., Garcia, S., Ayerbe, M. C., Noriega, A. R. and Alcami, J. Heterosexual transmission of HIV-1 is associated with high plasma viral load levels and a positive viral isolation in the infected partner. J Acquir Immune Defic Syndr. 1999; 21 (2): 120-5. | Study focusses on viral load, not on the risk of sexual transmission |
| Pence, B. W., Raper, J. L., Reif, S., Thielman, N. M., Leserman, J. and Mugavero, M. J. Incident stressful and traumatic life events and human immunodeficiency virus sexual transmission risk behaviors in a longitudinal, multisite cohort study. Psychosom Med. 2010; 72 (7): 720-6. | Study focusses on risk behaviour, not on the risk of sexual transmission |
| Powers, K. A., Poole, C., Pettifor, A. E. and Cohen, M. S. Rethinking the heterosexual infectivity of HIV-1: a systematic review and meta-analysis. Lancet Infect Dis. 2008; 8 (9): 553-63. | Replaced by a more recent systematic review |
| Rawstorne, P., Fogarty, A., Crawford, J., Prestage, G., Grierson, J., Grulich, A. and Kippax, S. Differences between HIV-positive gay men who 'frequently', 'sometimes' or 'never' engage in unprotected anal intercourse with serononconcordant casual partners: positive Health cohort, Australia. AIDS Care. 2007; 19 (4): 514-22. | Study focusses on risk behaviour, not on the risk of sexual transmission |
| Richters, J., Grulich, A., Ellard, J., Hendry, O. and Kippax, S. HIV transmission among gay men through oral sex and other uncommon routes: case series of HIV seroconverters, Sydney. Aids. 2003; 17 (15): 2269-71. | Study focusses on risk behaviour, not on the risk of sexual transmission |
| Sawada, I., Tanuma, J., Do, C. D., Doan, T. T., Luu, Q. P., Nguyen, L. A., Vu, T. V., Nguyen, T. Q., Tsuchiya, N., Shiino, T., Yoshida, L. M., Pham, T. T., Ariyoshi, K. and Oka, S. High | HCV coinfection in the study population |

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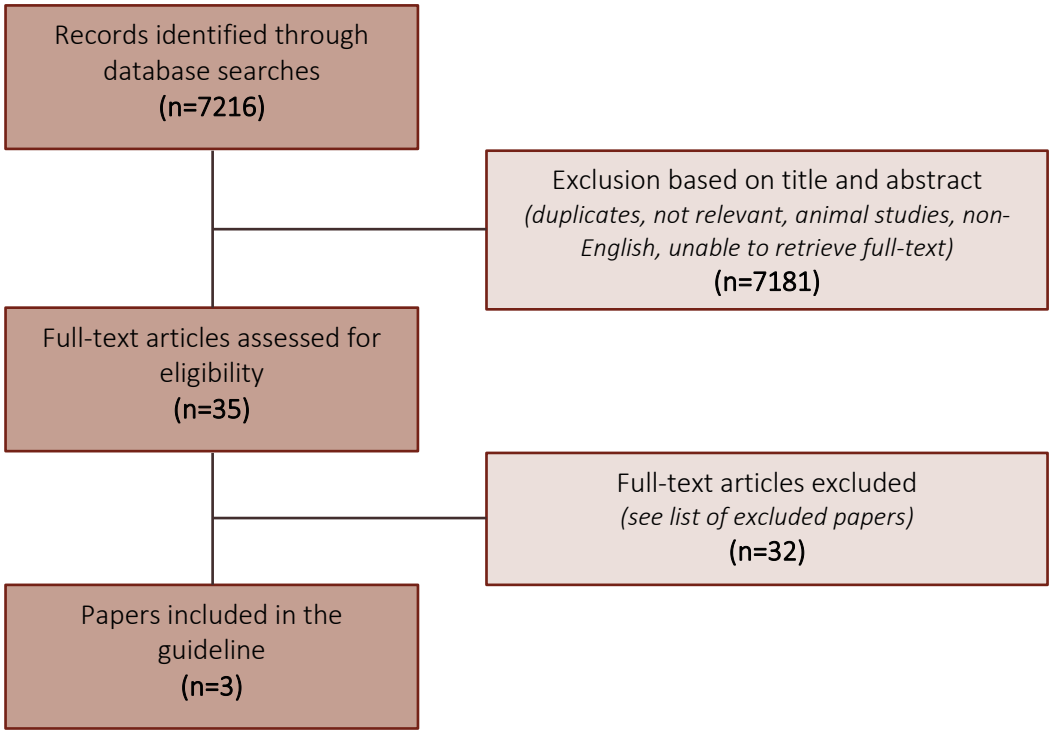
| proportion of HIV serodiscordance among HIV-affected married couples in northern Vietnam. PLoS One. 2015; 10 (4): e0125299. | |
| Serwadda, D., Gray, R. H., Wawer, M. J., Stallings, R. Y., Sewankambo, N. K., Konde-Lule, J. K., Lainjo, B. and Kelly, R. The social dynamics of HIV transmission as reflected through discordant couples in rural Uganda. Aids. | Study focusses on risk behaviour, not on the risk of sexual transmission |
| Skurnick, J. H., Kennedy, C. A., Perez, G., Abrams, J., Vermund, S. H., Denny, T., Wright, T., Quinones, M. A. and Louria, D. B. Behavioral and demographic risk factors for transmission of human immunodeficiency virus type 1 in heterosexual couples: report from the Heterosexual HIV Transmission Study. Clin Infect Dis. 1998; 26 (4): 855-64. | Study focusses on risk behaviour, not on the risk of sexual transmission |
| Stansfield, S. E., Mittler, J. E., Gottlieb, G. S., Murphy, J. T., Hamilton, D. T., Detels, R., Wolinsky, S. M., Jacobson, L. P., Margolick, J. B., Rinaldo, C. R., Herbeck, J. T. and Goodreau, S. M. Sexual role and HIV-1 set point viral load among men who have sex with men. Epidemics. 2019; 26 68-76. | Mathematical models |
| Supervie, V. and Breban, R. Brief Report: Per Sex-Act Risk of HIV Transmission Under Antiretroviral Treatment: A Data-Driven Approach. J Acquir Immune Defic Syndr. 2018; 79 (4): 440-444. | Mathematical models |
| Supervie, V., Viard, J. P., Costagliola, D. and Breban, R. Heterosexual risk of HIV transmission per sexual act under combined antiretroviral therapy: systematic review and bayesian modeling. Clin Infect Dis. 2014; 59 (1): 115-22. | Replaced by a more recent systematic review |
| Wilson, D. P., Law, M. G., Grulich, A. E., Cooper, D. A. and Kaldor, J. M. Relation between HIV viral load and infectiousness: a model-based analysis. Lancet. 2008; 372 (9635): 314-20. | Mathematical models |
| Yang, Y., Lewis, F. M. and Kraushaar, D. L. HIV transmission from husbands to wives in Cambodia: a systematic review of the literature. Cult Health Sex. 2013; 15 (9): 1115-28. | Systematic review without meta-analysis |

## IS THERE A THRESHOLD BELOW WHICH TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS IS UNLIKELY?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Maternal viral load and vertical transmission of HIV-1: an important factor but not the only one. The European Collaborative Study. Aids. 1999; 13 (11): 1377-85. | Samples for maternal viral load determination were collected either during pregnancy or within 2 months of delivery |
| Ahir, S. P., Chavan, V., Kerkar, S., Samant-Mavani, P., Nanavati, R., Mehta, P. R. and Mania-Pramanik, J. Antiretroviral treatment, viral load of mothers & perinatal HIV transmission in Mumbai, India. Indian J Med Res. 2013; 138 201-8. | Maternal viral load was determined at delivery |
| Arvold, N. D., Ngo-Giang-Huong, N., McIntosh, K., Suraseranivong, V., Warachit, B., Piyaworawong, S., Changchit, T., Lallemant, M. and Jourdain, G. Maternal HIV-1 DNA load and mother-to-child transmission. AIDS Patient Care STDS. 2007; 21 (9): 638-43. | Maternal viral load was determined before ZDV initiation at 28 and 35 weeks of pregnancy |
| Baza, M. B., Jerónimo, A., Río, I., Rodriguez, C., Vera, M., Hernando, V., Castilla, J. and Del Romero, J. Natural Conception is Safe for HIV-Serodiscordant Couples with Persistent Suppressive Antiretroviral Therapy for the Infected Partner. J Womens Health (Larchmt). 2019; 28 (11): 1555-1562. | No threshold for transmission was determined |
| Chakraborty, H., Sen, P. K., Helms, R. W., Vernazza, P. L., Fiscus, S. A., Eron, J. J., Patterson, B. K., Coombs, R. W., Krieger, J. N. and Cohen, M. S. Viral burden in genital secretions determines male-to-female sexual transmission of HIV-1: a probabilistic empiric model. Aids. 2001; 15 (5): 621-7. | Mathematical model, no clinical threshold |

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| Chetty, T., Newell, M. L., Thorne, C. and Coutsoudis, A. Viraemia before, during and after pregnancy in HIV-infected women on antiretroviral therapy in rural KwaZulu-Natal, South Africa, 2010-2015. Trop Med Int Health. 2018; 23 (1): 79-91. | No threshold for transmission was determined |
| Coll, O., Hernandez, M., Boucher, C. A., Fortuny, C., de Tejada, B. M., Canet, Y., Caragol, I., Tijnagel, J., Bertran, J. M. and Espanol, T. Vertical HIV-1 transmission correlates with a high maternal viral load at delivery. J Acquir Immune Defic Syndr Hum Retrovirol. 1997; 14 (1): 26-30. | Maternal viral load was determined at delivery |
| Fang, G., Burger, H., Grimson, R., Tropper, P., Nachman, S., Mayers, D., Weislow, O., Moore, R., Reyelt, C., Hutcheon, N., Baker, D. and Weiser, B. Maternal plasma human immunodeficiency virus type 1 RNA level: a determinant and projected threshold for mother-to-child transmission. Proc Natl Acad Sci U S A. 1995; 92 (26): 12100-4. | Viral load was determined during pregnancy or at delivery |
| Herbeck, J. T., Mittler, J. E., Gottlieb, G. S. and Mullins, J. I. An HIV epidemic model based on viral load dynamics: value in assessing empirical trends in HIV virulence and community viral load. PLoS Comput Biol. 2014; 10 (6): e1003673. | Mathematical model, no clinical threshold |
| Hisada, M., O'Brien, T. R., Rosenberg, P. S. and Goedert, J. J. Virus load and risk of heterosexual transmission of human immunodeficiency virus and hepatitis C virus by men with hemophilia. The Multicenter Hemophilia Cohort Study. J Infect Dis. 2000; 181 (4): 1475-8. | Very small numbers of included couples |
| Hollingsworth, T. D., Laeyendecker, O., Shirreff, G., Donnelly, C. A., Serwadda, D., Wawer, M. J., Kiwanuka, N., Nalugoda, F., Collinson-Streng, A., Ssempijja, V., Hanage, W. P., Quinn, T. C., Gray, R. H. and Fraser, C. HIV-1 transmitting couples have similar viral load set-points in Rakai, Uganda. PLoS Pathog. 2010; 6 (5): e1000876. | No threshold for transmission was determined |
| Hyman, J. M., Li, J. and Stanley, E. A. Threshold conditions for the spread of the HIV infection in age-structured populations of homosexual men. J Theor Biol. 1994; 166 (1): 9-31. | Mathematical model, no clinical threshold |
| Ioannidis, J. P., Tatsioni, A., Abrams, E. J., Bulterys, M., Coombs, R. W., Goedert, J. J., Korber, B. T., Mayaux, M. J., Mofenson, L. M., Moye, J., Jr., Newell, M. L., Shapiro, D. E., Teglas, J. P., Thompson, B. and Wiener, J. Maternal viral load and rate of disease progression among vertically HIV-1-infected children: an international meta-analysis. Aids. 2004; 18 (1): 99-108. | Maternal viral load was determined during pregnancy or <1 mo postpartum |
| Joao, E. C., Gouvea, M. I., Menezes, J. A., Sidi, L. C., Cruz, M. L., Berardo, P. T., Ceci, L., Cardoso, C. A., Teixeira Mde, L., Calvet, G. A. and Matos, H. J. Factors associated with viral load suppression in HIV-infected pregnant women in Rio de Janeiro, Brazil. Int J STD AIDS. 2012; 23 (1): 44-7. | In the transmission rate calculation, maternal viral load near delivery was used |
| Kahle, E. M., Hughes, J. P., Lingappa, J. R., John-Stewart, G., Celum, C., Nakku-Joloba, E., Njuguna, S., Mugo, N., Bukusi, E., Manongi, R. and Baeten, J. M. An empiric risk scoring tool for identifying high-risk heterosexual HIV-1-serodiscordant couples for targeted HIV-1 prevention. J Acquir Immune Defic Syndr. 2013; 62 (3): 339-47. | HSV-2 coinfection in study population |
| Katz, I. T., Leister, E., Kacanek, D., Hughes, M. D., Bardeguez, A., Livingston, E., Stek, A., Shapiro, D. E. and Tuomala, R. Factors associated with lack of viral suppression at delivery among highly active antiretroviral therapy-naive women with HIV: a cohort study. Ann Intern Med. 2015; 162 (2): 90-9. | Maternal viral load determined near delivery |
| Kittinunvorakoon, C., Morris, M. K., Neeyapun, K., Jetsawang, B., Buehring, G. C. and Hanson, C. V. Mother to child transmission of HIV-1 in a Thai population: role of virus characteristics and maternal humoral immune response. J Med Virol. 2009; 81 (5): 768-78. | Blood sample for viral load determination was taken at 36 weeks gestation |
| Leroy, V., Montcho, C., Manigart, O., Van de Perre, P., Dabis, F., Msellati, P., Meda, N., You, B., Simonon, A. and Rouzioux, C. Maternal plasma viral load, zidovudine and mother-to-child transmission of HIV-1 in Africa: DITRAME ANRS 049a trial. Aids. 2001; 15 (4): 517-22. | Women were enrolled in the trial at 36-38 weeks gestation and viral load was determined on the blood sample from baseline |

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| Magder, L. S., Mofenson, L., Paul, M. E., Zorrilla, C. D., Blattner, W. A., Tuomala, R. E., LaRussa, P., Landesman, S. and Rich, K. C. Risk factors for in utero and intrapartum transmission of HIV. J Acquir Immune Defic Syndr. 2005; 38 (1): 87-95. | Maternal viral load was measured during pregnancy and at delivery |
| Malamba, S. S., Mermin, J. H., Bunnell, R., Mubangizi, J., Kalule, J., Marum, E., Hu, D. J., Wangalwa, S., Smith, D. and Downing, R. Couples at risk: HIV-1 concordance and discordance among sexual partners receiving voluntary counseling and testing in Uganda. J Acquir Immune Defic Syndr. 2005; 39 (5): 576-80. | No threshold for transmission was determined |
| Marks, G., Gardner, L. I., Rose, C. E., Zinski, A., Moore, R. D., Holman, S., Rodriguez, A. E., Sullivan, M. and Giordano, T. P. Time above 1500 copies: a viral load measure for assessing transmission risk of HIV-positive patients in care. Aids. 2015; 29 (8): 947-54. | No threshold for transmission was determined |
| Mayaux, M. J., Dussaix, E., Isopet, J., Rekacewicz, C., Mandelbrot, L., Ciraru-Vigneron, N., Allemon, M. C., Chambrin, V., Katlama, C., Delfraissy, J. F. and Puel, J. Maternal virus load during pregnancy and mother-to-child transmission of human immunodeficiency virus type 1: the French perinatal cohort studies. SEROGEST Cohort Group. J Infect Dis. 1997; 175 (1): 172-5. | Maternal viral load was determined during pregnancy |
| Mofenson, L. M., Lambert, J. S., Stiehm, E. R., Bethel, J., Meyer, W. A., 3rd, Whitehouse, J., Moye, J., Jr., Reichelderfer, P., Harris, D. R., Fowler, M. G., Mathieson, B. J. and Nemo, G. J. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. N Engl J Med. 1999; 341 (6): 385-93. | HIV viral load was determined at base line (20-30 weeks gestation), 3rd trimester, and at delivery. |
| Montano, M., Russell, M., Gilbert, P., Thior, I., Lockman, S., Shapiro, R., Chang, S. Y., Lee, T. H. and Essex, M. Comparative prediction of perinatal human immunodeficiency virus type 1 transmission, using multiple virus load markers. J Infect Dis. 2003; 188 (3): 406-13. | Maternal viral load was determined after birth |
| Onoya, D., Nattey, C., Jinga, N., Mongwenyana, C. and Sherman, G. Time of HIV diagnosis, CD4 count and viral load at antenatal care start and delivery in South Africa. PLoS One. 2020; 15 (2): e0229111. | Maternal viral load was determined during pregnancy and at delivery |
| Phuapradit, W., Panburana, P., Jaovisidha, A., Vichitphun, N., Kongsin, P., Chantratita, W., Bhodhiphala, P. and Pairoj, W. Maternal viral load and vertical transmission of HIV-1 in mid-trimester gestation. Aids. 1999; 13 (14): 1927-31. | Maternal viral load determined upon admission |
| Pilcher, C. D., Tien, H. C., Eron, J. J., Jr., Vernazza, P. L., Leu, S. Y., Stewart, P. W., Goh, L. E. and Cohen, M. S. Brief but efficient: acute HIV infection and the sexual transmission of HIV. J Infect Dis. 2004; 189 (10): 1785-92. | Mathematical model, no clinical threshold |
| Read, P. J., Mandalia, S., Khan, P., Harrisson, U., Naftalin, C., Gilleece, Y., Anderson, J., Hawkins, D. A., Taylor, G. P. and de Ruiter, A. When should HAART be initiated in pregnancy to achieve an undetectable HIV viral load by delivery? Aids. 2012; 26 (9): 1095-103. | Maternal viral load was determined at baseline (during pregnancy) and at delivery |
| Rolland, M., Tovanabutra, S., Dearlove, B., Li, Y., Owen, C. L., et al. Molecular dating and viral load growth rates suggested that the eclipse phase lasted about a week in HIV-1 infected adults in East Africa and Thailand. PLoS Pathog. 2020; 16 (2): e1008179. | Maternal viral load was determined during pregnancy or after delivery |
| Sperling, R. S., Shapiro, D. E., Coombs, R. W., Todd, J. A., Herman, S. A., McSherry, G. D., O'Sullivan, M. J., Van Dyke, R. B., Jimenez, E., Rouzioux, C., Flynn, P. M. and Sullivan, J. L. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med. 1996; 335 (22): 1621-9. | Blood samples for maternal viral load determination were obtained at entry of the study (14-34 weeks pregnant) and at delivery |
| Sun, L., Wang, F., Liu, A., Xin, R., Zhu, Y., Li, J., Shao, Y., Ye, J., Chen, D. and Li, Z. Natural Conception May Be an Acceptable Option in HIV-Serodiscordant Couples in Resource Limited Settings. PloS One. 2015; 10 (11): e0142085. | Maternal viral load determined at delivery |

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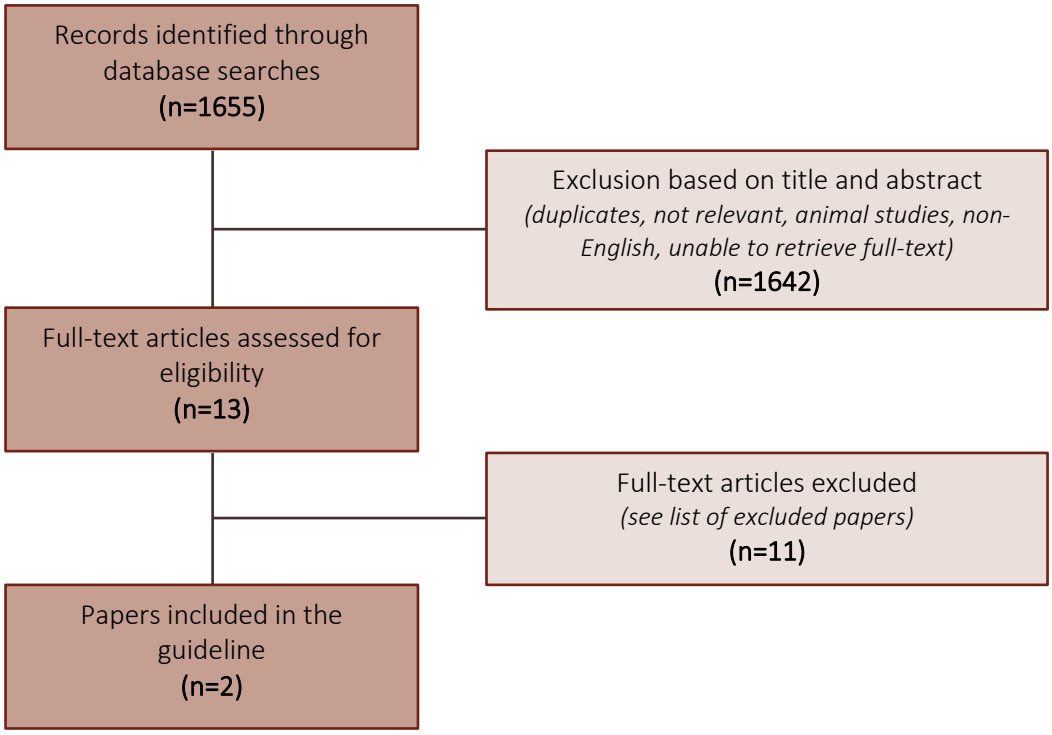
| Weiser, B., Nachman, S., Tropper, P., Viscosi, K. H., Grimson, R., Baxter, G., Fang, G., Reyelt, C., Hutcheon, N. and Burger, H. Quantitation of human immunodeficiency virus type 1 during pregnancy: relationship of viral titer to mother-to-child transmission and stability of viral load. Proc Natl Acad Sci U S A. 1994; 91 (17): 8037-41. | Maternal viral load was determined during pregnancy and/or at delivery |

