Semen as virus reservoir?

Walter D. Cardona Maya¹ · Stefan S. Du Plessis² · Paula A. Velilla³

Received: 26 April 2016 / Accepted: 20 May 2016 / Published online: 30 May 2016
© Springer Science+Business Media New York 2016

The recent Ebola outbreak prompted our group to perform a systematic literature search about semen and the Ebola virus. Of interest was the fact that the Ebola virus has been cultured from semen samples collected 2 and 3 months after disease onset, despite that the virus was cleared from the blood of these patients [1–3]. Based on this information, we advocate the evident need to avoid unprotected sexual intercourse for at least 3 months after clearance of the Ebola virus from the blood [4].

More recently, NEJM published two interesting papers regarding the Ebola virus and semen. In the first paper, the authors found that semen samples from Ebola virus disease (EVD) survivors remained positive for up to 9 months (272 days) after the onset of symptoms. However, the detection was done by quantitative RT-PCR, thereby indicating the presence of the virus but not whether it is infectious [5]. The second article is based on a case report regarding a 44-year-old woman infected with the Ebola virus after unprotected vaginal intercourse with a male survivor of EVD [6]. This persistence of the Ebola virus (and declining persistence with increasing

months) since the onset of EVD is a proof that semen can act as an Ebola virus reservoir.

Similarly, Foy et al. reported in 2011 that the Zika virus (family: *Flaviviridae*, genus: *Flavivirus*), a mosquito-borne arbovirus, was transferred directly from person-to-person (husband to wife, Colorado, USA). This most probably occurred through sexual intercourse in the days after the husband was infected during a trip to Senegal but before the onset of his clinical illness [7]. A further case of sexual transmission was reported in Texas early in 2016 when a traveler returning from Venezuela's sexual partner also became infected [8]. Likewise to the Ebola findings, semen samples tested positive for the Zika virus even though it came up negative in blood [9].

In addition, human immunodeficiency virus (HIV) shedding was shown to persist in semen [10, 11 and revised in 12] from individuals receiving suppressive highly active antiretroviral therapy, thereby indicating that the male genital tract may be acting as a constitutive viral reservoir. Likewise, HIV transfer by spermatozoa into the oocyte [13] or macrophages [14] has been shown, indicating at least that spermatozoa can act as vectors of HIV constituting a potential source of infection during intercourse. In vitro results from our studies show the presence of viral RNA, but not DNA, in sperm samples from HIV-1-negative individuals, after in vitro exposure to HIV particles. These findings suggest an interaction between HIV and spermatozoa [15, 16] whereby the virus use cellular receptors such as the mannose receptor [15, 17] and the heparin sulfate proteoglycan endocytosis receptor [18, 19] for entry into the cell. Additionally, previous detection of proviral DNA in spermatozoa from HIV-infected men has also been shown [13, 20–22].

The notion of semen as a virus reservoir begs several concerns [23]. These include the possible testing of semen as a more accurate screening method for viral infections, establishing the time for clearance of viral particles from the semen

✉ Walter D. Cardona Maya
wdario.cardona@udea.edu.co

¹ Grupo Reproducción, Departamento de Microbiología y Parasitología, Facultad de Medicina, Universidad de Antioquia, Medellín, Antioquia, Colombia

² Division of Medical Physiology, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa

³ Grupo de Inmunovirología, Departamento de Microbiología y Parasitología, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia

which could impact on delaying of pregnancies and the safety of sperm donations (sperm banks), as well as the effects on the male reproductive system and future fertility [8, 24].

Recently, Rowland et al. [25] posed a question about the duration that semen remain Zika infectious. The answer to this question is not only important for the Zika virus as any information on the clearance of viral particles from semen is central to making evidence-based recommendations on the management of males with viral infections.

Therefore, programs focusing on viral screening of semen as well as preventative behavioral counseling are needed to help survivors of viral infections to mitigate the possible risk of further sexual transmission. In addition, innovative research regarding testicular, semen, and sperm biology will be necessary to better understand these newly discovered biological events.