## SHOULD IUI, IVF OR ICSI BE PREFERENTIALLY USED FOR MEDICALLY ASSISTED REPRODUCTION IN HUMAN IMMUNODEFICIENCY VIRUS INFECTED COUPLES?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Manigart, Y., Rozenberg, S., Barlow, P., Gerard, M., Bertrand, E. and Delvigne, A. ART outcome in HIV-infected patients. Hum Reprod. 2006; 21 (11): 2935-40. | Included in SR Barnes et al., 2014 |
| Marina, S., Marina, F., Alcolea, R., Exposito, R., Huguet, J., Nadal, J. and Verges, A. Human immunodeficiency virus type 1--serodiscordant couples can bear healthy children after undergoing intrauterine insemination. Fertil Steril. 1998; 70 (1): 35-9. | No treatment comparison group |
| Mencaglia, L., Falcone, P., Lentini, G. M., Consigli, S., Pisoni, M., Lofiego, V., Guidetti, R., Piomboni, P. and De Leo, V. ICSI for treatment of human immunodeficiency virus and hepatitis C virus-serodiscordant couples with infected male partner. Hum Reprod. 2005; 20 (8): 2242-6. | No treatment comparison group |
| Nicopoullos, J. D., Almeida, P. A., Ramsay, J. W. and Gilling-Smith, C. The effect of human immunodeficiency virus on sperm parameters and the outcome of intrauterine insemination following sperm washing. Hum Reprod. 2004; 19 (10): 2289-97. | Only IUI |
| Nicopoullos, J. D., Almeida, P., Vourliotis, M., Goulding, R. and Gilling-Smith, C. A decade of the sperm-washing programme: where are we now? Hum Fertil (Camb). 2010; 13 (2): 90-7. | Excluded from the SR Barnes et al., 2014 |
| Ohl, J., Partisani, M., Wittemer, C., Lang, J. M., Viville, S. and Favre, R. Encouraging results despite complexity of multidisciplinary care of HIV-infected women using assisted reproduction techniques. Hum Reprod. 2005; 20 (11): 3136-40. | Excluded from the SR Barnes et al., 2014 |
| Ohl, J., Partisani, M., Wittemer, C., Schmitt, M. P., Cranz, C., Stoll-Keller, F., Rongieres, C., Bettahar-Lebugle, K., Lang, J. M. and Nisand, I. Assisted reproduction techniques for HIV serodiscordant couples: 18 months of experience. | Excluded from the SR Barnes et al., 2014 |
| Pena, J. E., Thornton, M. H. and Sauer, M. V. Assessing the clinical utility of in vitro fertilization with intracytoplasmic sperm injection in human immunodeficiency virus | No treatment comparison group |

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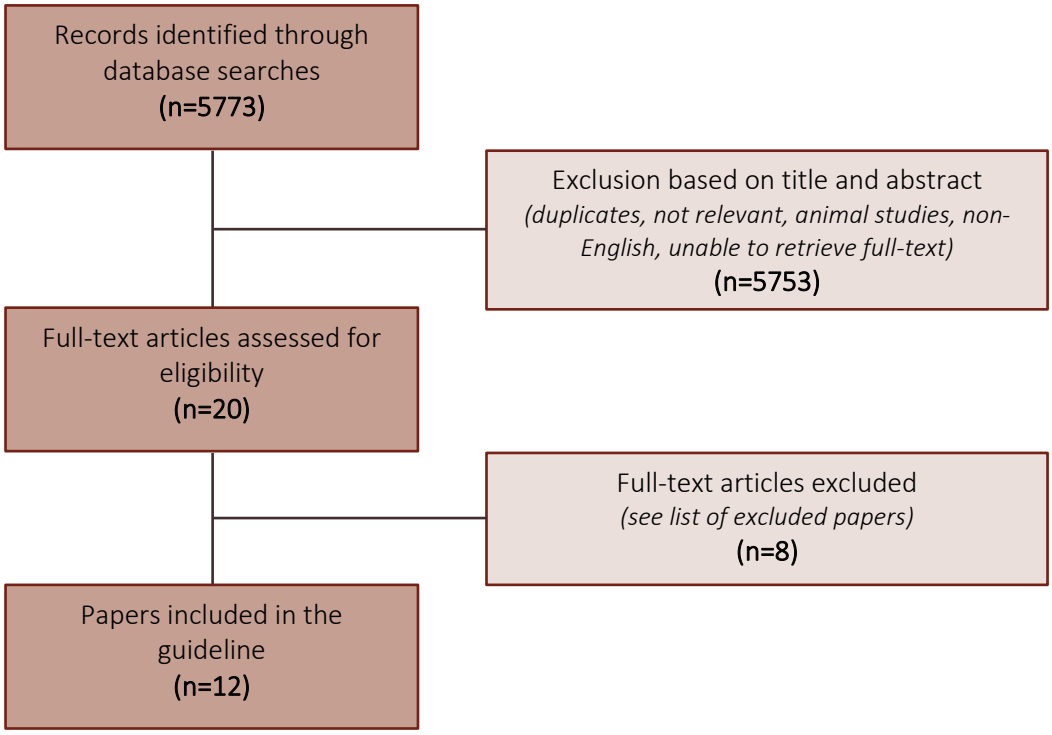
| type 1 serodiscordant couples: report of 113 consecutive cycles. Fertil Steril. 2003; 80 (2): 356-62. | |
| Sauer, M. V. and Chang, P. L. Establishing a clinical program for human immunodeficiency virus 1-seropositive men to father seronegative children by means of in vitro fertilization with intracytoplasmic sperm injection. Am J Obstet Gynecol. 2002; 186 (4): 627-33. | Included in SR Vitorino et al., 2011 |
| Savasi, V., Ferrazzi, E., Lanzani, C., Oneta, M., Parrilla, B. and Persico, T. Safety of sperm washing and ART outcome in 741 HIV-1-serodiscordant couples. Hum Reprod. 2007; 22 (3): 772-7. | Included in SR Barnes et al., 2014 |
| Semprini, A. E., Macaluso, M., Hollander, L., Vucetich, A., Duerr, A., Mor, G., Ravizza, M. and Jamieson, D. J. Safe conception for HIV-discordant couples: insemination with processed semen from the HIV-infected partner. Am J Obstet Gynecol. 2013; 208 (5): 402.e1-9. | Excluded from the SR Barnes et al., 2014 |

## CAN HUMAN IMMUNODEFICIENCY VIRUS DNA BE DETECTED IN OOCYTES/ SPERM/ PLACENTA?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Baccetti, B., Benedetto, A., Collodel, G., di Caro, A., Garbuglia, A. R. and Piomboni, P. The debate on the presence of HIV-1 in human gametes. J Reprod Immunol. 1998; 41 (1-2): 41-67 | The original data is in the other manuscripts |
| Burton, G. J., O'Shea, S., Rostron, T., Mullen, J. E., Aiyer, S., Skepper, J. N., Smith, R. and Banatvala, J. E. Significance of placental damage in vertical transmission of human immunodeficiency virus. J Med Virol. 1996; 50 (3): 237-43. | No histochemistry or PCR on the placental tissue to confirm HIV infection of placental tissue |
| Cardona-Maya, W., Velilla, P., Montoya, C. J., Cadavid, A. and Rugeles, M. T. Presence of HIV-1 DNA in spermatozoa from HIV-positive patients: changes in the semen parameters. Curr HIV Res. 2009; 7 (4): 418-24. | Focus on sperm parameters and the detection of HIV DNA after density gradient. |
| Maury, W., Potts, B. J. and Rabson, A. B. HIV-1 infection of first-trimester and term human placental tissue: a possible mode of maternal-fetal transmission. J Infect Dis. 1989; 160 (4): 583-8. | Very old article, CD4 testing, not HIV |
| Obimbo, M. M., Zhou, Y., McMaster, M. T., Cohen, C. R., Qureshi, Z., Ong'ech, J., Ogeng'o, J. A. and Fisher, S. J. Placental Structure in Preterm Birth Among HIV-Positive Versus HIV-Negative Women in Kenya. J Acquir Immune Defic Syndr. 2019; 80 (1): 94-102. | No histochemistry or PCR on the placental tissue to confirm HIV infection of placental tissue |
| Savchenko, S. E., Dyadyk, O. O., Chaika, K. V., Onyshchyk, L. M., Vorobey, L. I., Zhykharskyi, R. V. and Bondaruk, V. P. Pathomorphological characteristics and | No histochemistry or PCR on the placental tissue to confirm HIV |

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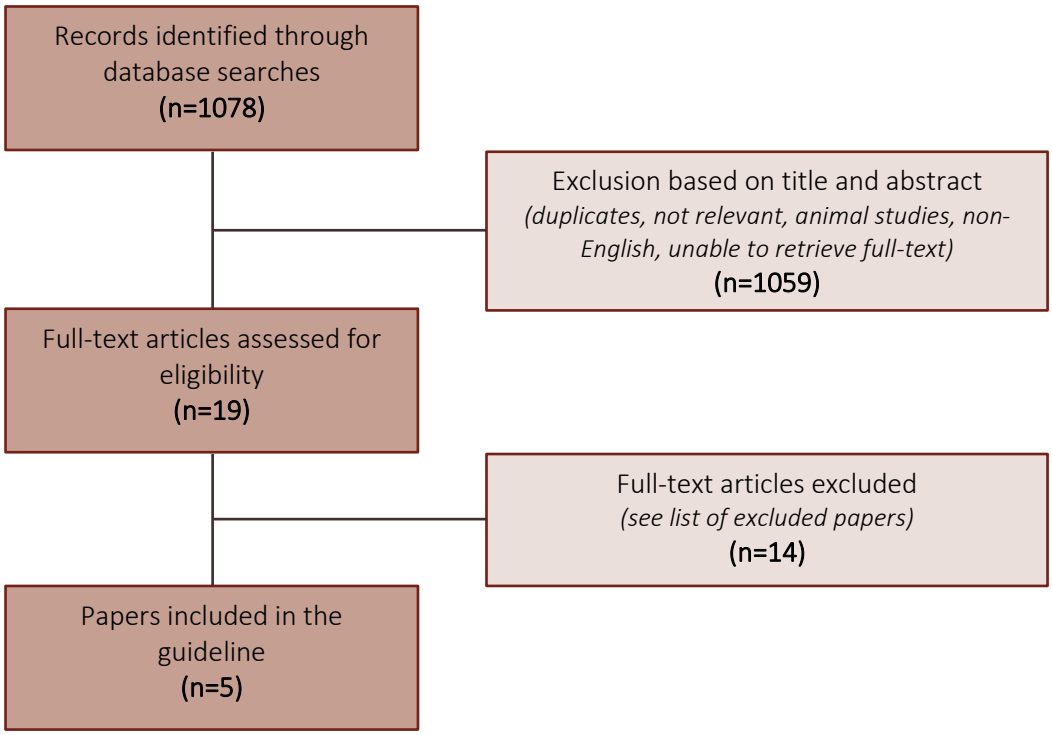
| immunohistochemical features of placentae from hiv-positive pregnant women with fetal growth retardation. Wiad Lek. 2020; 73 (2): 215-219. | infection of placental tissue |
| Schwartz, D. A., Sungkarat, S., Shaffer, N., Laosakkitiboran, J., Supapol, W., Charoenpanich, P., Chuangsuwanich, T. and Mastro, T. D. Placental abnormalities associated with human immunodeficiency virus type 1 infection and perinatal transmission in Bangkok, Thailand. J Infect Dis. 2000; 182 (6): 1652-7. | No histochemistry or PCR on the placental tissue to confirm HIV infection of placental tissue |
| Vermaak, A., Theron, G. B., Schubert, P. T., Kidd, M., Rabie, U., Adjiba, B. M. and Wright, C. A. Morphologic changes in the placentas of HIV-positive women and their association with degree of immune suppression. Int J Gynaecol Obstet. 2012; 119 (3): 239-43. | No histochemistry or PCR on the placental tissue to confirm HIV infection of placental tissue |

## DOES HUMAN IMMUNODEFICIENCY VIRUS/TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS BEFORE ASSISTED REPRODUCTION IMPACT THE OUTCOME OF ASSISTED REPRODUCTION?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Bujan, L., Sergerie, M., Kiffer, N., Moinard, N., Seguela, G., Mercadier, B., Rhone, P., Pasquier, C. and Daudin, M. Good efficiency of intrauterine insemination programme for serodiscordant couples with HIV-1 infected male partner: a retrospective comparative study. Eur J Obstet Gynecol Reprod Biol. 2007; 135 (1): 76-82. | Retrospective case-control study in the presence of higher quality evidence |
| Cleary-Goldman, J., Pena, J. E., Thornton, M. H., 2nd, Robinson, J. N., D'Alton, M. E. and Sauer, M. V. Obstetric outcomes of human immunodeficiency virus-1-serodiscordant couples following in vitro fertilization with intracytoplasmic sperm injection. Am J Perinatol. 2003; 20 (6): 305-11. | No comparison to HIV negative couples |
| Coll, O., Suy, A., Figueras, F., Vernaeve, V., Martinez, E., Mataro, D., Durban, M., Lonca, M., Vidal, R. and Gatell, J. M. Decreased pregnancy rate after in-vitro fertilization in HIV-infected women receiving HAART. Aids. 2006; 20 (1): 121-3. | Included in SR Marques et al., 2015 |
| Giles, M. L., Barak, S., Baker, G., Perna, S., Tabrizi, S., Greengrass, V., Bourne, H., Clarke, G. N., Peak, S. A., Hoy, J. F., Foster, P. and Knight, R. L. Outcomes from the first assisted reproduction program for HIV-serodiscordant couples in Australia. Med J Aust. 2011; 195 (10): 599-601. | Very small patient cohort |
| Manigart, Y., Rozenberg, S., Barlow, P., Gerard, M., Bertrand, E. and Delvigne, A. ART outcome in HIV-infected patients. Hum Reprod. 2006; 21 (11): 2935-40. | No comparison to HIV negative couples |
| Mataró, D., García, D., Coll, O., Vassena, R. and Rodríguez, A. Lower endometrial receptivity in HIV-infected women receiving oocyte donation: a comorbidity of HIV infection? Hum Reprod Open. 2017; 2017 (3): hox019. | Oocyte donation cycles |
| Melo, M. A., Meseguer, M., Bellver, J., Remohi, J., Pellicer, A. and Garrido, N. Human immunodeficiency type-1 virus (HIV-1) infection in serodiscordant couples (SDCs) does | Coinfections in the study population |

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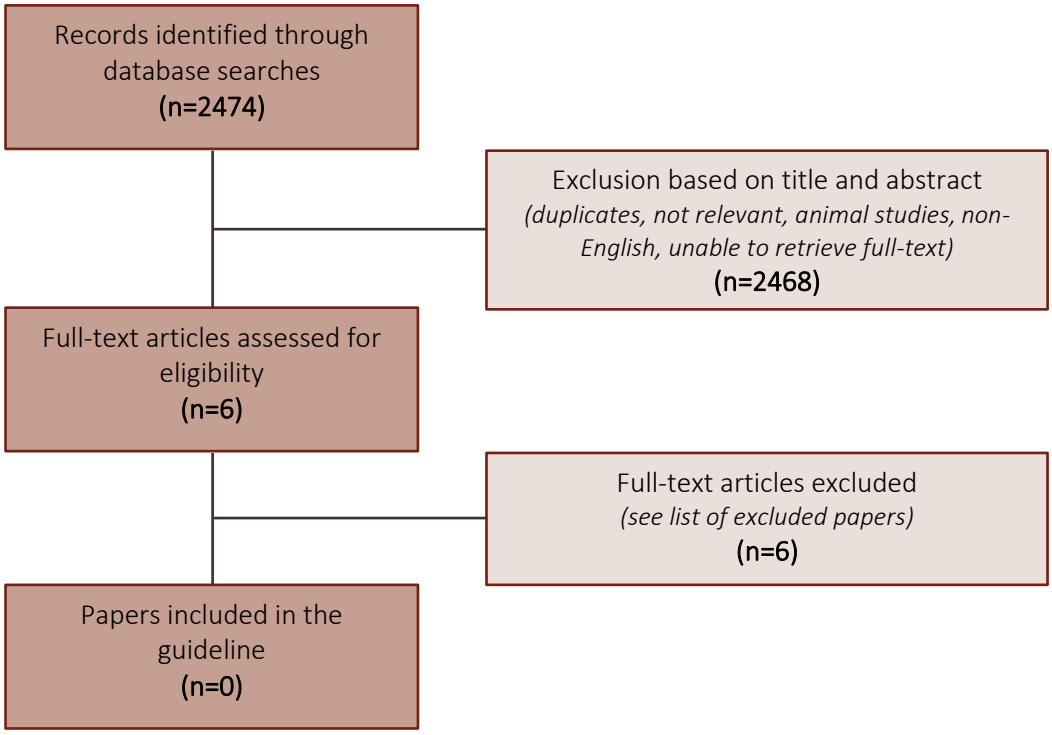
| not have an impact on embryo quality or intracytoplasmic sperm injection (ICSI) outcome. Fertil Steril. 2008; 89 (1): 141-50. | |
| Molina, I., Carmen Del Gonzalvo, M., Clavero, A., Angel Lopez-Ruz, M., Mozas, J., Pasquau, J., Sampedro, A., Martinez, L. and Castilla, J. A. Assisted reproductive technology and obstetric outcome in couples when the male partner has a chronic viral disease. Int J Fertil Steril. 2014; 7 (4): 291-300. | No comparison to a HIV negative control group |
| Santulli, P., Gayet, V., Fauque, P., Chopin, N., Dulioust, E., Wolf, J. P., Chapron, C. and de Ziegler, D. HIV-positive patients undertaking ART have longer infertility histories than age-matched control subjects. Fertil Steril. 2011; 95 (2): 507-12. | Included in SR Marques et al., 2015 |
| Semprini, A. E., Macaluso, M., Hollander, L., Vucetich, A., Duerr, A., Mor, G., Ravizza, M. and Jamieson, D. J. Safe conception for HIV-discordant couples: insemination with processed semen from the HIV-infected partner. Am J Obstet Gynecol. 2013; 208 (5): 402.e1-9. | No comparison to HIV negative couples |
| Stora, C., Epelboin, S., Devouche, E., Matheron, S., Epelboin, L., Yazbeck, C., Damond, F., Longuet, P., Dzineku, F., Rajguru, M., Delaroche, L., Mandelbrot, L., Luton, D. and Patrat, C. Women infected with human immunodeficiency virus type 1 have poorer assisted reproduction outcomes: a case-control study. Fertil Steril. 2016; 105 (5): 1193-1201. | Coinfections in the study population |
| Terriou, P., Auquier, P., Chabert-Orsini, V., Chinchole, J. M., Cravello, L., Giorgetti, C., Halfon, P., Salzmann, J. and Roulier, R. Outcome of ICSI in HIV-1-infected women. Hum Reprod. 2005; 20 (10): 2838-43. | Included in SR Marques et al., 2015 |
| Vankerkem, P., Manigart, Y., Delvigne, A., Ameye, L., Konopnicki, D., Shaw-Jackson, C., Rozenberg, S. and Autin, C. In vitro fertilization when men, women, or both partners are positive for HIV: a case-control study. Arch Gynecol Obstet. 2017; 295 (6): 1493-1507. | Coinfections in the study population |
| Wu, M. Y., Chang, L. J., Chen, M. J., Chao, K. H., Yang, Y. S. and Ho, H. N. Outcomes of assisted reproductive techniques for HIV-1-discordant couples using thawed washed sperm in Taiwan: comparison with control and testicular sperm extraction/microscopic epididymal sperm aspiration groups. J Formos Med Assoc. 2011; 110 (8): 495-500. | Very small patient cohort |

## WHICH TECHNIQUES CAN BE USED TO PREVENT/REDUCE HUMAN IMMUNODEFICIENCY VIRUS TRANSMISSION DURING MEDICALLY ASSISTED REPRODUCTION?

### Flowchart

PrEP




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Dorenbaum, A., Cunningham, C. K., Gelber, R. D., Culnane, M., Mofenson, L., Britto, P., Rekacewicz, C., Newell, M. L., Delfraissy, J. F., Cunningham-Schrader, B., Mirochnick, M. and Sullivan, J. L. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. Jama. 2002; 288 (2): 189-98. | Not PrEP during MAR |
| Fowler, M. G., Qin, M., Fiscus, S. A., Currier, J. S., Flynn, P. M., Chipato, T., McIntyre, J., Gnanashanmugam, D., Siberry, G. K., Coletti, A. S., Taha, T. E., Klingman, K. L., Martinson, F. E., Owor, M., Violari, A., Moodley, D., Theron, G. B., Bhosale, R., Bobat, R., Chi, B. H., Strehlau, R., Mlay, P., Loftis, A. J., Browning, R., Fenton, T., Purdue, L., Basar, M., Shapiro, D. E. and Mofenson, L. M. Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention. N Engl J Med. 2016; 375 (18): 1726-1737. | Not PrEP during MAR |
| Gibb, D. M., Kizito, H., Russell, E. C., Chidziva, E., Zalwango, E., Nalumenya, R., Spyer, M., Tumukunde, D., Nathoo, K., Munderi, P., Kyomugisha, H., Hakim, J., Grosskurth, H., Gilks, C. F., Walker, A. S. and Musoke, P. Pregnancy and infant outcomes among HIV-infected women taking long-term ART with and without tenofovir in the DART trial. PLoS Med. 2012; 9 (5): e1001217. | Not PrEP during MAR |
| Morrison, S., John-Stewart, G., Egessa, J. J., Mubezi, S., Kusemererwa, S., Bii, D. K., Bulya, N., Mugume, F., Campbell, J. D., Wangisi, J., Bukusi, E. A., Celum, C. and Baeten, J. M. Rapid Antiretroviral Therapy Initiation for Women in an HIV-1 Prevention Clinical Trial Experiencing Primary HIV-1 Infection during Pregnancy or Breastfeeding. PLoS One. 2015; 10 (10): e0140773. | Not PrEP during MAR |

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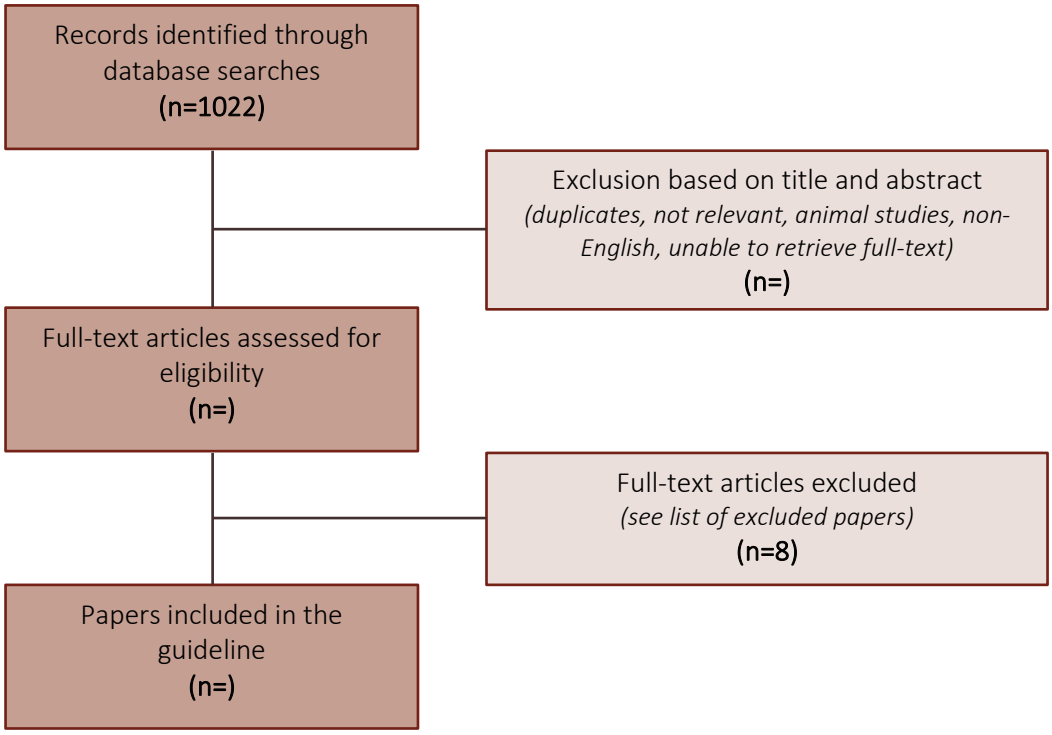
| Mugo, N. R., Hong, T., Celum, C., Donnell, D., Bukusi, E. A., John-Stewart, G., Wangisi, J., Were, E., Heffron, R., Matthews, L. T., Morrison, S., Ngure, K. and Baeten, J. M. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. Jama. 2014; 312 (4): 362-71. | Not PrEP during MAR |
| Mandelbrot, L., Tubiana, R., Le Chenadec, J., Dollfus, C., Faye, A., Pannier, E., Matheron, S., Khuong, M. A., Garrait, V., Reliquet, V., Devidas, A., Berrebi, A., Allisy, C., Elleau, C., Arvieux, C., Rouzioux, C., Warszawski, J. and Blanche, S. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. Clin Infect Dis. 2015; 61 (11): 1715-25. | Not PrEP during MAR |

## WHAT IS THE BEST TECHNIQUE FOR SEMEN PROCESSING TO REDUCE HUMAN IMMUNODEFICIENCY VIRUS VIRAL LOAD?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Bujan, L., Daudin, M., Moinard, N., Plante, P., Parinaud, J. and Pasquier, C. Azoospermic HIV-1 infected patients wishing to have children: proposed strategy to reduce HIV-1 transmission risk during sperm retrieval and intracytoplasmic sperm injection: Case Report. Hum Reprod. 2007; 22 (9): 2377-81. | Included in SR Zafer et al., 2016 |
| Garrido, N., Meseguer, M., Bellver, J., Remohi, J., Simon, C. and Pellicer, A. Report of the results of a 2 year programme of sperm wash and ICSI treatment for human immunodeficiency virus and hepatitis C virus serodiscordant couples. Hum Reprod. 2004; 19 (11): 2581-6. | Included in SR Zafer et al., 2016 |
| Garrido, N., Meseguer, M., Remohi J., Simon C., Pellicer, A. Semen characteristics in human immunodeficiency virus (HIV)- and hepatitis C (HCV)-seropositive males: predictors of the success of viral removal after sperm washing. Hum Reprod. 2005; 20(4): 1028-34 | Coinfections in the study population |
| Hanabusa, H., Kuji, N., Kato, S., Tagami, H., Kaneko, S., Tanaka, H. and Yoshimura, Y. An evaluation of semen processing methods for eliminating HIV-1. Aids. 2000; 14 (11): 1611-6. | Significant risk of bias due to incomplete reporting of methodology |
| Kato, S., Hanabusa, H., Kaneko, S., Takakuwa, K., Suzuki, M., Kuji, N., Jinno, M., Tanaka, R., Kojima, K., Iwashita, M., Yoshimura, Y. and Tanaka, K. Complete removal of HIV-1 RNA and proviral DNA from semen by the swim-up method: assisted reproduction technique using spermatozoa free from HIV-1. Aids. 2006; 20 (7): 967-73. | Included in SR Zafer et al., 2016 |
| Lasheeb, A. S., King, J., Ball, J. K., Curran, R., Barratt, C. L., Afnan, M. and Pillay, D. Semen characteristics in HIV-1 positive men and the effect of semen washing. Genitourin Med. 1997; 73 (4): 303-5. | Very small sample size |

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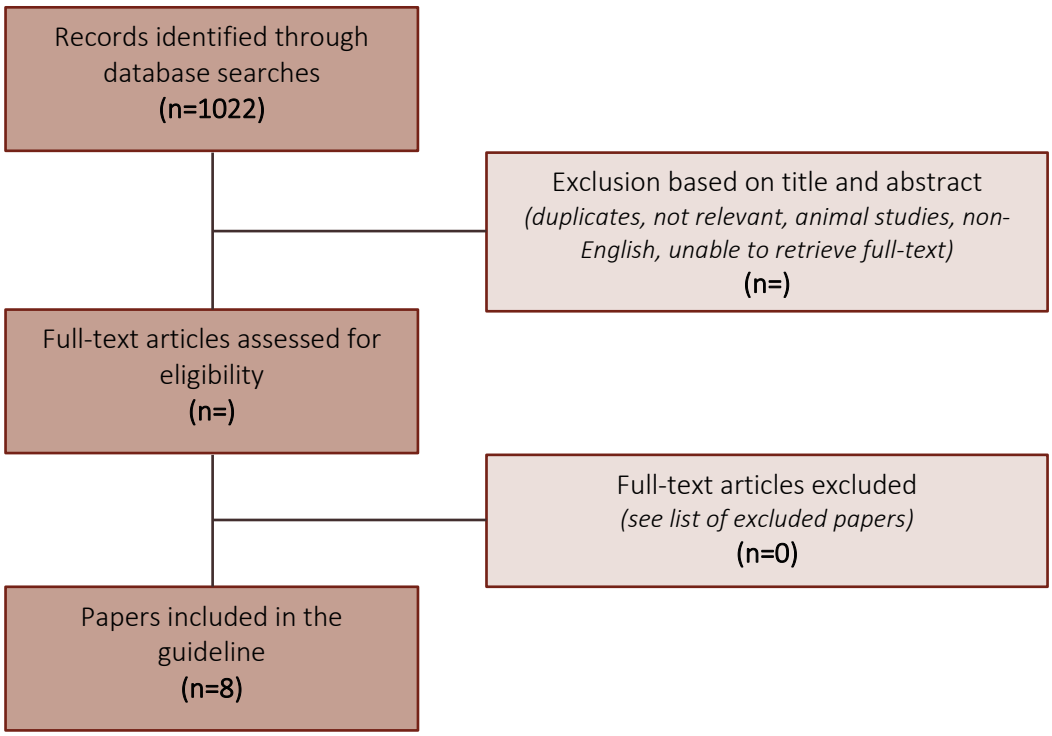
| Marina, S., Marina, F., Alcolea, R., Exposito, R., Huguet, J., Nadal, J. and Verges, A. Human immunodeficiency virus type 1--serodiscordant couples can bear healthy children after undergoing intrauterine insemination. Fertil Steril. 1998; 70 (1): 35-9. | Included in SR Zafer et al., 2016 |
| Nicopoullos, J. D., Almeida, P., Vourliotis, M., Goulding, R. and Gilling-Smith, C. A decade of sperm washing: clinical correlates of successful insemination outcome. Hum Reprod. 2010; 25 (8): 1869-76. | Included in SR Zafer et al., 2016 |

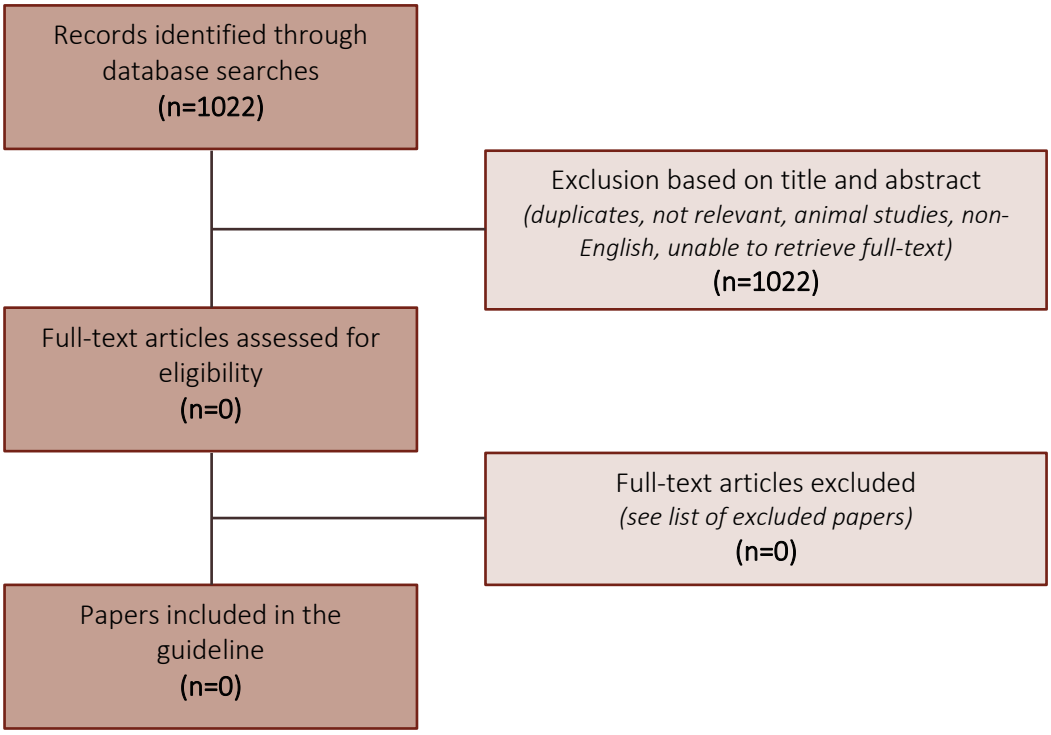
## IS THERE A NEED FOR PCR TESTING OF POST-WASHED SPERM?

### Flowchart



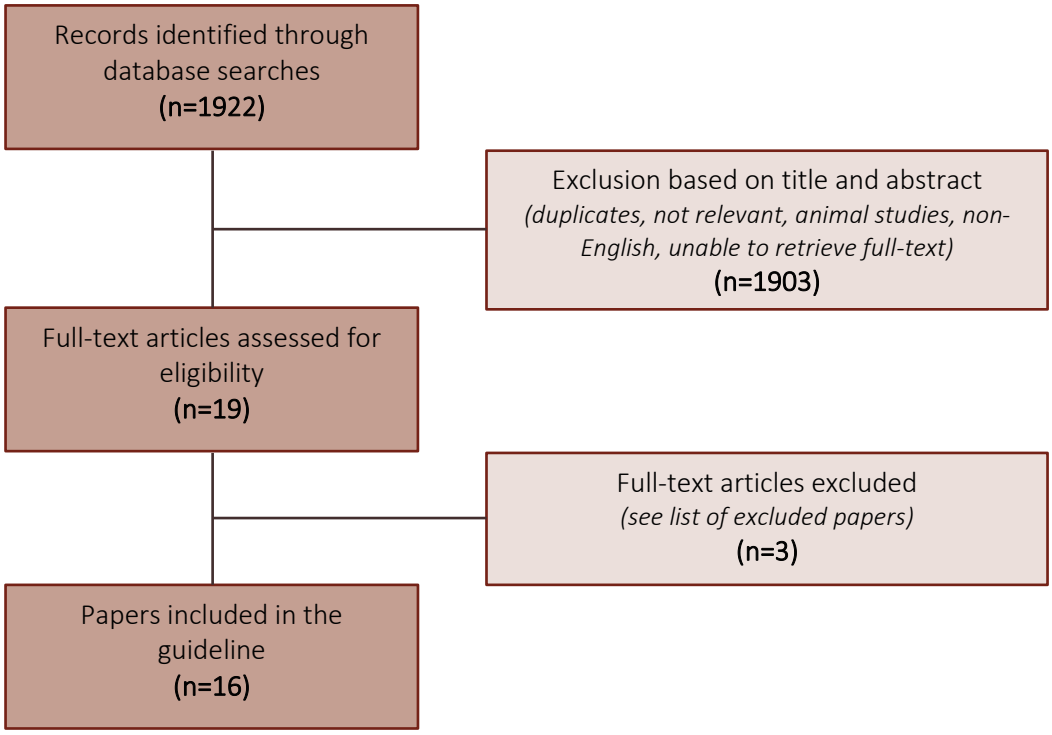
## IS THERE A NEED FOR SEMEN PROCESSING WHEN BOTH THE MALE AND FEMALE ARE INFECTED?

Flowchart



## DOES THE PLASMATIC VIRAL LOAD CORRELATE WITH HUMAN IMMUNODEFICIENCY VIRUS IN SEMEN?

### Flowchart

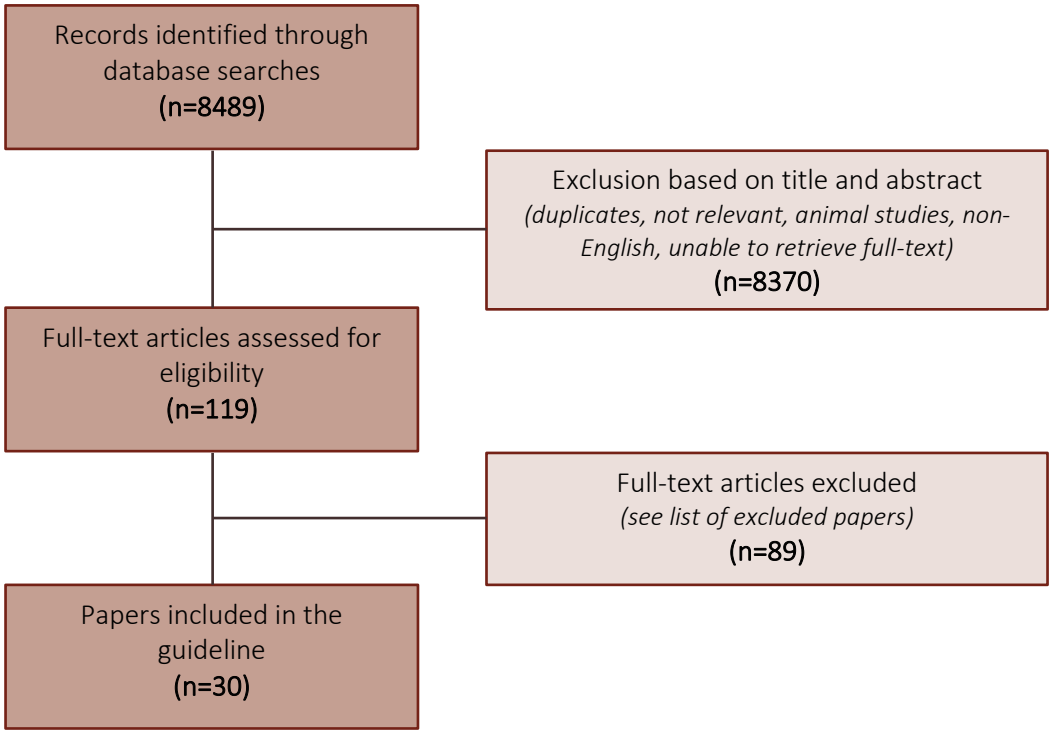



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Barroso, P. F., Schechter, M., Gupta, P., Melo, M. F., Vieira, M., Murta, F. C., Souza, Y. and Harrison, L. H. Effect of antiretroviral therapy on HIV shedding in semen. Ann Intern Med. 2000; 133 (4): 280-4. | Focus on reduction of viral load |
| Kariuki, S. M., Selhorst, P., Anthony, C., Matten, D., Abrahams, M. R., Martin, D. P., Ariën, K. K., Rebe, K., Williamson, C. and Dorfman, J. R. Compartmentalization and Clonal Amplification of HIV-1 in the Male Genital Tract Characterized Using Next-Generation Sequencing. J Virol. 2020; 94 (12): | Focus on compartimentalization of HIV |
| Pilcher, C. D., Joaki, G., Hoffman, I. F., Martinson, F. E., Mapanje, C., Stewart, P. W., Powers, K. A., Galvin, S., Chilongozi, D., Gama, S., Price, M. A., Fiscus, S. A. and Cohen, M. S. Amplified transmission of HIV-1: comparison of HIV-1 concentrations in semen and blood during acute and chronic infection. Aids. 2007; 21 (13): 1723-30. | Significant risk of bias due to poor methodology |

## WHICH INTERVENTIONS CAN BE USED TO REDUCE/AVOID VERTICAL TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TO THE NEW-BORN?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
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| Sirinavin, S., Phaupradit, W., Taneepanichskul, S., Atamasirikul, K. and Hetrakul, P. Effect of immediate neonatal zidovudine on prevention of vertical transmission of human immunodeficiency virus type 1. International Journal of Infectious Diseases. 2000; 4 (3): 148-152. | Higher quality evidence available |
| Some, E. N., Engebretsen, I. M., Nagot, N., Meda, N., Lombard, C., Vallo, R., Peries, M., Kankasa, C., Tumwine, J. K., Hofmeyr, G. J., Singata, M., Harper, K., Van De Perre, P. and Tylleskar, T. Breastfeeding patterns and its determinants among mothers living with Human Immuno-deficiency Virus -1 in four African countries participating in the ANRS 12174 trial. International Breastfeeding Journal. 2017; 12 (22): 1-12. | No treatment comparison group |
| Sripan, P., Le Coeur, S., Amzal, B., Ingsrisawang, L., Traisathit, P., Ngo-Giang-Huong, N., McIntosh, K., Cressey, T. R., Sangsawang, S., Rawangban, B., Kanjanavikai, P., Treluyer, J. M., Jourdain, G., Lallemant, M. and Urien, S. Modeling of In-Utero and Intra-Partum Transmissions to Evaluate the Efficacy of Interventions for the Prevention of Perinatal HIV. PLoS One. 2015; 10 (5): e0126647. | Intra uterine and intrapartum HIV transmission |
| Stringer, J. S., Sinkala, M., Chapman, V., Acosta, E. P., Aldrovandi, G. M., Mudenda, V., Stout, J. P., Goldenberg, R. L., Kumwenda, R. and Vermund, S. H. Timing of the | No treatment comparison group |

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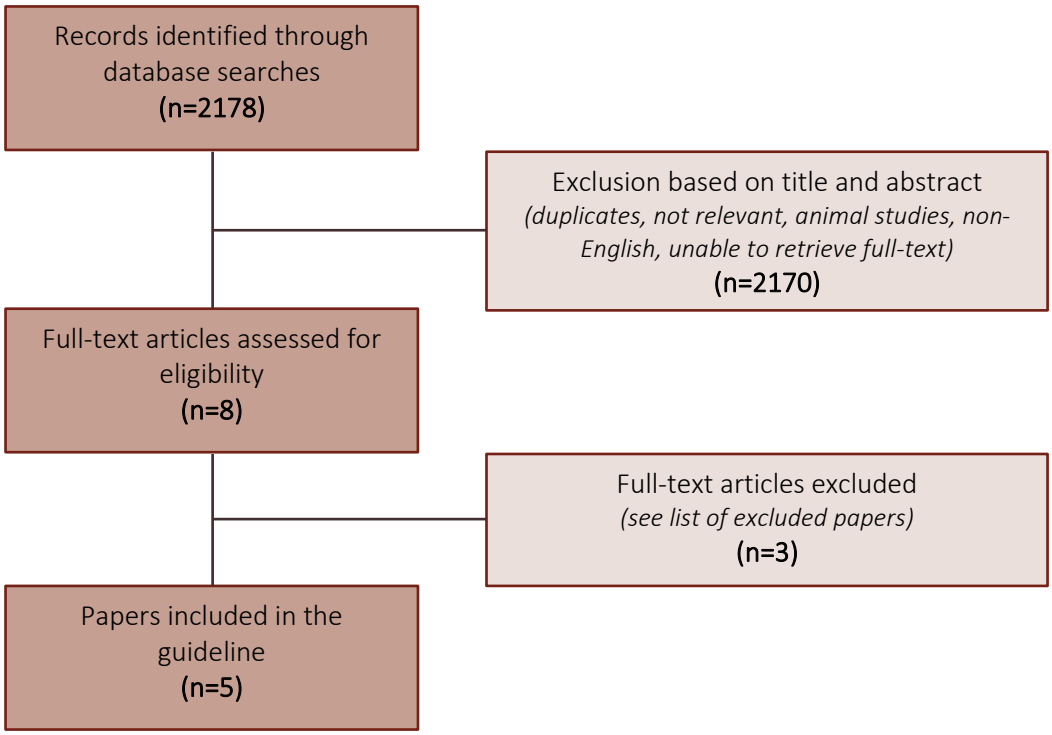
|---|---|
| maternal drug dose and risk of perinatal HIV transmission in the setting of intrapartum and neonatal single-dose nevirapine. Aids. 2003; 17 (11): 1659-65. | |
| Taha, T. E., Kumwenda, N. I., Gibbons, A., Broadhead, R. L., Fiscus, S., Lema, V., Liomba, G., Nkhoma, C., Miotti, P. G. and Hoover, D. R. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. Lancet. 2003; 362 (9391): 1171-7. | Included in SR Chigwedere et al., 2008 |
| Taha, T. E., Kumwenda, N. I., Hoover, D. R., Fiscus, S. A., Kafulafula, G., Nkhoma, C., Nour, S., Chen, S., Liomba, G., Miotti, P. G. and Broadhead, R. L. Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled trial. Jama. 2004; 292 (2): 202-9. | Included in SR Chigwedere et al., 2008 |
| Thistle, P., Spitzer, R. F., Glazier, R. H., Pilon, R., Arbess, G., Simor, A., Boyle, E., Chitsike, I., Chipato, T., Gottesman, M. and Silverman, M. A randomized, double-blind, placebo-controlled trial of combined nevirapine and zidovudine compared with nevirapine alone in the prevention of perinatal transmission of HIV in Zimbabwe. Clin Infect Dis. 2007; 44 (1): 111-9. | Included in SR Chigwedere et al., 2008 |
| Urbani, G., de Vries, M. M., Cronje, H. S., Niemand, I., Bam, R. H. and Beyer, E. Complications associated with cesarean section in HIV-infected patients. Int J Gynaecol Obstet. 2001; 74 (1): 9-15. | No treatment comparison group |
| Venkatesh, K. K., Morrison, L., Livingston, E. G., Stek, A., Read, J. S., Shapiro, D. E. and Tuomala, R. E. Changing Patterns and Factors Associated With Mode of Delivery Among Pregnant Women With Human Immunodeficiency Virus Infection in the United States. Obstet Gynecol. 2018; 131 (5): 879-890. | Not reporting the required outcomes |
| Zunza, M., Esser, M., Slogrove, A., Bettinger, J. A., Machekano, R. and Cotton, M. F. Early Breastfeeding Cessation Among HIV-Infected and HIV-Uninfected Women in Western Cape Province, South Africa. AIDS Behav. 2018; 22 (Suppl 1): 114-120. | Focus on feeding practices, not risk of transmission |