References

- Bausch DG, Towner JS, Dowell SF, Kaducu F, Lukwiya M, Sanchez A, et al. Assessment of the risk of Ebola virus transmission from bodily fluids and fomites. *J Infect Dis*. 2007;196 Suppl 2: S142–7.
- Rodriguez LL, De Roo A, Guimard Y, Trappier SG, Sanchez A, Bressler D, et al. Persistence and genetic stability of Ebola virus during the outbreak in Kikwit, Democratic Republic of the Congo, 1995. *J Infect Dis*. 1999;179 Suppl 1:S170–6.
- Emond RT, Evans B, Bowen ET, Lloyd G. A case of Ebola virus infection. *Br Med J*. 1977;2(6086):541–4.
- Cardona-Maya WD, Hernandez PA, Henao DE. Male Ebola survivors: do not forget to use a condom! *Reproductive sciences*. 2014.
- Deen GF, Knust B, Broutet N, Sesay FR, Formenty P, Ross C, et al. Ebola RNA persistence in semen of Ebola virus disease survivors—preliminary report. *The New England journal of medicine*. 2015.
- Mate SE, Kugelman JR, Nyenswah TG, Ladner JT, Wiley MR, Cordier-Lassalle T, et al. Molecular evidence of sexual transmission of Ebola virus. *The New England journal of medicine*. 2015.
- Foy BD, Kobylinski KC, Chilson Foy JL, Blitvich BJ, Travassos da Rosa A, Haddock AD, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. *Emerg Infect Dis*. 2011;17(5): 880–2.
- McCarthy M. Zika virus was transmitted by sexual contact in Texas, health officials report. *BMJ*. 2016;352:i720.
- Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. *Emerg Infect Dis*. 2015;21(2):359–61.
- Sturmer M, Doerr HW, Berger A, Gute P. Is transmission of HIV-1 in non-viraemic serodiscordant couples possible? *Antivir Ther*. 2008;13(5):729–32.
- Lu W, Zeng G, Luo J, Duo S, Xing G, Guo-Wei D, et al. HIV transmission risk among serodiscordant couples: a retrospective study of former plasma donors in Henan, China. *J Acquir Immune Defic Syndr*. 2010;55(2):232–8.
- Houzet L, Matusali G, Dejucq-Rainsford N. Origins of HIV-infected leukocytes and virions in semen. *J Infect Dis*. 2014;210 Suppl 3:S622–30.
- Baccetti B, Benedetto A, Burrini AG, Collodel G, Ceccarini EC, Crisa N, et al. HIV-particles in spermatozoa of patients with AIDS and their transfer into the oocyte. *J Cell Biol*. 1994;127(4):903–14.
- Sánchez JA, Cardona-Maya W, Rugeles MT. Implicaciones de la transmisión del VIH a partir de espermatozoides humanos durante la fecundación. *Rev Cuba Obstet Ginecol*. 2013;39(3):249–59.
- Cardona-Maya W, Velilla PA, Montoya CJ, Cadavid A, Rugeles MT. In vitro human immunodeficiency virus and sperm cell interaction mediated by the mannose receptor. *J Reprod Immunol*. 2011;92(1–2):1–7.
- Cardona Maya W, Rugeles MT, Cadavid AP. Interaccion entre espermatozoides humanos y el virus de la inmunodeficiencia humana. *Actas Urol Esp*. 2009;33(3):223–6.
- Cardona-Maya W, Lopez-Herrera A, Velilla-Hernandez P, Rugeles MT, Cadavid AP. The role of mannose receptor on HIV-1 entry into human spermatozoa. *Am J Reprod Immunol*. 2006;55(4):241–5.
- Ceballos A, Lenicov FR, Sabatté J, Rodrigues CR, Cabrini M, Jancic C, et al. Spermatozoa capture HIV-1 through heparan sulfate and efficiently transmit the virus to dendritic cells. *J Exp Med*. 2009;206(12):2717–33.
- Christianson HC, Belting M. Heparan sulfate proteoglycan as a cell-surface endocytosis receptor. *Matrix Biol*. 2014;35:51–5.
- Bagasra O, Farzadegan H, Seshamma T, Oakes JW, Saah A, Pomerantz RJ. Detection of HIV-1 proviral DNA in sperm from HIV-1-infected men. *Aids*. 1994;8(12):1669–74.
- Nuovo GJ, Becker J, Simsir A, Margiotta M, Khalife G, Shevchuk M. HIV-1 nucleic acids localize to the spermatogonia and their progeny. A study by polymerase chain reaction in situ hybridization. *Am J Pathol*. 1994;144(6):1142–8.
- Cardona-Maya W, Velilla P, Montoya CJ, Cadavid A, Rugeles MT. Presence of HIV-1 DNA in spermatozoa from HIV-positive patients: changes in the semen parameters. *Curr HIV Res*. 2009;7(4):418–24.
- Zea-Mazo JW, Negrette-Mejia YA, Cardona-Maya W. Virus of sexual transmission: semen and virus relationship. *Actas Urol Esp*. 2010;34(10):845–53.
- McCarthy M. Couples at risk from exposure to Zika virus should consider delaying pregnancy, says CDC. *BMJ (Clinical research ed)*. 2016;352:i1813.
- Rowland A, Washington CI, Sheffield JS, Pardo-Villamizar CA, Segars JH. Zika virus infection in semen: a call to action and research. *J Assist Reprod Genet*. 2016;33(4):435–7.