# Human Papilloma virus

## WHAT ARE THE RISKS OF HUMAN PAPILLOMA VIRUS TRANSMISSION THROUGH VAGINAL/ANAL INTERCOURSE?

### Flowchart

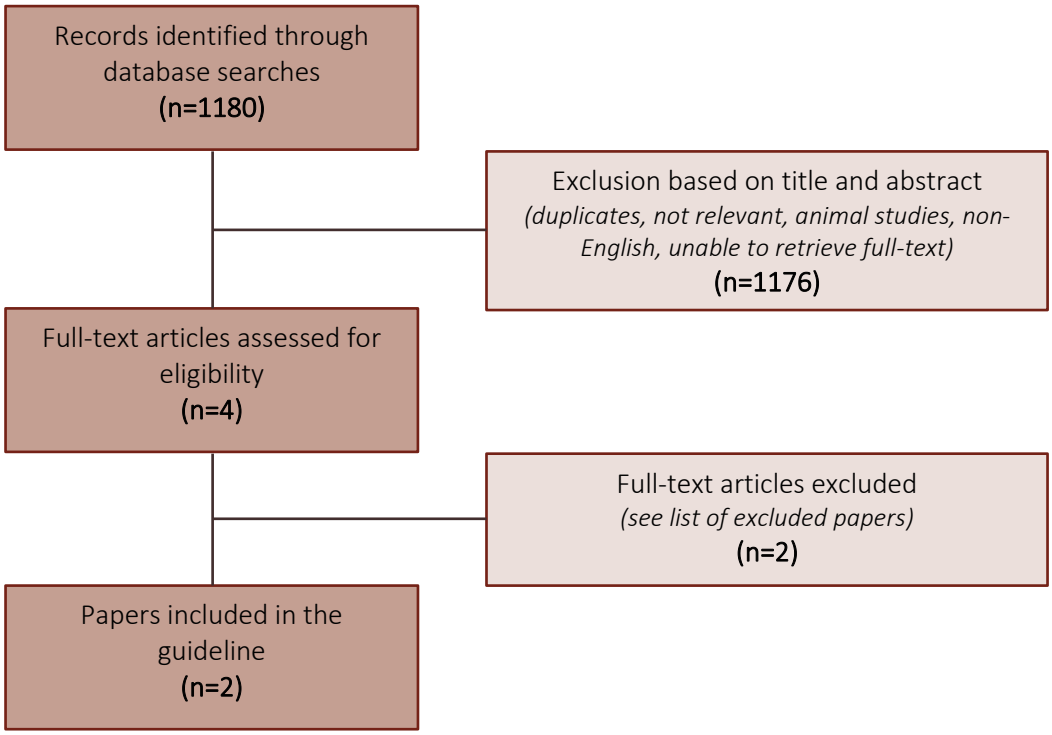



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Farsi, N. J., El-Zein, M., Gaied, H., Lee, Y. C., Hashibe, M., Nicolau, B. and Rousseau, M. C. Sexual behaviours and head and neck cancer: A systematic review and meta-analysis. Cancer Epidemiol. 2015; 39 (6): 1036-46. | Focus on the outcome of head and neck cancer |
| Kyo, S., Inoue, M., Koyama, M., Fujita, M., Tanizawa, O. and Hakura, A. Detection of high-risk human papillomavirus in the cervix and semen of sex partners. J Infect Dis. 1994; 170 (3): 682-5. | Old data |
| Martín-Ezquerra, G., Fuste, P., Larrazabal, F., Lloveras, B., Fernandez-Casado, A., Belosillo, B., Mancebo, G., Masferrer, E., Segura, S., Carreras, R., Alameda, F. and Pujol, R. M. Incidence of human papillomavirus infection in male sexual partners of women diagnosed with CIN II-III. Eur J Dermatol. 2012; 22 (2): 200-4. | Coinfections with other STDs |

## IS THERE A THRESHOLD BELOW WHICH TRANSMISSION OF HUMAN PAPILLOMA VIRUS IS UNLIKELY?

### Flowchart

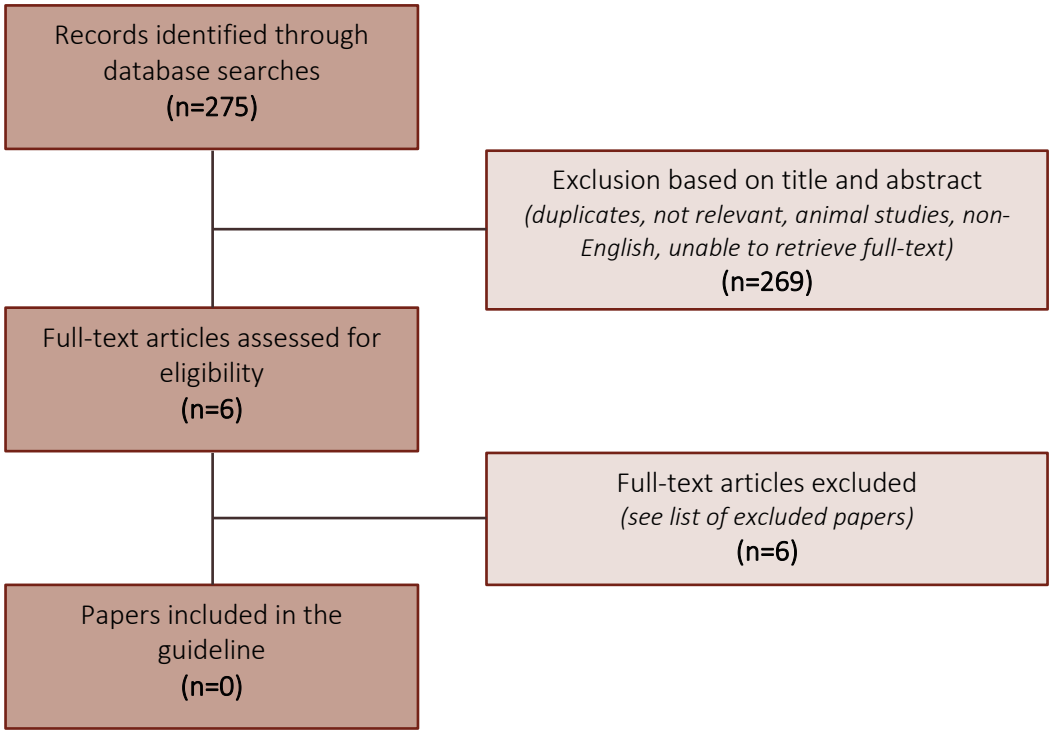



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Guevara, A. M., Suarez, E., Victoria, A., Ngan, H. Y. S., Hirschberg, A. L., Fedrizzi, E., Bautista, O., Shields, C., Joshi, A. and Luxembourg, A. Maternal transfer of anti HPV 6 and 11 antibodies upon immunization with the 9-valent HPV vaccine. Human vaccines and immunotherapeutics. 2019; 15 (1): 141-145. | Antibody titers not viral threshold |
| Wissing, M. D., Louvanto, K., Comète, E., Burchell, A. N., El-Zein, M., Rodrigues, A., Tellier, P. P., Coutlée, F. and Franco, E. L. Human Papillomavirus Viral Load and Transmission in Young, Recently Formed Heterosexual Couples. J Infect Dis. 2019; 220 (7): 1152-1161. | No threshold for transmission specified |

## WHICH TECHNIQUE FOR MEDICALLY ASSISTED REPRODUCTION SHOULD BE USED IN COUPLES WITH HUMAN PAPILLOMA VIRUS?

### Flowchart

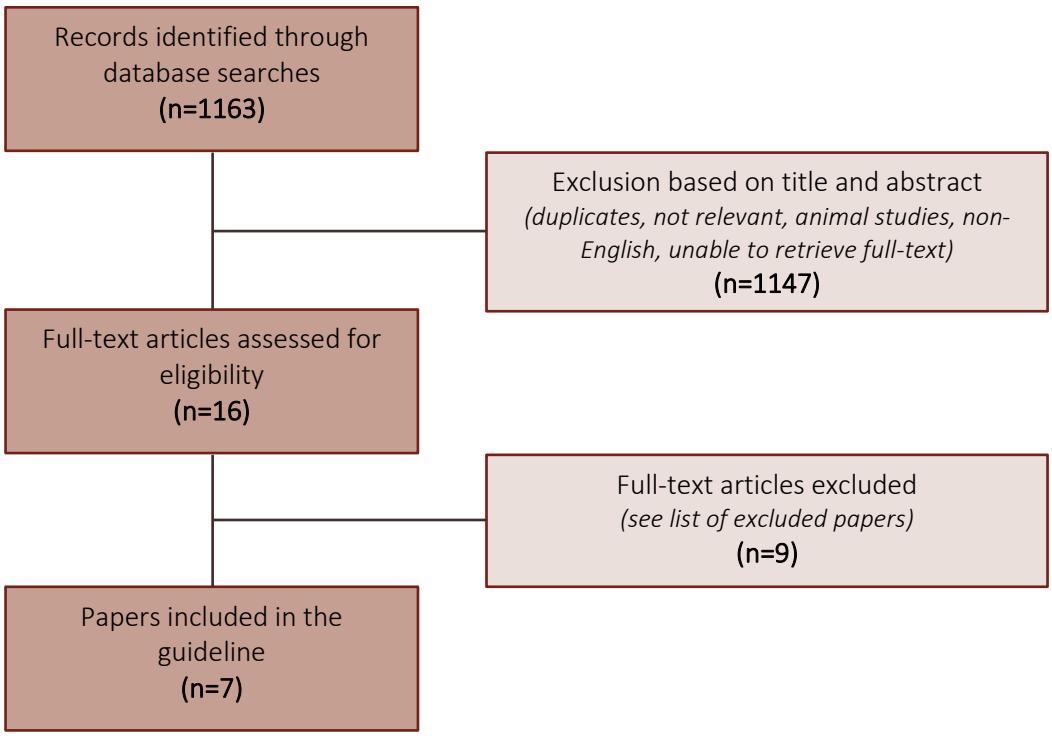



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Depuydt CE, Donders GGG, Verstraete L, Vanden Broeck D, Beert JFA, Salembier G, Bosmans E, Ombelet W. Fertil Steril 2019; 111(6):1135-1144 | No treatment comparison group |
| Depuydt CE, Verstraete L, Berth M, Beert J, Bogers JP, Salembier G, Vereecken AJ, Bosmans E. Gynecol Obstet Invest. 2016;81(1):41-6. | No treatment comparison group |
| Depuydt CE, Donders GGG, Verstraete L, Vanden Broeck D, Beert JFA, Salembier G, Bosmans E, Dhont N., Van Der Auwera I., Vandenborne K., Ombelet W. Facts Views Vis Obgyn. 2018 Dec;10(4):201-205. | No treatment comparison group |
| Garolla A, Engl B, Pizzol D, Ghezzi M, Bertoldo A, Bottacin A, Noventa M, Foresta C. FertilSteril. 2016 Jan;105(1):65-72.e1. (26453270) | Results for IUI and ICSI not analysed separately |
| Perino A., Giovannelli L., Schillaci R., Ruvolo G., Paolo Fiorentino F., Alimondi P., Cefalù E., Ammatuna P. Human papillomavirus infection in couples undergoing in vitro fertilization procedures: impact on reproductive outcomes. FertilSteril 2011;95:1845–8 | Results for IVF and ICSI not analysed separately |
| Spandorfer SD, Bongiovanni AM, Fasioulotis S, Rosenwaks Z, Ledger WJ, Witkin SS. Prevalence of human papilloma virus in women undergoing invitro fertilization and association with outcome. Fertility and Sterility, 16 Jun 2006, 86(3):765-767 | No treatment comparison group |

## CAN HUMAN PAPILLOMA VIRUS DNA BE DETECTED IN OOCYTES/ SPERM/ PLACENTA?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Bober, L., Guzowski, G., Moczulska, H. and Sieroszewski, P. Influence of human Papilloma Virus (hPV) infection on early pregnancy. Ginekol Pol. 2019; 90 (2): 72-75. | Biased study population |
| Hermonat, P. L., Kechelava, S., Lowery, C. L. and Korourian, S. Trophoblasts are the preferential target for human papilloma virus infection in spontaneously aborted products of conception. Hum Pathol. 1998; 29 (2): 170-4. | Biased study population |
| Kadze, R., Chan, P. J., Jacobson, J. D., Corselli, J. U. and King, A. Temperature variable and the efficiency of sperm mediated transfection of HPV16 DNA into cells. Asian J Androl. 2002; 4 (3): 169-73. | Spiking experiment |
| Perez-Andino, J., Buck, C. B. and Ribbeck, K. Adsorption of human papillomavirus 16 to live human sperm. PLoS One. 2009; 4 (6): e5847. | No clinical data |
| Reily-Bell, A. L., Fisher, A., Harrison, B., Bowie, S., Ray, S., Hawkes, M., Wise, L. M., Fukuzawa, R., Macaulay, E. C., Devenish, C. J., Hung, N. A. and Slatter, T. L. Human Papillomavirus E6/E7 Expression in Preeclampsia-Affected Placentae. Pathogens. 2020; 9 (3): | Biased study population |
| Ruffin, M. T. th, Bailey, J. M., Roulston, D., Lee, D. R., Tucker, R. A., Swan, D. C. and Unger, E. R. Human papillomavirus in amniotic fluid. BMC Pregnancy Childbirth. 2006; 6 28. | No placental samples were analysed |
| Slatter, T. L., Hung, N. G., Clow, W. M., Royds, J. A., Devenish, C. J. and Hung, N. A. A clinicopathological study of episomal papillomavirus infection of the human placenta and pregnancy complications. Mod Pathol. 2015; 28 (10): 1369-82. | No data on infertility<br>Cohort was biased towards complications |
| Trottier, H., Mayrand, M. H., Coutlee, F., Monnier, P., Laporte, L., Niyibizi, J., Carceller, A. M., Fraser, W. D., Brassard, P., Lacroix, J., Francoeur, D., Bedard, M. J., Girard, I. and Audibert, F. Human papillomavirus (HPV) perinatal transmission and risk of HPV persistence among children: Design, methods and preliminary results of the HERITAGE study. Papillomavirus Res. 2016; 2 145-152. | Incomplete data<br>Study design and preliminary data |

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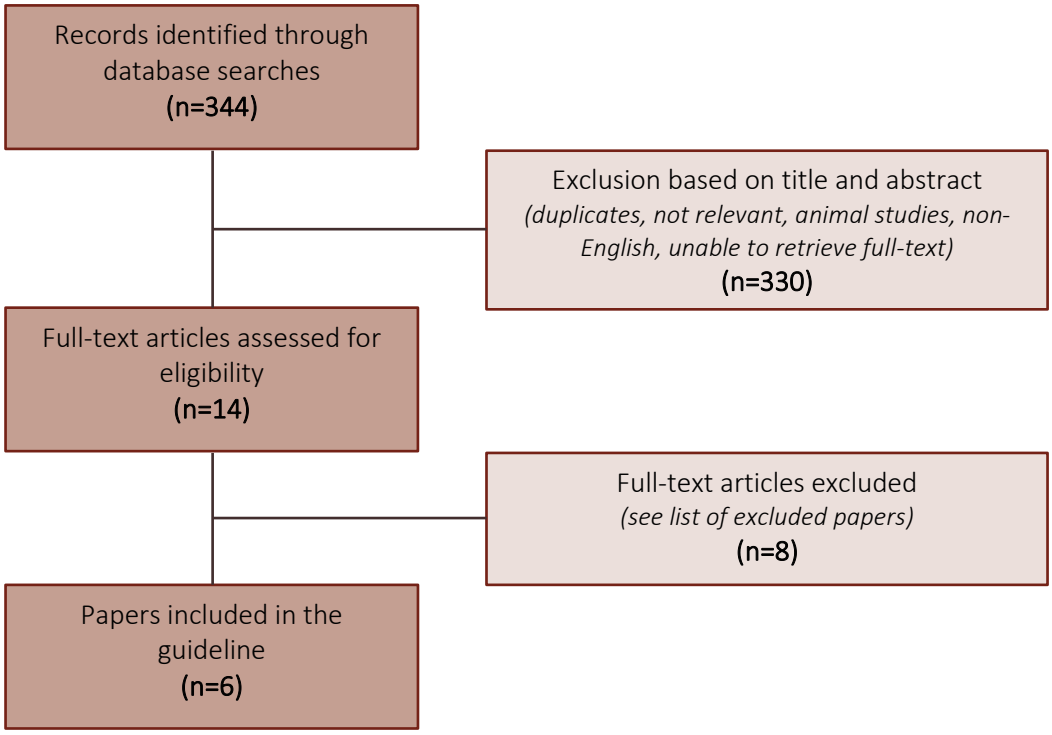
|---|---|
| Weyn, C., Thomas, D., Jani, J., Guizani, M., Donner, C., Van Rysselberge, M., Hans, C., Bossens, M., Englert, Y. and Fontaine, V. Evidence of human papillomavirus in the placenta. J Infect Dis. 2011; 203 (3): 341-3. | No data on vertical transmission |

## DOES HUMAN PAPILLOMA VIRUS IMPACT THE OUTCOME OF MEDICALLY ASSISTED REPRODUCTION?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Comar M., Monasta L., Zanotta N., Vecchi Brumatti L., Ricci G., Zauli G. Human papillomavirus infection is associated with decreased levels of GM-CSF in cervico-vaginal fluid of infected women. J Clin Virol 2013; 58(2): 479-81. | Small study size |
| Depuydt, C. E., Verstraete, L., Berth, M., Beert, J., Bogers, J. P., Salembier, G., Vereecken, A. J. and Bosmans, E. Human Papillomavirus Positivity in Women Undergoing Intrauterine Insemination Has a Negative Effect on Pregnancy Rates. Gynecol Obstet Invest. 2016; 81 (1): 41-6. | Included in SR Xiong et al., 2018 |
| Garolla A., Pizzol D., Bertoldo A., De Toni L., Barzon L., Foresta C. Association, prevalence, and clearance of human papillomavirus and antisperm antibodies in infected semen samples from infertile patients. Fertil Steril 2013; 99(1): 125-31. | Reports no pregnancy outcomes |
| Siristatidis, C., Vaidakis, D., Sertedaki, E. and Martins, W. P. Effect of human papilloma virus infection on in-vitro fertilization outcome: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018; 51 (1): 87-93.( 28608497) | Data on MAR techniques was analysed together |
| Souho, T., Benlemlih, M. and Bennani, B. Human papillomavirus infection and fertility alteration: a systematic review. PLoS One. 2015; 10 (5): e0126936. | The part on effect on IVF outcomes is narrative |
| Spandorfer SD, Bongiovanni AM, Fasioulotis S, Rosenwaks Z, Ledger WJ, Witkin SS Prevalence of human papilloma virus in women undergoing invitro fertilization and association with outcome. Fertility and Sterility, 16 Jun 2006, 86(3):765-767 | Included in SR Xiong et al., 2018 |
| Weinberg, M., Sar-Shalom Nahshon, C., Feferkorn, I. and Bornstein, J. Evaluation of human papilloma virus in semen as a risk factor for low sperm quality and poor in vitro fertilization outcomes: a systematic review and meta-analysis. FertilSteril. 2020; 113 (5): 955-969.e4. | Systematic review without meta-analysis |

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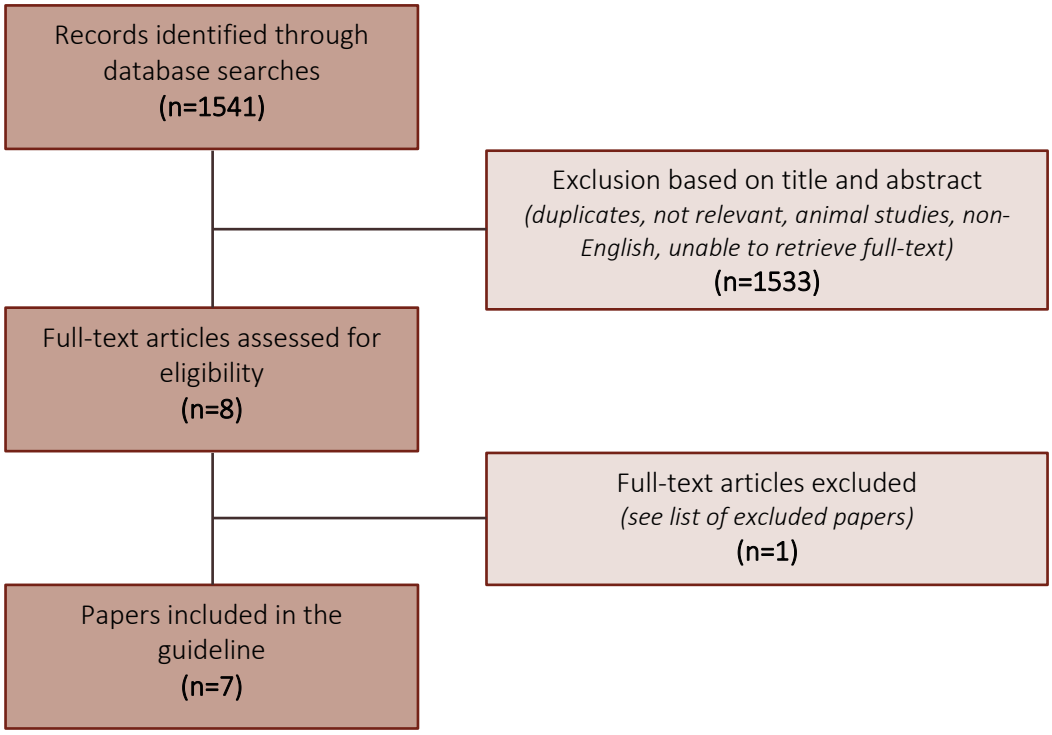
|---|---|
| Yang, R., Wang, Y., Qiao, J., Liu, P., Geng, L. and Guo, Y. L. Does human papillomavirus infection do harm to in-vitro fertilization outcomes and subsequent pregnancy outcomes? Chin Med J (Engl). 2013; 126 (4): 683-7. | Included in SR Xiong et al., 2018 |

## WHICH TECHNIQUES CAN BE USED TO PREVENT/REDUCE HUMAN PAPILLOMA VIRUS TRANSMISSION DURING MEDICALLY ASSISTED REPRODUCTION?

### Flowchart

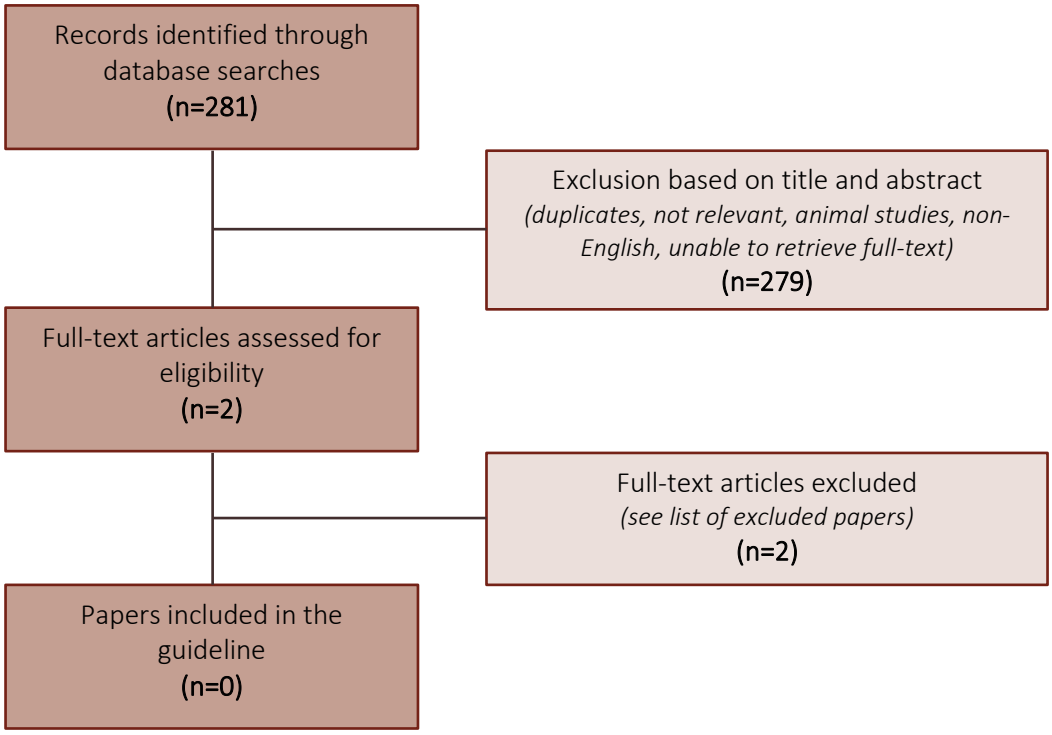



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Chan, P. J., Su, B. C., Kalugdan, T., Seraj, I. M., Tredway, D. R. and King, A. Human papillomavirus gene sequences in washed human sperm deoxyribonucleic acid. Fertil Steril. 1994; 61 (5): 982-5. | No semen processing was performed. |

## DOES THE PLASMATIC VIRAL LOAD CORRELATE WITH HUMAN PAPILLOMA VIRUS LOAD IN SEMEN?

### Flowchart

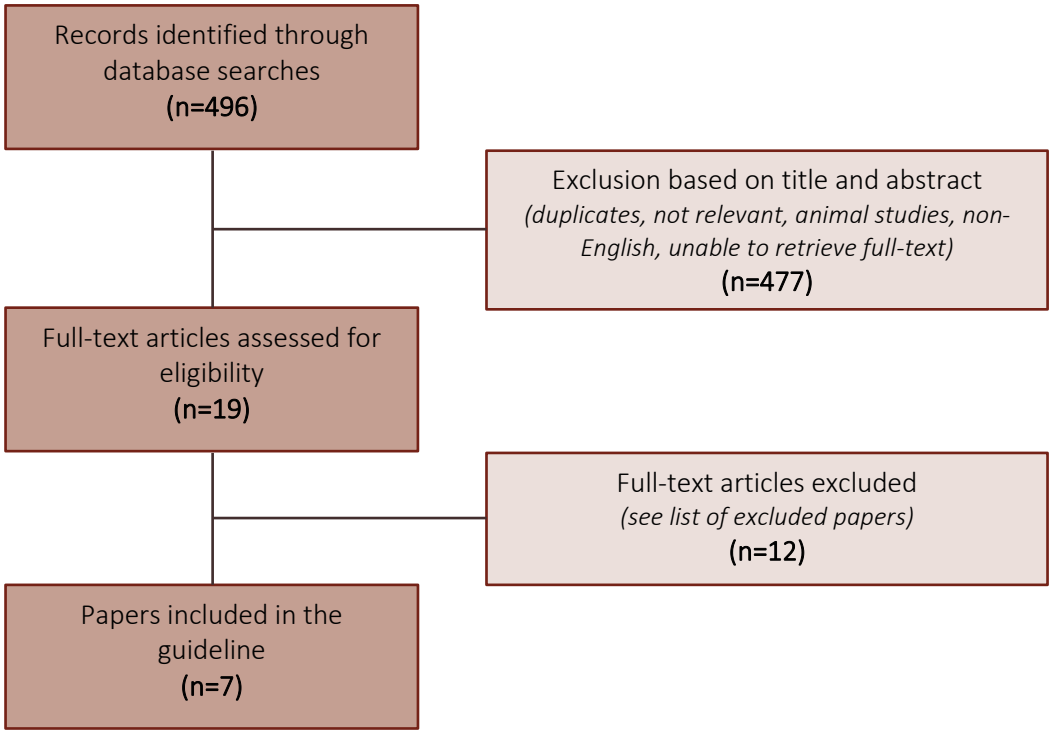



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Capra, G., Schillaci, R., Bosco, L., Roccheri, M. C., Perino, A. and Ragusa, M. A. HPV infection in semen: results from a new molecular approach. Epidemiol Infect. 2019; 147 e177. | This work did not analyse the viral DNA load in sera |
| Foresta, C., Bertoldo, A., Garolla, A., Pizzol, D., Mason, S., Lenzi, A. and De Toni, L. Human papillomavirus proteins are found in peripheral blood and semen Cd20+ and Cd56+ cells during HPV-16 semen infection. BMC Infect Dis. 2013; 13 593. | HPV load was not determined in either serum or semen |

## WHICH INTERVENTIONS CAN BE USED TO REDUCE/AVOID VERTICAL TRANSMISSION OF HUMAN PAPILLOMA VIRUS TO THE NEW-BORN?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Bandyopadhyay, S., Sen, S., Majumdar, L. and Chatterjee, R. Human papillomavirus infection among Indian mothers and their infants. Asian Pac J Cancer Prev. 2003; 4 (3): 179-84. | Included in SR Chatzistamatiou et al., 2016 |
| Favre, M., Majewski, S., De Jesus, N., Malejczyk, M., Orth, G. and Jablonska, S. A possible vertical transmission of human papillomavirus genotypes associated with epidermodysplasia verruciformis. J Invest Dermatol. 1998; 111 (2): 333-6. | Case report in the presence of higher quality evidence |
| Hahn, H. S., Kee, M. K., Kim, H. J., Kim, M. Y., Kang, Y. S., Park, J. S. and Kim, T. J. Distribution of maternal and infant human papillomavirus: risk factors associated with vertical transmission. Eur J ObstetGynecolReprod Biol. 2013; 169 (2): 202-6. | Included in SR Chatzistamatiou et al., 2016 |
| Kosko, J. R. and Derkay, C. S. Role of cesarean section in prevention of recurrent respiratory papillomatosis--is there one? Int J Pediatr Otorhinolaryngol. 1996; 35 (1): 31-8. | Old article, in the presence of higher quality evidence |
| Medeiros, L. R., Ethur, A. B., Hilgert, J. B., Zanini, R. R., Berwanger, O., Bozzetti, M. C. and Mylius, L. C. Vertical transmission of the human papillomavirus: a systematic quantitative review. Cad Saude Publica. 2005; 21 (4): 1006-15. (16021238) | Replaced by a more recent systematic review |
| Park, H., Lee, S. W., Lee, I. H., Ryu, H. M., Cho, A. R., Kang, Y. S., Hong, S. R., Kim, S. S., Seong, S. J., Shin, S. M. and Kim, T. J. Rate of vertical transmission of human papillomavirus from mothers to infants: relationship between infection rate and mode of delivery. Virol J. 2012; 9 80. | Included in SR Chatzistamatiou et al., 2016 |
| Puranen, M. H., Yliskoski, M. H., Saarikoski, S. V., Syrjanen, K. J. and Syrjanen, S. M. Exposure of an infant to cervical human papillomavirus infection of the mother is common. Am J Obstet Gynecol. 1997; 176 (5): 1039-45. | Included in SR Chatzistamatiou et al., 2016 |

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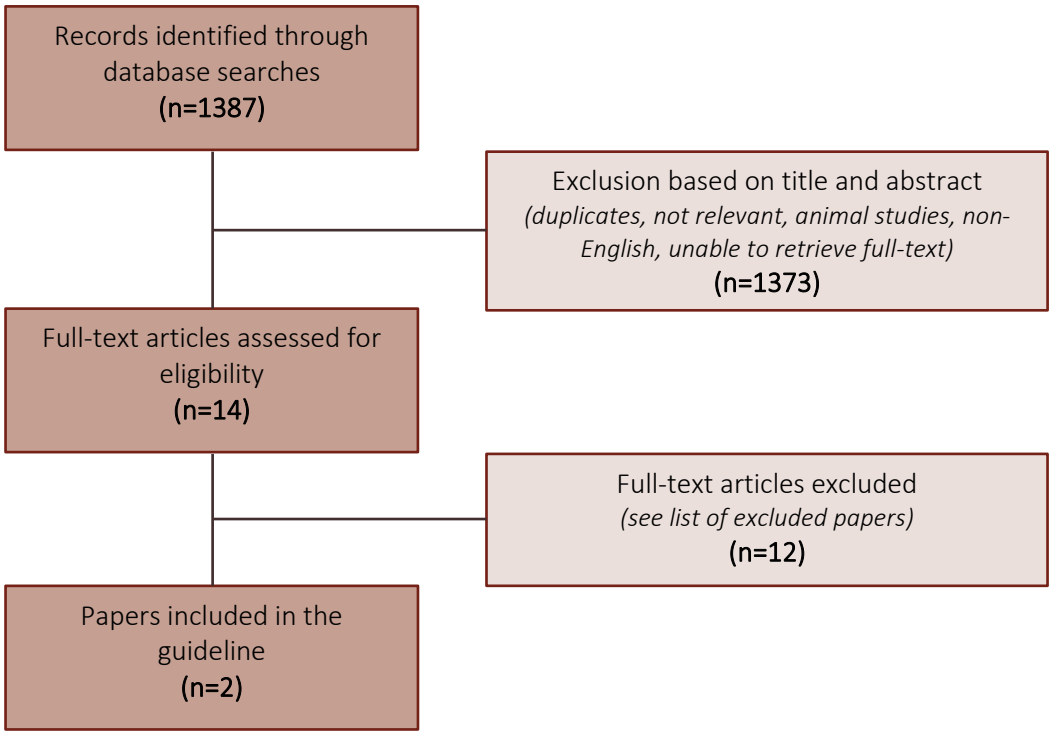
| Sarkola, M., Rintala, M., Grenman, S. and Syrjanen, S. Human papillomavirus DNA detected in breast milk. Pediatr Infect Dis J. 2008; 27 (6): 557-8. | No information on HPV infection in the offspring |
| Shah, K. V., Stern, W. F., Shah, F. K., Bishai, D. and Kashima, H. K. Risk factors for juvenile onset recurrent respiratory papillomatosis. Pediatr Infect Dis J. 1998; 17 (5): 372-6. | Higher quality evidence available |
| Tseng, C. J., Liang, C. C., Soong, Y. K. and Pao, C. C. Perinatal transmission of human papillomavirus in infants: Relationship between infection rate and mode of delivery. Obstetrics and Gynecology. 1998; 91 (1): 92-96. | Included in SR Chatzistamatiou et al., 2016 |
| Worda, C., Huber, A., Hudelist, G., Schatten, C., Leipold, H., Czerwenka, K. and Eppel, W. Prevalence of cervical and intrauterine human papillomavirus infection in the third trimester in asymptomatic women. J Soc Gynecol Investig. 2005; 12 (6): 440-4. | Included in SR Zouridis 2018 |
| Xu, S., Liu, L., Lu, S. and Ren, S. Clinical observation on vertical transmission of human papillomavirus. Chin Med Sci J. 1998; 13 (1): 29-31. | Not comparing vaginal with caesarean delivery |

# HTLV I/II

## WHAT ARE THE RISKS OF HTLV I/II TRANSMISSION THROUGH VAGINAL/ANAL INTERCOURSE?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Giuliani, M., Rezza, G., Lepri, A. C., Di Carlo, A., Maini, A., Crescimbeni, E., Palamara, G., Prignano, G. and Caprilli, F. Risk factors for HTLV-I and II in individuals attending a clinic for sexually transmitted diseases. Sexually Transmitted Diseases. 2000; 27 (2): 87-90. | Aim of study, population selection and methodology. No data on intercourse |
| Ho, G. Y., Nomura, A. M., Nelson, K., Lee, H., Polk, B. F. and Blattner, W. A. Declining seroprevalence and transmission of HTLV-I in Japanese families who immigrated to Hawaii. Am J Epidemiol. 1991; 134 (9): 981-7. | Aim of the study. No data on intercourse |
| Kaplan, J. E., Khabbaz, R. F., Murphy, E. L., Hermansen, S., Roberts, C., Lal, R., Heneine, W., Wright, D., Matijas, L., Thomson, R., Rudolph, D., Switzer, W. M., Kleinman, S., Busch, M. and Schreiber, G. B. Male-to-female transmission of human T-cell lymphotropic virus types I and II: association with viral load. The Retrovirus Epidemiology Donor Study Group. J Acquir Immune Defic Syndr Hum Retrovirol. 1996; 12 (2): 193-201. | Focus on viral load not risk of sexual transmission |
| Momita, S., Ikeda, S., Amagasaki, T., Soda, H., Yamada, Y., Kamihira, S., Tomonaga, M., Kinoshita, K. and Ichimaru, M. Survey of anti-human T-cell leukemia virus type I antibody in family members of patients with adult T-cell leukemia. Jpn J Cancer Res. 1990; 81 (9): 884-9. | Aim of the study. No data on intercourse |
| Murphy, E. L., Wilks, R., Hanchard, B., Cranston, B., Figueroa, J. P., Gibbs, W. N., Murphy, J. and Blattner, W. A. A case-control study of risk factors for seropositivity to human T-lymphotropic virus type I (HTLV-I) in Jamaica. Int J Epidemiol. 1996; 25 (5): 1083-9. | Aim of study, population selection and methodology. No data on intercourse |

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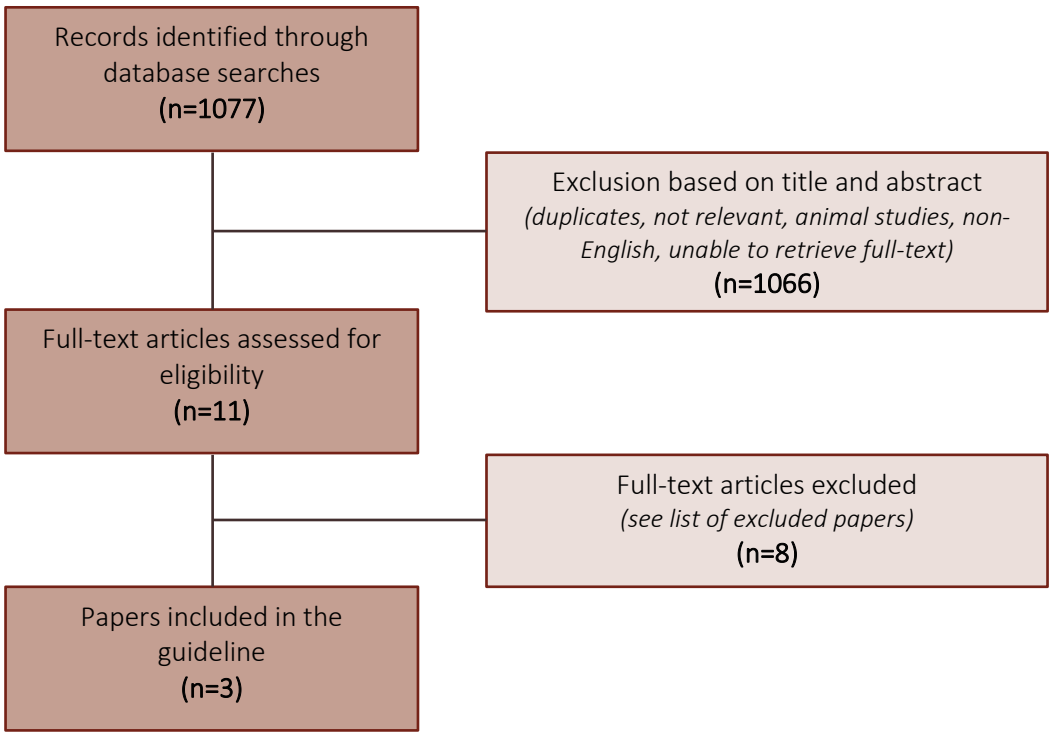
|---|---|
| Nunes, D., Boa-Sorte, N., Grassi, M. F., Taylor, G. P., Teixeira, M. G., Barreto, M. L., Dourado, I. and Galvão-Castro, B. HTLV-1 is predominantly sexually transmitted in Salvador, the city with the highest HTLV-1 prevalence in Brazil. PLoS One. 2017; 12 (2): e0171303. | Coinfection in study population |
| Paiva, A., Smid, J., Haziot, M. E. J., Assone, T., Pinheiro, S., Fonseca, L. A. M., de Oliveira, A. C. P. and Casseb, J. High risk of heterosexual transmission of human T-cell lymphotropic virus type 1 infection in Brazil. J Med Virol. 2017; 89 (7): 1287-1294. | Coinfection in study population |
| Sullivan, M. T., Williams, A. E., Fang, C. T., Notari, E. P., Poiesz, B. J. and Ehrlich, G. D. Human T-lymphotropic virus (HTLV) types I and II infection in sexual contacts and family members of blood donors who are seropositive for HTLV type I or II. American Red Cross HTLV-I/II Collaborative Study Group. Transfusion. 1993; 33 (7): 585-90. | Same study population as Roucoux et al., 2005 |
| Take, H., Umemoto, M., Kusuhara, K. and Kuraya, K. Transmission routes of HTLV-I: an analysis of 66 families. Jpn J Cancer Res. 1993; 84 (12): 1265-7. | Aim of the study. No data on intercourse |
| van Doornum, G. J., Hooykaas, C., Huisman, J. G., van der Linden, M. M. and Coutinho, R. A. Prevalence of human T-cell leukemia virus antibody among heterosexuals living in Amsterdam, The Netherlands. J Med Virol. 1990; 32 (3): 183-8. | Aim of study and selection study population |
| Vitek, C. R., Gracia, F. I., Giusti, R., Fukuda, K., Green, D. B., Castillo, L. C., Armien, B., Khabbaz, R. F., Levine, P. H., Kaplan, J. E. and et al. Evidence for sexual and mother-to-child transmission of human T lymphotropic virus type II among Guaymi Indians, Panama. J Infect Dis. 1995; 171 (4): 1022-6. | Aim of the study. No data on intercourse |
| Wignall, F. S., Hyams, K. C., Phillips, I. A., Escamilla, J., Tejada, A., Li, O., Lopez, F., Chauca, G., Sanchez, S. and Roberts, C. R. Sexual transmission of human T-lymphotropic virus type I in Peruvian prostitutes. J Med Virol. 1992; 38 (1): 44-8. | Aim of the study. No data on intercourse |

## IS THERE A THRESHOLD BELOW WHICH TRANSMISSION OF HTLV I/II IS UNLIKELY?

### Flowchart



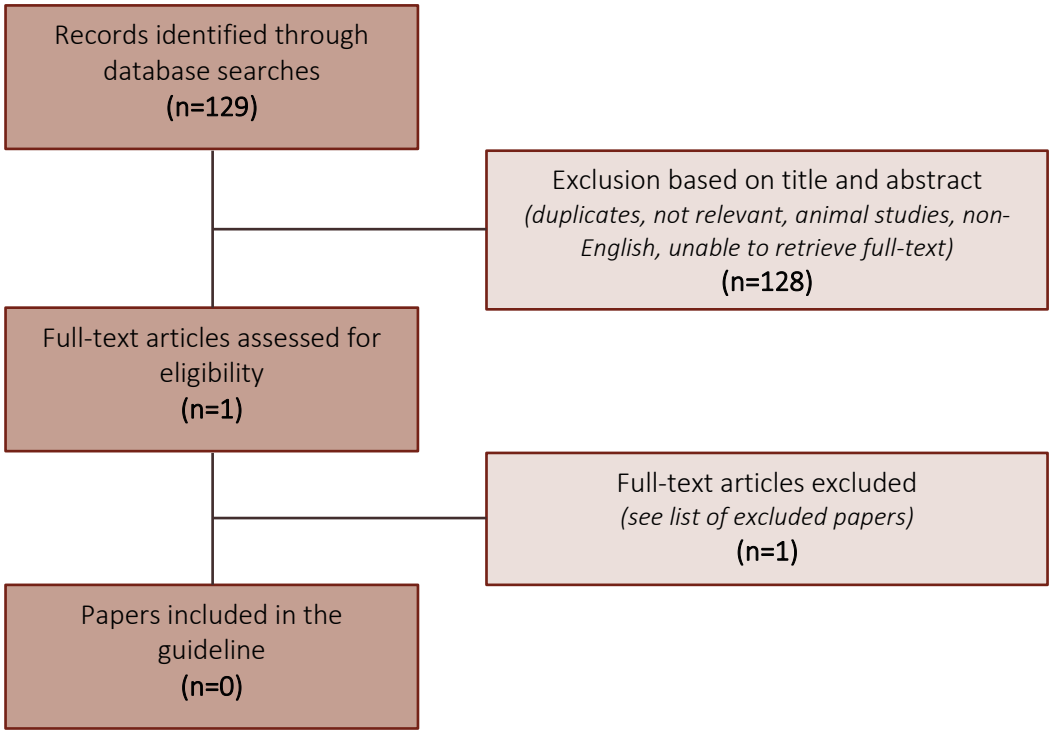

### List of excluded papers

| | Exclusion criterion |
|---|---|
| Caterino-de-Araujo, A. and de los Santos-Fortuna, E. No evidence of vertical transmission of HTLV-I and HTLV-II in children at high risk for HIV-1 infection from Sao Paulo, Brazil. J Trop Pediatr. 1999; 45 (1): 42-7. | No threshold determined |
| Hino, S., Doi, H., Yoshikuni, H., Sugiyama, H., Ishimaru, T., Yamabe, T., Tsuji, Y. and Miyamoto, T. HTLV-I carrier mothers with high-titer antibody are at high risk as a source of infection. Jpn J Cancer Res. 1987; 78 (11): 1156-8. | Testing was not available at the time to determine viral load. |
| Hisada, M., Maloney, E. M., Sawada, T., Miley, W. J., Palmer, P., Hanchard, B., Goedert, J. J. and Manns, A. Virus markers associated with vertical transmission of human T lymphotropic virus type 1 Jamaica. Clin Infect Dis. 2002; 34 (12): 1551-7. | Viral load determined at delivery |
| Ho, G. Y., Nomura, A. M., Nelson, K., Lee, H., Polk, B. F. and Blattner, W. A. Declining seroprevalence and transmission of HTLV-I in Japanese families who immigrated to Hawaii. Am J Epidemiol. 1991; 134 (9): 981-7. | No threshold determined |
| Rosadas, C., Tosswill, J. H., Tedder, R. and Taylor, G. P. Pregnancy does not adversely impact diagnostic tests for HTLV-1/2 infection. PLoS Negl Trop Dis. 2019; 13 (9): e0007736 | No data of transmission to the fetus |
| Saji, F., Tokugawa, Y., Kamiura, S., Samejima, Y., Ohashi, K., Azuma, C. and Tanizawa, O. Vertical transmission of human T-cell leukemia virus type I (HTLV-I): detection of proviral DNA in HTLV-I carrier gravida. J Clin Immunol. 1989; 9 (5): 409-14. | No threshold determined |
| van Tienen, C., McConkey, S. J., de Silva, T. I., Cotten, M., Kaye, S., Sarge-Njie, R., da Costa, C., Goncalves, N., Parker, J., Vincent, T., Jaye, A., Aaby, P., Whittle, H. and Schim van der Loeff, M. Maternal proviral load and vertical transmission of human T cell lymphotropic virus type 1 in Guinea-Bissau. AIDS Res Hum Retroviruses. 2012; 28 (6): 584-90. | Viral load determined after birth |

| | |
|---|---|
| Wiktor, S. Z., Pate, E. J., Murphy, E. L., Palker, T. J., Champegnie, E., Ramlal, A., Cranston, B., Hanchard, B. and Blattner, W. A. Mother-to-child transmission of human T-cell lymphotropic virus type I (HTLV-I) in Jamaica: association with antibodies to envelope glycoprotein (gp46) epitopes. J Acquir Immune Defic Syndr. 1993; 6 (10): 1162-7. | Viral load determined during pregnancy |

## WHICH TECHNIQUE FOR MEDICALLY ASSISTED REPRODUCTION SHOULD BE USED IN COUPLES WITH HTLV I/II?

### Flowchart

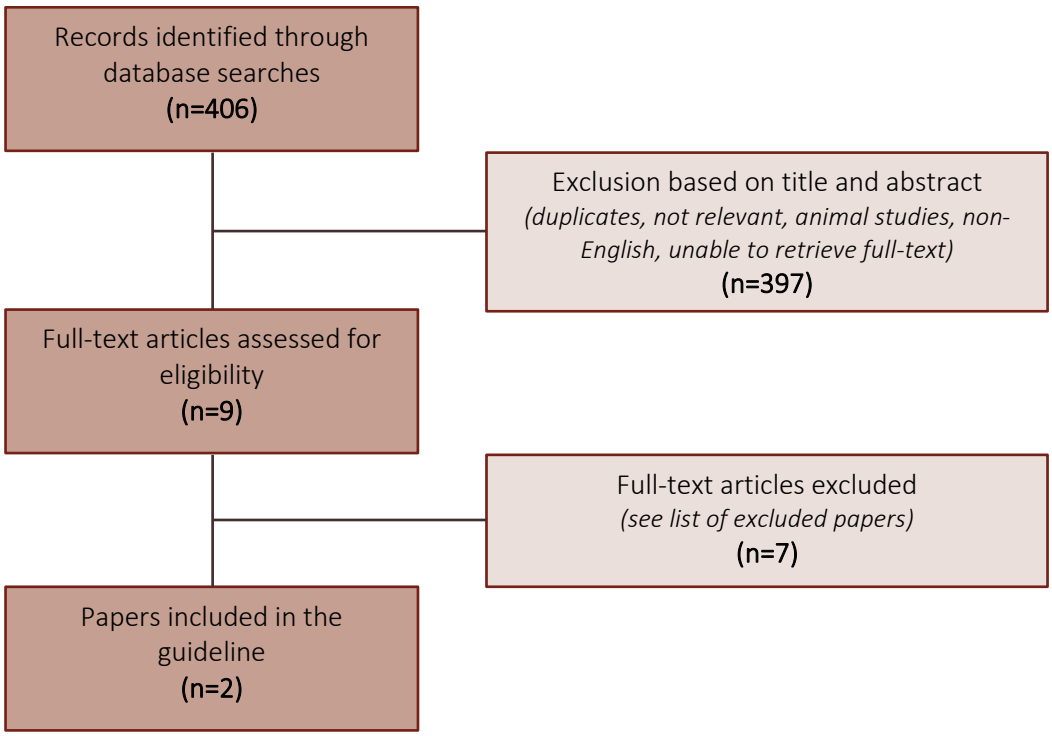



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Mansouri Torshizi, M., Khalighi, A. R., Fadavi Islam, M., Aram, R., Sabouri, E., Khalilifar, H. and Roustaee, H. Iran J Reprod Med. 2014; 12 (1): 15-8. | No treatment comparison group |

## CAN HTLV I/II VIRUS DNA BE DETECTED IN OOCYTES/ SPERM/ PLACENTA?

### Flowchart

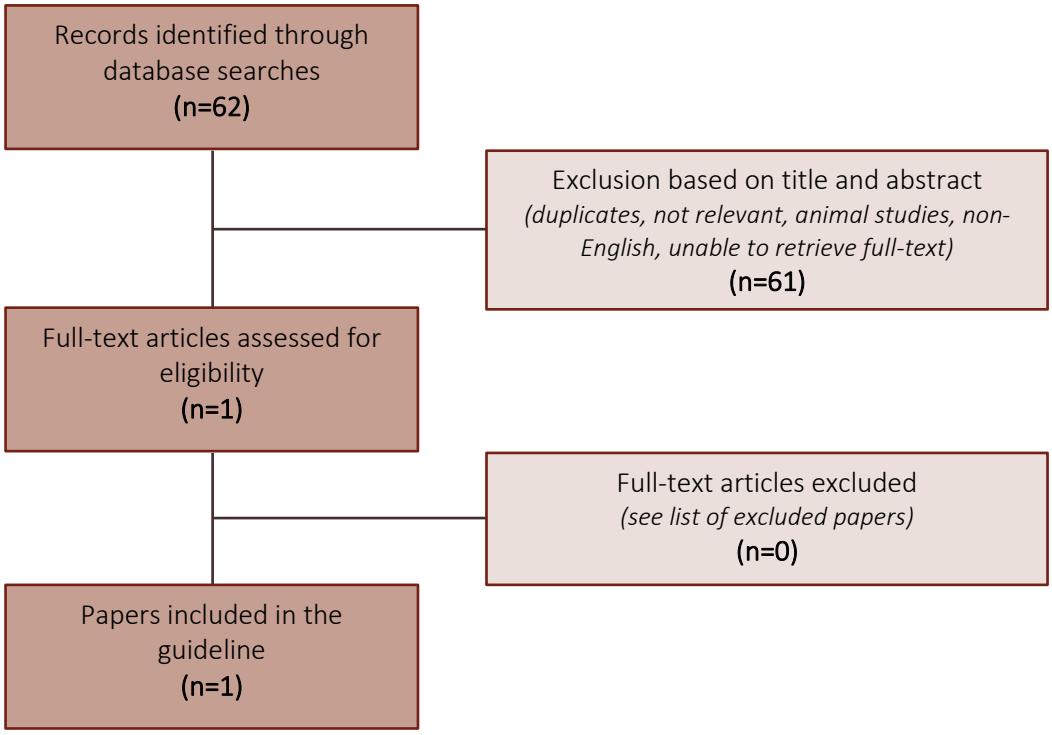



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Chironna, M., Quarto, M. and Barbuti, S. Lack of HTLV-II infection in newborns born from HIV-1 infected mothers in southern Italy. Eur J Epidemiol. 1997; 13 (1): 121-2. | HIV coinfection in study population |
| Fujino, T., Iwamoto, I., Otsuka, H., Ikeda, T., Takesako, S. and Nagata, Y. Apoptosis in placentas from human T-lymphotropic virus type I-seropositive pregnant women: a possible defense mechanism against transmission from mother to fetus. Obstet Gynecol. 1999; 94 (2): 279-83. | No placental tissue were tested |
| Katamine, S., Moriuchi, R., Yamamoto, T., Terada, K., Eguchi, K., Tsuji, Y., Yamabe, T., Miyamoto, T. and Hino, S. HTLV-I proviral DNA in umbilical cord blood of babies born to carrier mothers. Lancet. 1994; 343 (8909): 1326-7. | No placental tissue were tested |
| Moriuchi, M. and Moriuchi, H. Seminal fluid enhances replication of human T-cell leukemia virus type 1: implications for sexual transmission. J Virol. 2004; 78 (22): 12709-11. | Spiking experiment |
| Nyambi, P. N., Ville, Y., Louwagie, J., Bedjabaga, I., Glowaczower, E., Peeters, M., Kerouedan, D., Dazza, M., Larouze, B., van der Groen, G. and Delaporte, E. Mother-to-child transmission of human T-cell lymphotropic virus types I and II (HTLV-I/II) in Gabon: a prospective follow-up of 4 years. J Acquir Immune Defic Syndr Hum Retrovirol. 1996; 12 (2): 187-92. | No placental tissue were tested |
| Saji, F., Ohashi, K., Tokugawa, Y., Kamiura, S., Azuma, C. and Tanizawa, O. Perinatal infection of human T-lymphotropic virus type I, the etiologic virus of adult T-cell leukemia/lymphoma. DNA amplification of specific human T-lymphotropic virus type I sequences. Cancer. 1990; 66 (9): 1933-7. | No placental tissue were tested |
| Satow, Y., Hashido, M., Ishikawa, K., Honda, H., Mizuno, M., Kawana, T. and Hayami, M. Detection of HTLV-I antigen in peripheral and cord blood lymphocytes from carrier mothers. Lancet. 1991; 338 (8772): 915-6. | No placental tissue were tested |

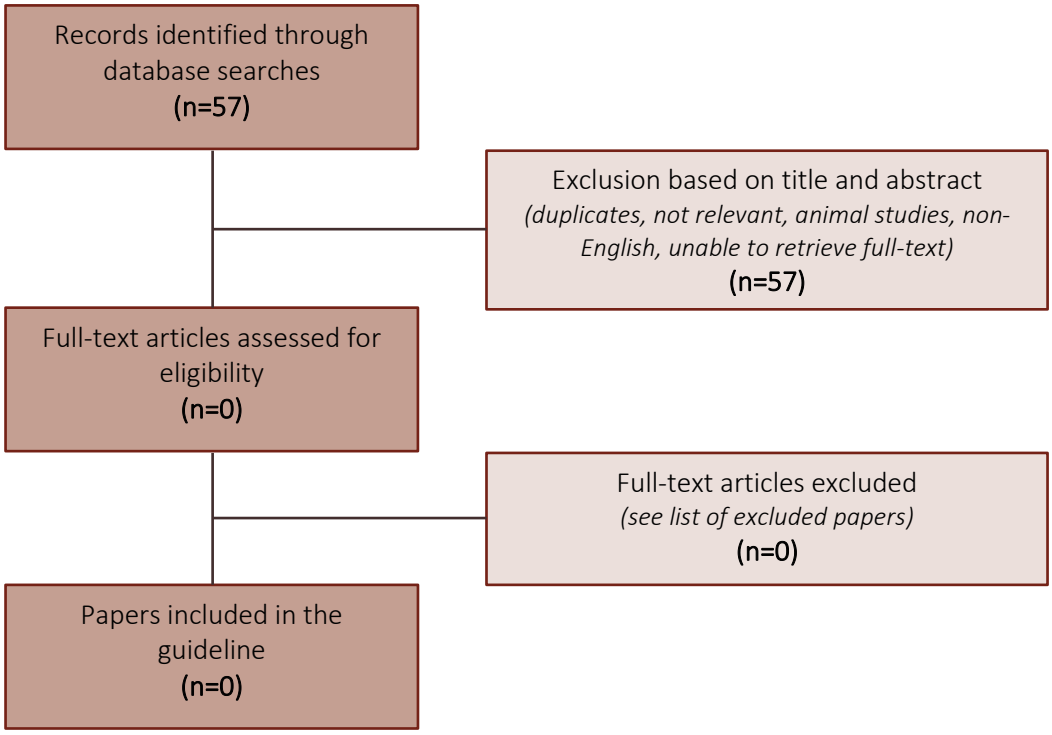
## DOES HTLV I/II /TREATMENT OF HTLV I/II BEFORE MEDICALLY ASSISTED REPRODUCTION IMPACT THE OUTCOME OF MEDICALLY ASSISTED REPRODUCTION?

Flowchart



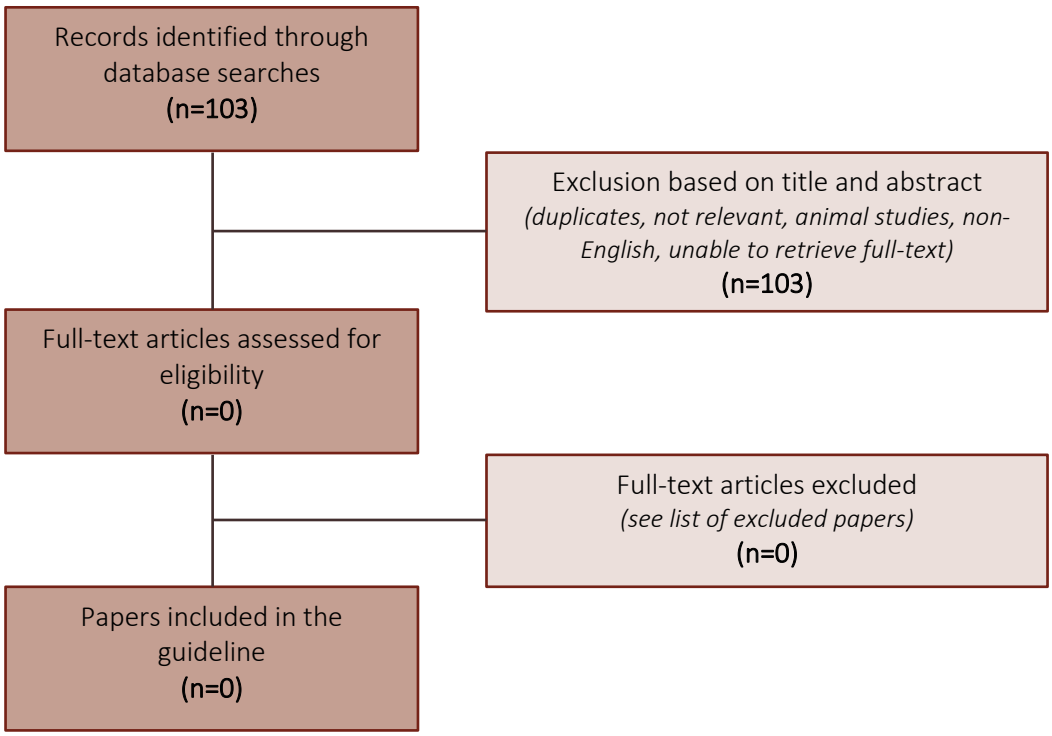
## WHICH TECHNIQUES CAN BE USED TO PREVENT/REDUCE HTLV I/II TRANSMISSION DURING MEDICALLY ASSISTED REPRODUCTION?

Flowchart



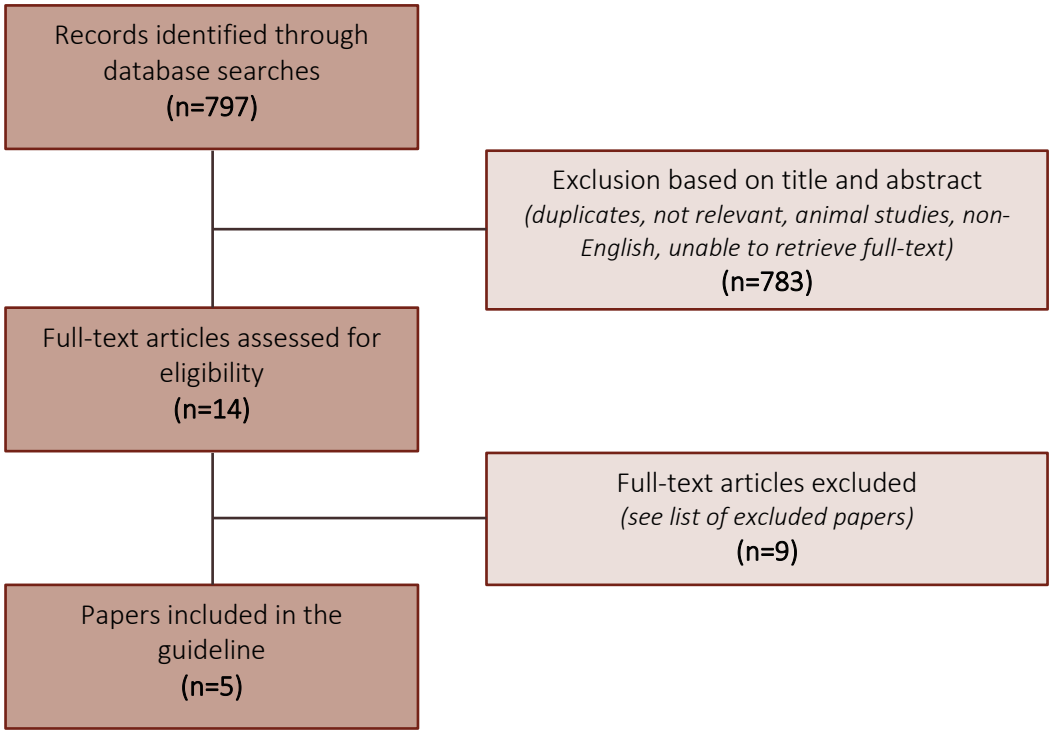
## DOES THE PLASMATIC VIRAL LOAD CORRELATE WITH HTLV I/II IN SEMEN?

Flowchart



## WHICH INTERVENTIONS CAN BE USED TO REDUCE/AVOID VERTICAL TRANSMISSION OF HTLV I/II TO THE NEW-BORN?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Ando, Y., Matsumoto, Y., Nakano, S., Saito, K., Kakimoto, K., Tanigawa, T., Ekuni, Y., Kawa, M. and Toyama, T. Long-term follow up study of vertical HTLV-I infection in children breast-fed by seropositive mothers. J Infect. 2003; 46 (3): 177-9 | No control group<br>No info on feeding |
| Ando, Y., Saito, K., Nakano, S., Kakimoto, K., Furuki, K., Tanigawa, T., Hashimoto, H., Moriyama, I., Ichijo, M. and Toyama, T. Bottle-feeding can prevent transmission of HTLV-I from mothers to their babies. J Infect. 1989; 19 (1): 25-9. | Included in SR Boostani et al., 2018 |
| Kashiwagi, K., Furusyo, N., Nakashima, H., Kubo, N., Kinukawa, N., Kashiwagi, S. and Hayashi, J. A decrease in mother-to-child transmission of human T lymphotropic virus type I (HTLV-I) in Okinawa, Japan. Am J Trop Med Hyg. 2004; 70 (2): 158-63. | Included in SR Boostani et al., 2018 |
| Kinoshita, K., Amagasaki, T., Hino, S., Doi, H., Yamanouchi, K., Ban, N., Momita, S., Ikeda, S., Kamihira, S., Ichimaru, M. and et al. Milk-borne transmission of HTLV-I from carrier mothers to their children. Jpn J Cancer Res. 1987; 78 (7): 674-80. | Very small number of patients |
| Oki, T., Yoshinaga, M., Otsuka, H., Miyata, K., Sonoda, S. and Nagata, Y. A sero-epidemiological study on mother-to-child transmission of HTLV-I in southern Kyushu, Japan. Asia Oceania J Obstet Gynaecol. 1992; 18 (4): 371-7. | Included in SR Boostani et al., 2018 |
| Ribeiro, M. A., Martins, M. L., Teixeira, C., Ladeira, R., Oliveira Mde, F., Januario, J. N., Proietti, F. A. and Carneiro-Proietti, A. B. Pediatr Infect Dis J. 2012; 31 (11): 1139-43. (22683674) | HTLV1/2 positive women stopped breast feeding |
| Takezaki, T., Tajima, K., Ito, M., Ito, S., Kinoshita, K., Tachibana, K. and Matsushita, Y. Short-term breast-feeding may reduce the risk of vertical transmission of HTLV-I. The Tsushima ATL Study Group. Leukemia. 1997; 11 Suppl 3 60-2. | Included in SR Boostani et al., 2018 |
| Takahashi, K., Takezaki, T., Oki, T., Kawakami, K., Yashiki, S., Fujiyoshi, T., Usuku, K., Mueller, N., Osame, M., Miyata, K. and et al. Inhibitory effect of maternal antibody on | Same study population as Oki et al., 1992 |

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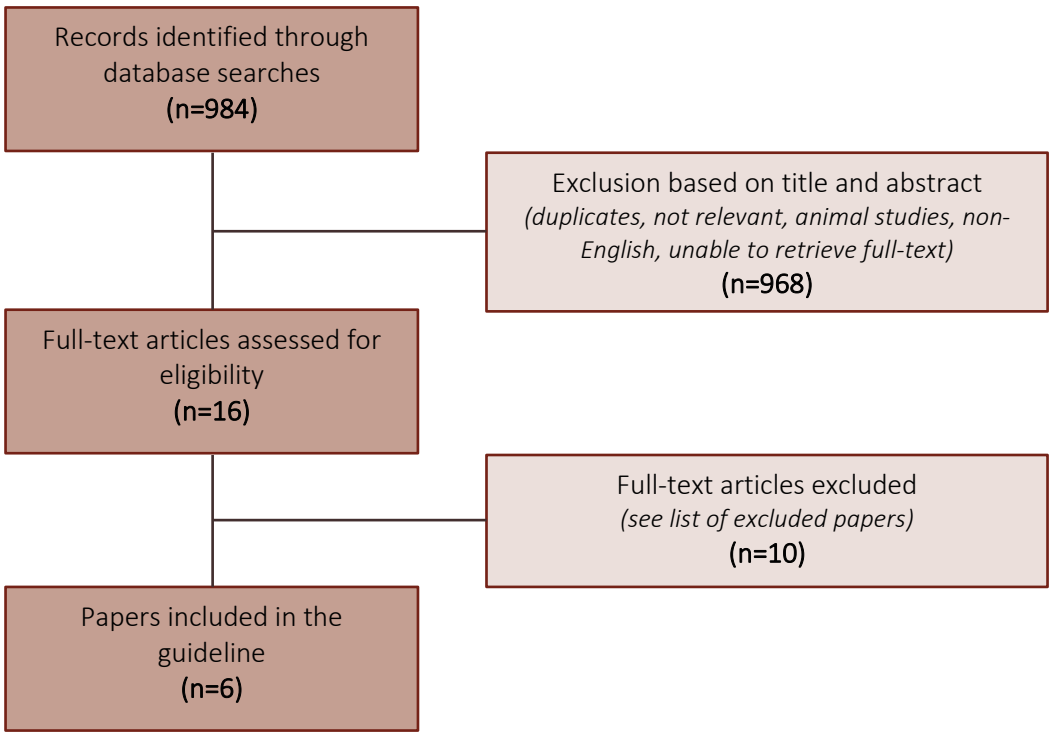
|---|---|
| mother-to-child transmission of human T-lymphotropic virus type I. The Mother-to-Child Transmission Study Group. Int J Cancer. 1991; 49 (5): 673-7. | |
| Van Dyke, R. B., Heneine, W., Perrin, M. E., Rudolph, D., Starszak, E., Woods, T., Switzer, W. M. and Kaplan, J. E. Mother-to-child transmission of human T-lymphotropic virus type II. J Pediatr. 1995; 127 (6): 924-8. | Very small number of patients |

# Zika virus

## WHAT ARE THE RISKS OF ZIKA VIRUS TRANSMISSION THROUGH VAGINAL/ANAL INTERCOURSE?

### Flowchart



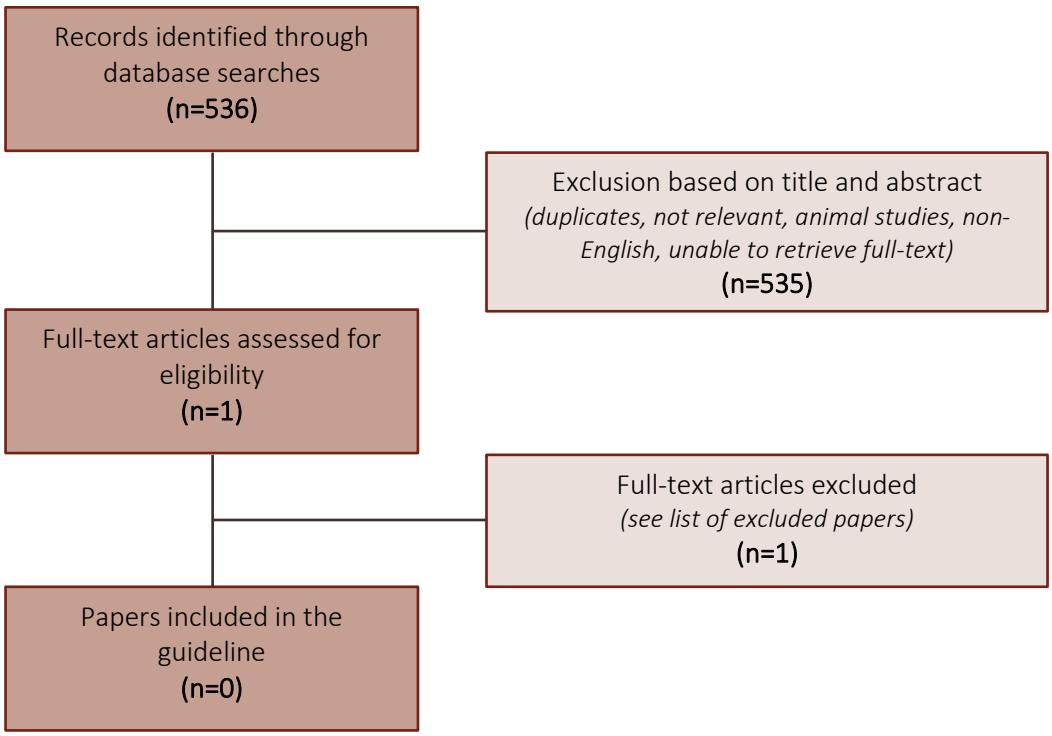

### List of excluded papers

| | Exclusion criterion |
|---|---|
| Brooks, R. B., Carlos, M. P., Myers, R. A., White, M. G., Bobo-Lenoci, T., Aplan, D., Blythe, D. and Feldman, K. A. Likely Sexual Transmission of Zika Virus from a Man with No Symptoms of Infection - Maryland, 2016. MMWR Morb Mortal Wkly Rep. 2016; 65 (34): 915-6. | Included in SR Counotte et al., 2018 |
| Deckard, D. T., Chung, W. M., Brooks, J. T., Smith, J. C., Woldai, S., Hennessey, M., Kwit, N. and Mead, P. Male-to-Male Sexual Transmission of Zika Virus--Texas, January 2016. MMWR Morb Mortal Wkly Rep. 2016; 65 (14): 372-4. | Included in SR Counotte et al., 2018 |
| D'Ortenzio, E., Matheron, S. and Yazdanpanah, Y. Evidence of sexual transmission of Zika Virus. New England Journal of Medicine. 2016; 374 (22): 2195-2198. | Included in SR Counotte et al., 2018 |
| Fréour, T., Mirallié, S., Hubert, B., Splingart, C., Barrière, P., Maquart, M. and Leparc-Goffart, I. Sexual transmission of Zika virus in an entirely asymptomatic couple returning from a Zika epidemic area, France, April 2016. Euro Surveill. 2016; 21 (23): | Included in SR Counotte et al., 2018 |
| Grossi, P. A., Percivalle, E., Campanini, G., Sarasini, A., Premoli, M., Zavattoni, M., Girello, A., Dalla Gasperina, D., Balsamo, M. L., Baldanti, F. and Rovida, F. An autochthonous sexually transmitted Zika virus infection in Italy 2016. New Microbiol. 2018; 41 (1): 80-82. | Included in SR Counotte et al., 2018 |
| Hills, S. L., Russell, K., Hennessey, M., Williams, C., Oster, A. M., Fischer, M. and Mead, P. Transmission of Zika Virus Through Sexual Contact with Travelers to Areas of Ongoing | Included in SR Counotte et al., 2018 |

| | |
|---|---|
| Transmission - Continental United States, 2016. MMWR Morb Mortal Wkly Rep. 2016; 65 (8): 215-6. | |
| Mansuy, J. M., Dutertre, M., Mengelle, C., Fourcade, C., Marchou, B., Delobel, P., Izopet, J. and Martin-Blondel, G. Zika virus: high infectious viral load in semen, a new sexually transmitted pathogen? Lancet Infect Dis. 2016; 16 (4): 405. | No sexual transmission |
| Moreira, J., Peixoto, T. M., Siqueira, A. M. and Lamas, C. C. Sexually acquired Zika virus: a systematic review. Clin Microbiol Infect. 2017; 23 (5): 296-305. | Replaced by a more recent systematic review |
| Russell, K., Hills, S. L., Oster, A. M., Porse, C. C., Danyluk, G., Cone, M., Brooks, R., Scotland, S., Schiffman, E., Fredette, C., White, J. L., Ellingson, K., Hubbard, A., Cohn, A., Fischer, M., Mead, P., Powers, A. M. and Brooks, J. T. Male-to-Female Sexual Transmission of Zika Virus-United States, January-April 2016. Clin Infect Dis. 2017; 64 (2): 211-213. | Included in SR Counotte et al., 2018 |
| Venturi, G., Zammarchi, L., Fortuna, C., Remoli, M. E., Benedetti, E., Fiorentini, C., Trotta, M., Rizzo, C., Mantella, A., Rezza, G. and Bartoloni, A. An autochthonous case of Zika due to possible sexual transmission, Florence, Italy, 2014. Euro Surveill. 2016; 21 (8): 30148. | Included in SR Counotte et al., 2018 |

## IS THERE A THRESHOLD BELOW WHICH TRANSMISSION OF ZIKA VIRUS IS UNLIKELY?

### Flowchart

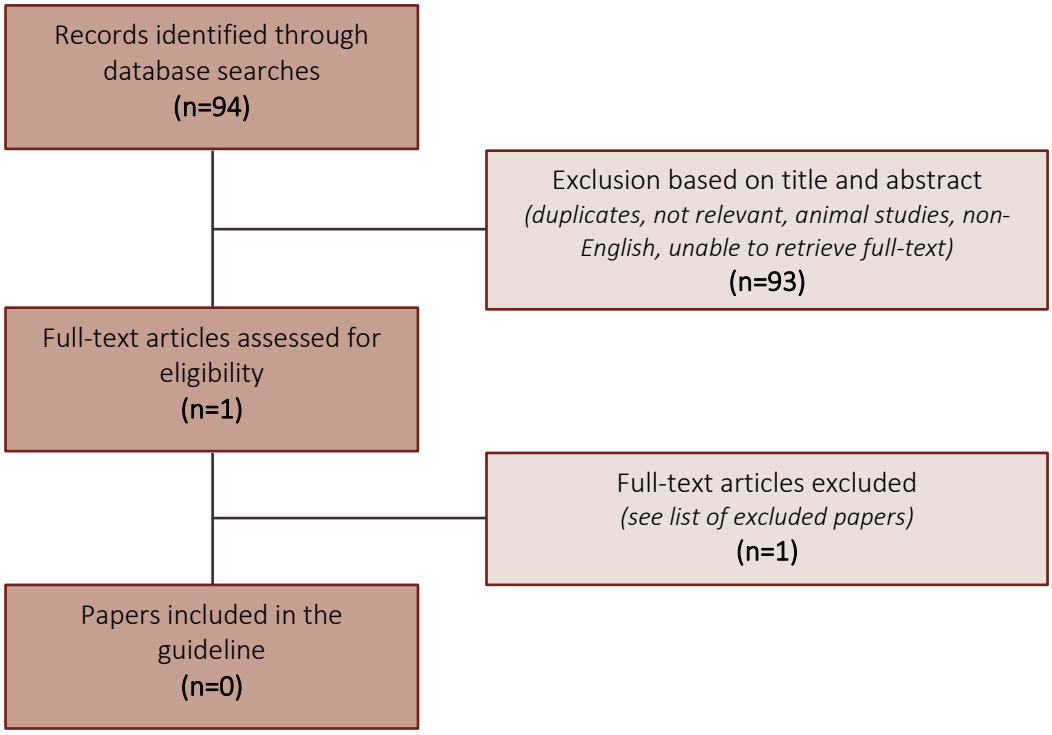



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Halai, U. A., Nielsen-Saines, K., Moreira, M. L., de Sequeira, P. C., Junior, J. P. P., de Araujo Zin, A., Cherry, J., Gabaglia, C. R., Gaw, S. L., Adachi, K., Tsui, I., Pilotto, J. H., Nogueira, R. R., de Filippis, A. M. B. and Brasil, P. Maternal Zika Virus Disease Severity, Virus Load, Prior Dengue Antibodies, and Their Relationship to Birth Outcomes. Clin Infect Dis. 2017; 65 (6): 877-883. | Viral load determined during pregnancy |

## WHICH TECHNIQUE FOR MEDICALLY ASSISTED REPRODUCTION SHOULD BE USED IN COUPLES WITH ZIKA VIRUS INFECTION?

### Flowchart

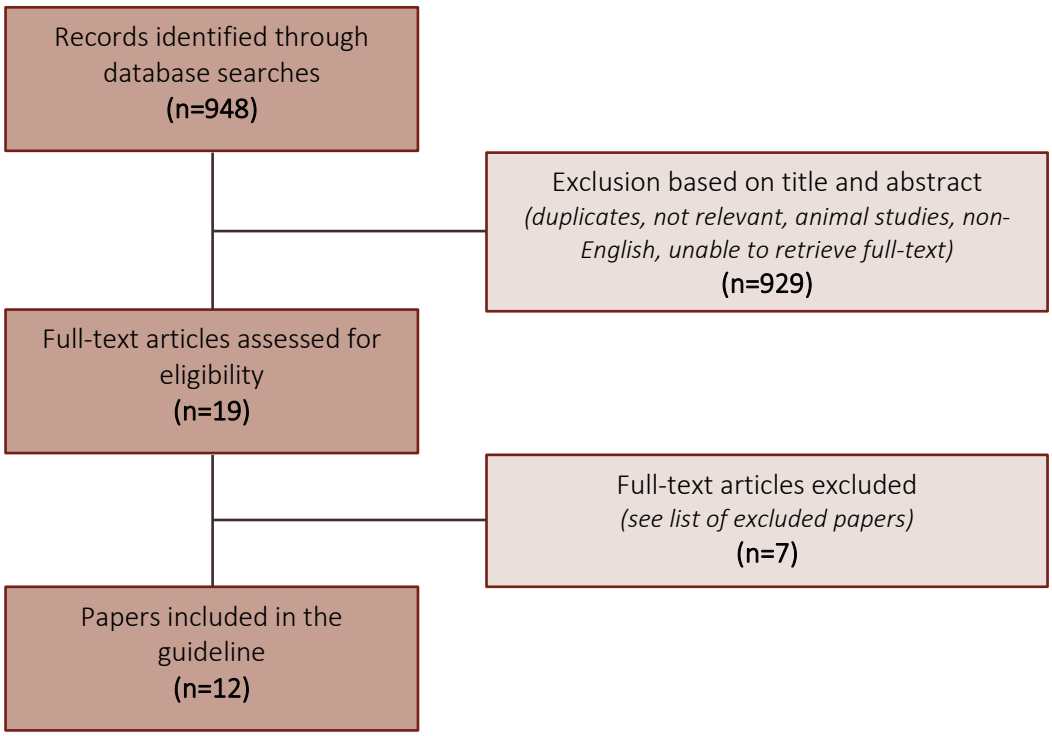



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Borges, E., Jr., Braga, Dpaf, Zanetti, B. F., Setti, A. S., Provenza, R. R. and Iaconelli, A., Jr. Zika Virus Outbreak - Should assisted reproduction patients avoid pregnancy? JBRA Assist Reprod. 2017; 21 (3): 208-211. | No patients had active disease at the time of treatment |

## CAN ZIKA VIRUS RNA BE DETECTED IN OOCYTES/ SPERM/ PLACENTA?

### Flowchart



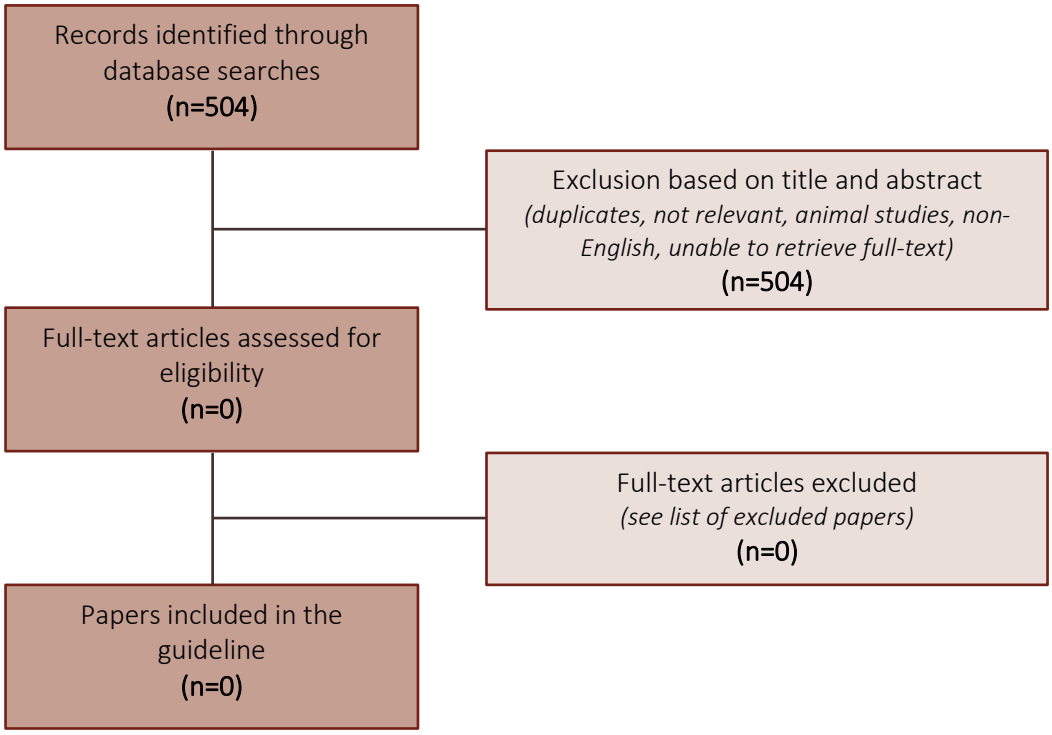

### List of excluded papers

| | Exclusion criterion |
|---|---|
| Benjamin, I., Fernandez, G., Figueira, J. V., Parpacen, L., Urbina, M. T. and Medina, R. Zika virus detected in amniotic fluid and umbilical cord blood in an in vitro fertilization-conceived pregnancy in Venezuela. Fertil Steril. 2017; 107 (6): 1319-1322. | No measurement of placental positivity, only amniotic fluid |
| Collier, A. Y., Borducchi, E. N., Chandrashekar, A., Moseley, E., Peter, L., Teodoro, N. S., Nkolola, J., Abbink, P. and Barouch, D. H. Sustained maternal antibody and cellular immune responses in pregnant women infected with Zika virus and mother to infant transfer of Zika-specific antibodies. Am J Reprod Immunol. 2020; e13288. | Significant risk of bias due to methodology |
| Medina, F. A., Torres, G., Acevedo, J., Fonseca, S., Casiano, L., De Leon-Rodriguez, C. M., Santiago, G. A., Doyle, K., Sharp, T. M., Alvarado, L. I., Paz-Bailey, G. and Munoz-Jordan, J. L. Duration of the Presence of Infectious Zika Virus in Semen and Serum. J Infect Dis. 2019; 219 (1): 31-40. | Not clear if spermatozoa or seminal plasma was tested. |
| Mercado, M., Ailes, E. C., Daza, M., Tong, V. T., Osorio, J., Valencia, D., Rico, A., Galang, R. R., González, M., Ricaldi, J. N., Anderson, K. N., Kamal, N., Thomas, J. D., Villanueva, J., Burkel, V. K., Meaney-Delman, D., Gilboa, S. M., Honein, M. A., Jamieson, D. J. and Ospina, M. L. Zika virus detection in amniotic fluid and Zika-associated birth defects. Am J Obstet Gynecol. 2020; 222 (6): 610.e1-610.e13. | No measurement of placental positivity, only amniotic fluid |
| Oliveira, J. V., Carvalho, T. C. X., Giovanetti, M., de Jesus, J. G., Santos, C. S., Pessoa, L. B., Magalhães Filho, C. F. Q., Lima, J. G. S., Carvalho, D. A. X., Figueiredo, E. M., Biron, A. C., Dos Santos, D. C., Viana, P., Duarte, A. O., Pessoa, R., Souza, G. B., Calcagno, J. I., Lima, F. W. M., Alcantara, L. C. J. and de Siqueira, I. C. Neonatal surveillance for congenital Zika infection during the 2016 microcephaly outbreak in Salvador, Brazil: Zika virus detection in asymptomatic newborns. Int J Gynaecol Obstet. 2020; 148 Suppl 2 (Suppl 2): 9-14. | The comparison of this study makes it difficult to draw conclusions |
| Pereira, J. P., Maykin, M. M., Vasconcelos, Z., Avvad-Portari, E., Zin, A. A., Tsui, I., Brasil, P., Nielsen-Saines, K., Moreira, M. E. and Gaw, S. L. The Role of Amniocentesis in the | Focus on amniocentesis, only 3 cases had placental |

| | |
|---|---|
| Diagnosis of Congenital Zika Syndrome. Clinical Infectious Diseases. 2019; 69 (4): 713-716. | testing, results table not complete |
| Rabelo, K., Souza, L. J., Salomao, N. G., Oliveira, E. R. A., Sentinelli, L. P., Lacerda, M. S., Saraquino, P. B., Rosman, F. C., Basilio-de-Oliveira, R., Carvalho, J. J. and Paes, M. V. Placental inflammation and fetal injury in a rare Zika case associated with Guillain-Barre Syndrome and abortion. Frontiers in Microbiology. 2018; 9 (MAY): 1018. | Case report in the presence of higher quality evidence |

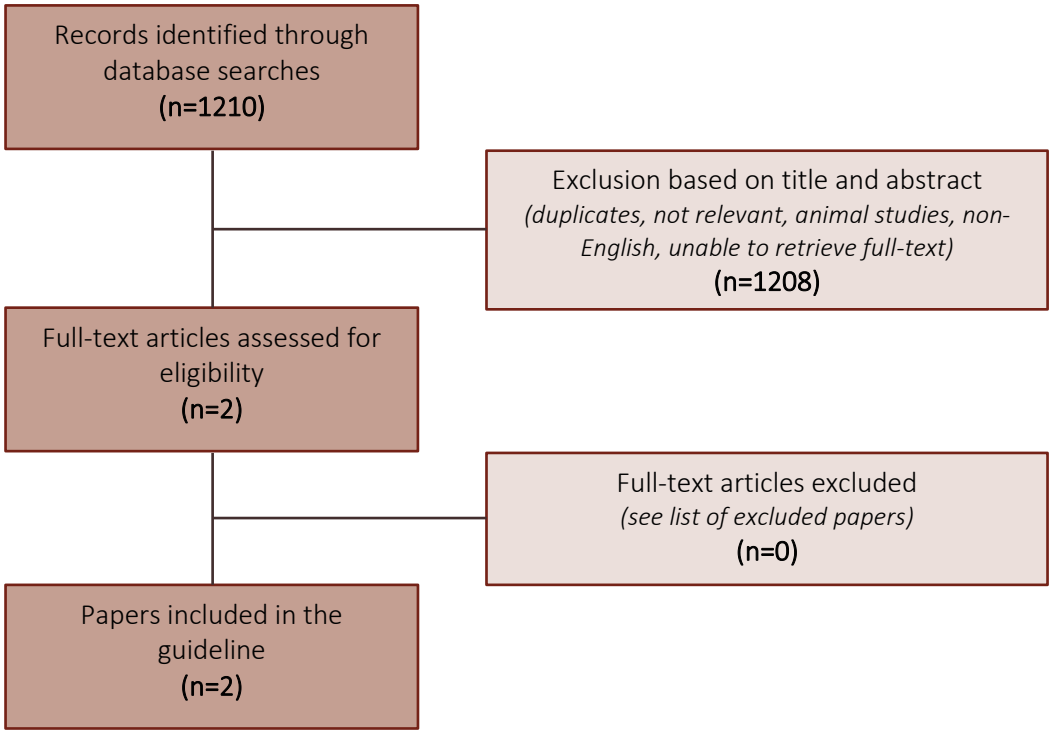
## DOES ZIKA VIRUS/TREATMENT OF ZIKA VIRUS BEFORE MEDICALLY ASSISTED REPRODUCTION IMPACT THE OUTCOME OF MEDICALLY ASSISTED REPRODUCTION?

Flowchart



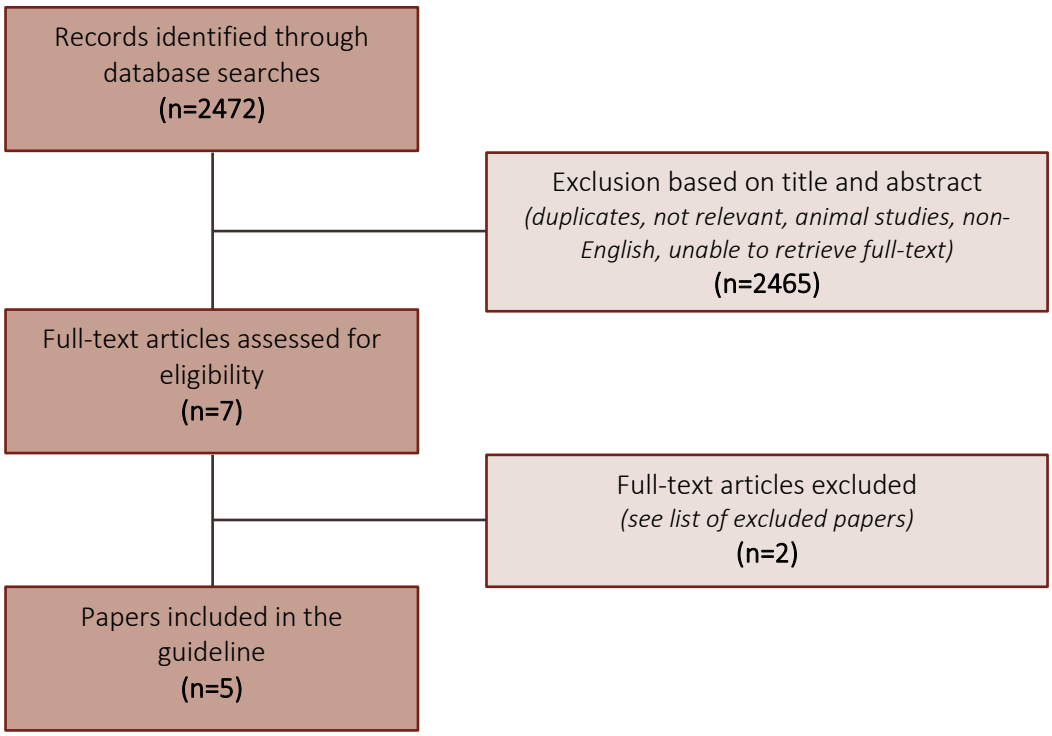
## WHICH TECHNIQUES CAN BE USED TO PREVENT/REDUCE ZIKA VIRUS TRANSMISSION DURING MEDICALLY ASSISTED REPRODUCTION?

Flowchart



## DOES THE PLASMATIC VIRAL LOAD CORRELATE WITH ZIKA VIRUS IN SEMEN?

### Flowchart

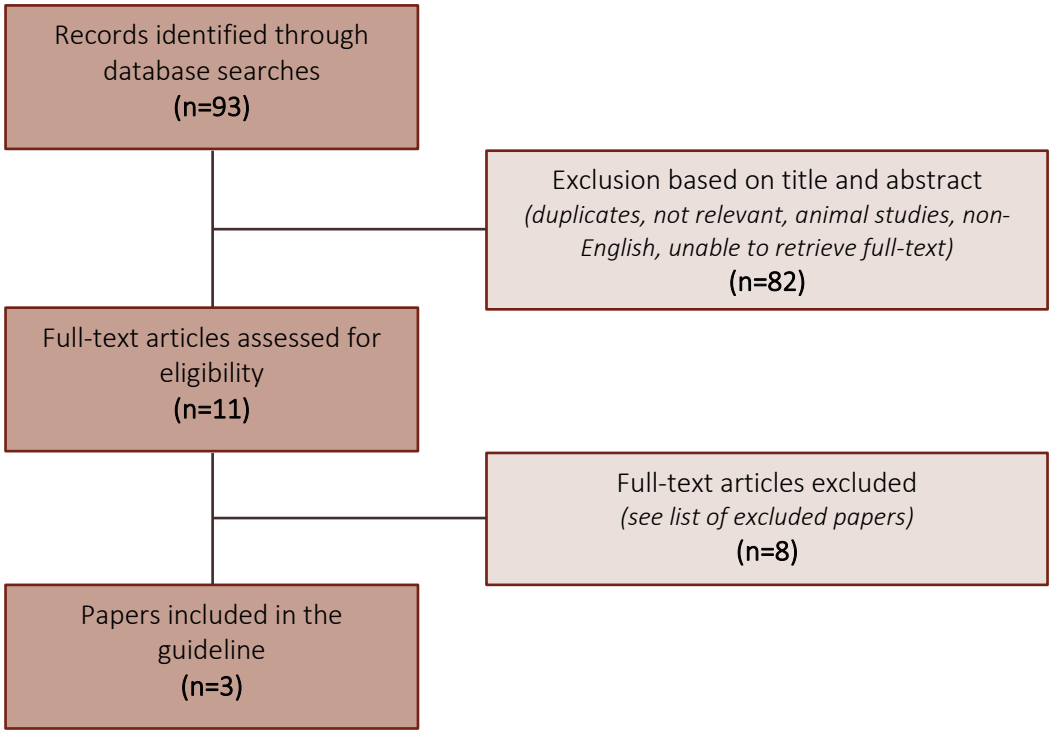



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Biava, M., Caglioti, C., Castilletti, C., Bordi, L., Carletti, F., Colavita, F., Quartu, S., Nicastri, E., Iannetta, M., Vairo, F., Liuzzi, G., Taglietti, F., Ippolito, G., Capobianchi, M. R. and Lalle, E. Persistence of ZIKV-RNA in the cellular fraction of semen is accompanied by a surrogate-marker of viral replication. Diagnostic implications for sexual transmission. New Microbiol. 2018; 41 (1): 30-33. | Case report in the presence of higher quality evidence |
| Medina, F. A., Torres, G., Acevedo, J., Fonseca, S., Casiano, L., De Leon-Rodriguez, C. M., Santiago, G. A., Doyle, K., Sharp, T. M., Alvarado, L. I., Paz-Bailey, G. and Munoz-Jordan, J. L. Duration of the Presence of Infectious Zika Virus in Semen and Serum. J Infect Dis. 2019; 219 (1): 31-40. | Same samples as Paz-Bailey et al., 2018 |

## WHICH INTERVENTIONS CAN BE USED TO REDUCE/AVOID VERTICAL TRANSMISSION OF ZIKA VIRUS TO THE NEW-BORN?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Blohm, G. M., Lednicky, J. A., Marquez, M., White, S. K., Loeb, J. C., Pacheco, C. A., Nolan, D. J., Paisie, T., Salemi, M., Rodriguez-Morales, A. J., Glenn Morris, J., Jr., Pulliam, J. R. C. and Paniz-Mondolfi, A. E. Evidence for Mother-to-Child Transmission of Zika Virus Through Breast Milk. Clin Infect Dis. 2018; 66 (7): 1120-1121. | Included in SR Sampieri et al., 2019 |
| Blohm, G. M., Lednicky, J. A., Marquez, M., White, S. K., Loeb, J. C., Pacheco, C. A., Nolan, D. J., Paisie, T., Salemi, M., Rodriguez-Morales, A. J., Morris, J. G., Jr., Pulliam, J. R. C., Carrillo, A. S., Plaza, J. D. and Paniz-Mondolfi, A. E. Complete Genome Sequences of Identical Zika virus Isolates in a Nursing Mother and Her Infant. Genome Announc. 2017; 5 (17):. | Included in SR Sampieri et al., 2019 |
| Calvet, G. A., Kara, E. O., Giozza, S. P., Botto-Menezes, C. H. A., Gaillard, P., de Oliveira Franca, R. F., de Lacerda, M. V. G., da Costa Castilho, M., Brasil, P., de Sequeira, P. C., de Mello, M. B., Bermudez, X. P. D., Modjarrad, K., Meurant, R., Landoulsi, S., Benzaken, A. S., de Filippis, A. M. B. and Broutet, N. J. N. Study on the persistence of Zika virus (ZIKV) in body fluids of patients with ZIKV infection in Brazil. BMC Infect Dis. 2018; 18 (1): 49. | Study protocol |
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| de Quental, O. B., França, E. L., Honório-França, A. C., Morais, T. C., Daboin, B. E. G., Bezerra, I. M. P., Komninakis, S. V. and de Abreu, L. C. Zika Virus Alters the Viscosity and Cytokines Profile in Human Colostrum. J Immunol Res. 2019; 2019 9020519. | Focus on cytokine profile in breastmilk |
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| Grischott, F., Puhan, M., Hatz, C. and Schlagenhauf, P. Non-vector-borne transmission of Zika virus: A systematic review. Travel Med Infect Dis. 2016; 14 (4): 313-30. | Replaced by a more recent systematic review |
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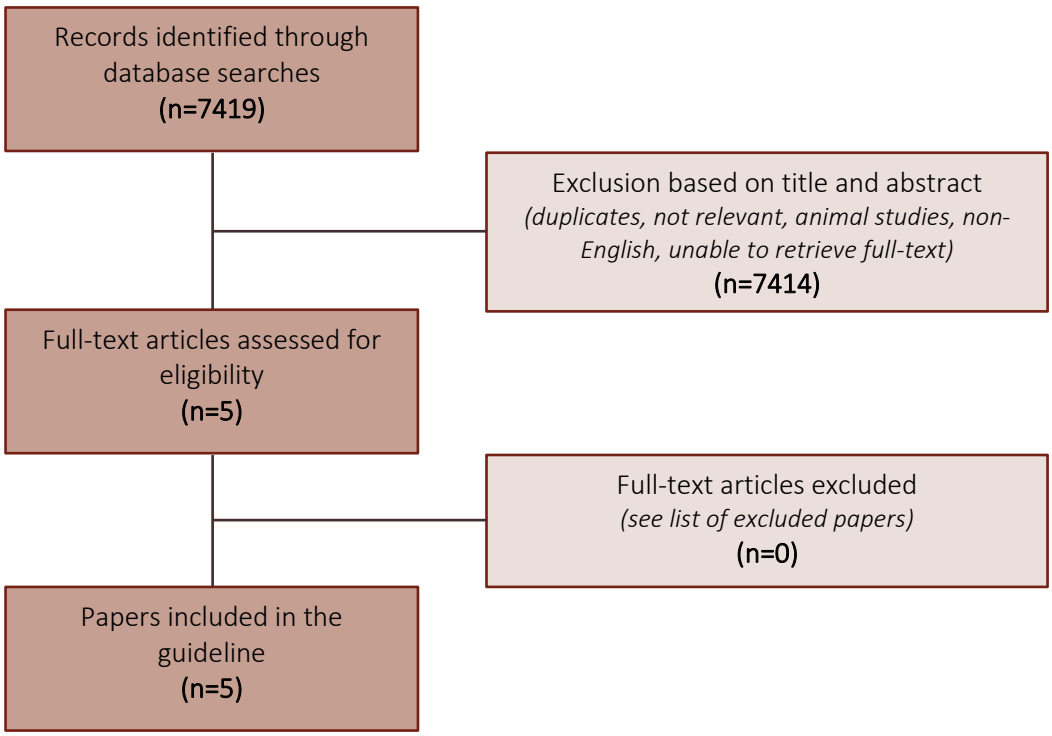
# Laboratory safety

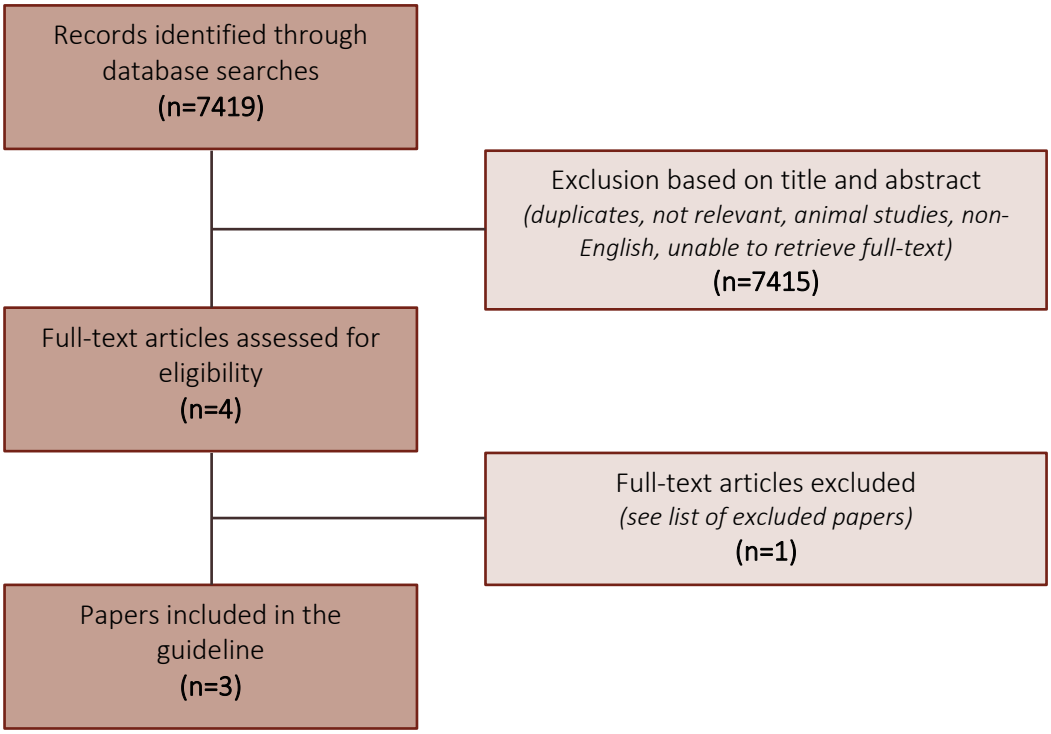
## CAN SEPARATE CRYO TANK STORAGE PREVENT CROSS CONTAMINATION OF STORED MATERIAL?

Flowchart



## CAN THE TYPE OF CRYOSTORAGE ENVIRONMENT (LIQUID VERSUS VAPOUR/OPEN VERSUS CLOSED SYSTEMS) PREVENT CROSS CONTAMINATION OF STORED MATERIAL?

### Flowchart

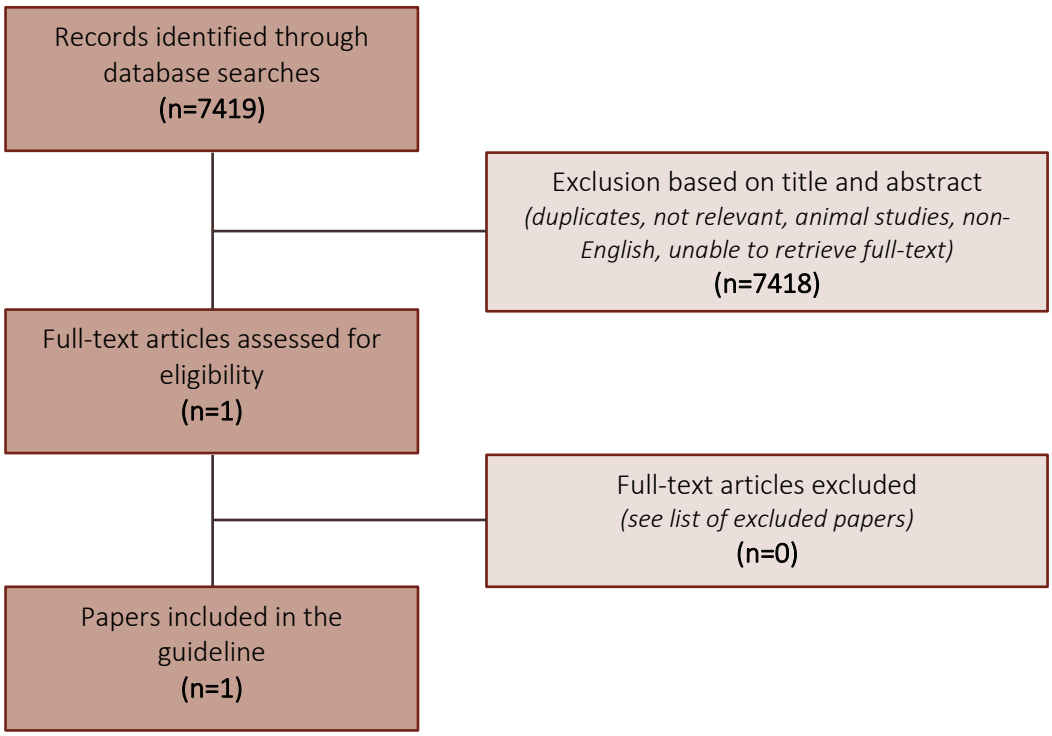



### List of excluded papers

| | Exclusion criterion |
|---|---|
| Benifla, J. L., Letur-Konirsch, H., Collin, G., Devaux, A., Kuttenn, F., Madelenat, P., Brun-Vezinet, F. and Feldmann, G. Safety of cryopreservation straws for human gametes or embryos: A preliminary study with human immunodeficiency virus-1. Human Reproduction. 2000; 15 (10): 2186-2189. | The straws were maintained at 37C during this study which is contrary to normal use |

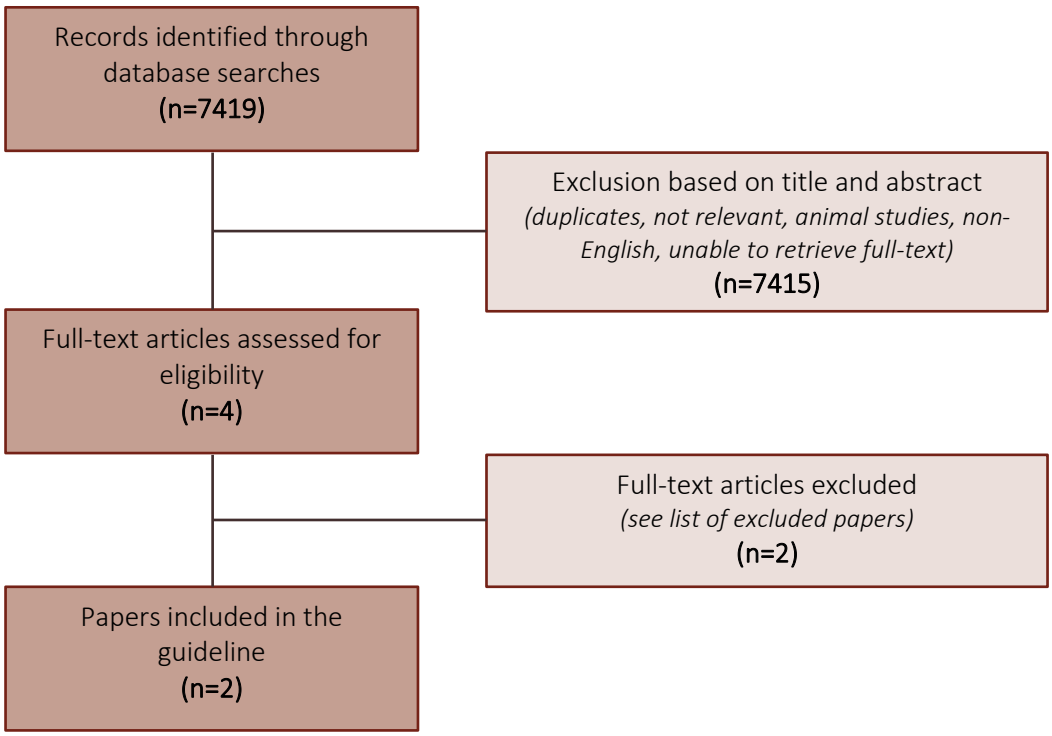
## CAN THE TYPE OF VIALS PREVENT CROSS-CONTAMINATION OF STORED MATERIAL?

Flowchart



## CAN HIGH SECURITY STRAWS PREVENT CROSS CONTAMINATION OF STORED MATERIAL?

### Flowchart




### List of excluded papers

| | Exclusion criterion |
|---|---|
| Benifla, J. L., Letur-Konirsch, H., Collin, G., Devaux, A., Kuttenn, F., Madelenat, P., Brun-Vezinet, F. and Feldmann, G. Safety of cryopreservation straws for human gametes or embryos: A preliminary study with human immunodeficiency virus-1. Human Reproduction. 2000; 15 (10): 2186-2189. | The straws were maintained at 37C during this study which is contrary to normal use |
| Woods EJ, Thirumala S. Packaging Considerations for Biopreservation. Transfus Med Hemother. 2011;38(2):149-156 | This paper promoted one commercial type of cryovial. However, the authors are employees of the vial company, so there is a conflict of interest. |

## CAN THE USE OF SEPARATE LABS PREVENT CROSS CONTAMINATION?

### Flowchart