From Ancient to Emerging Infections: The Odyssey of Viruses in the Male Genital Tract

Anna Le Tortorec, Giulia Matusali, Dominique Mahé, Florence Aubry, S Mazaud-Guittot, Laurent Houzet, Nathalie Dejucq-Rainsford

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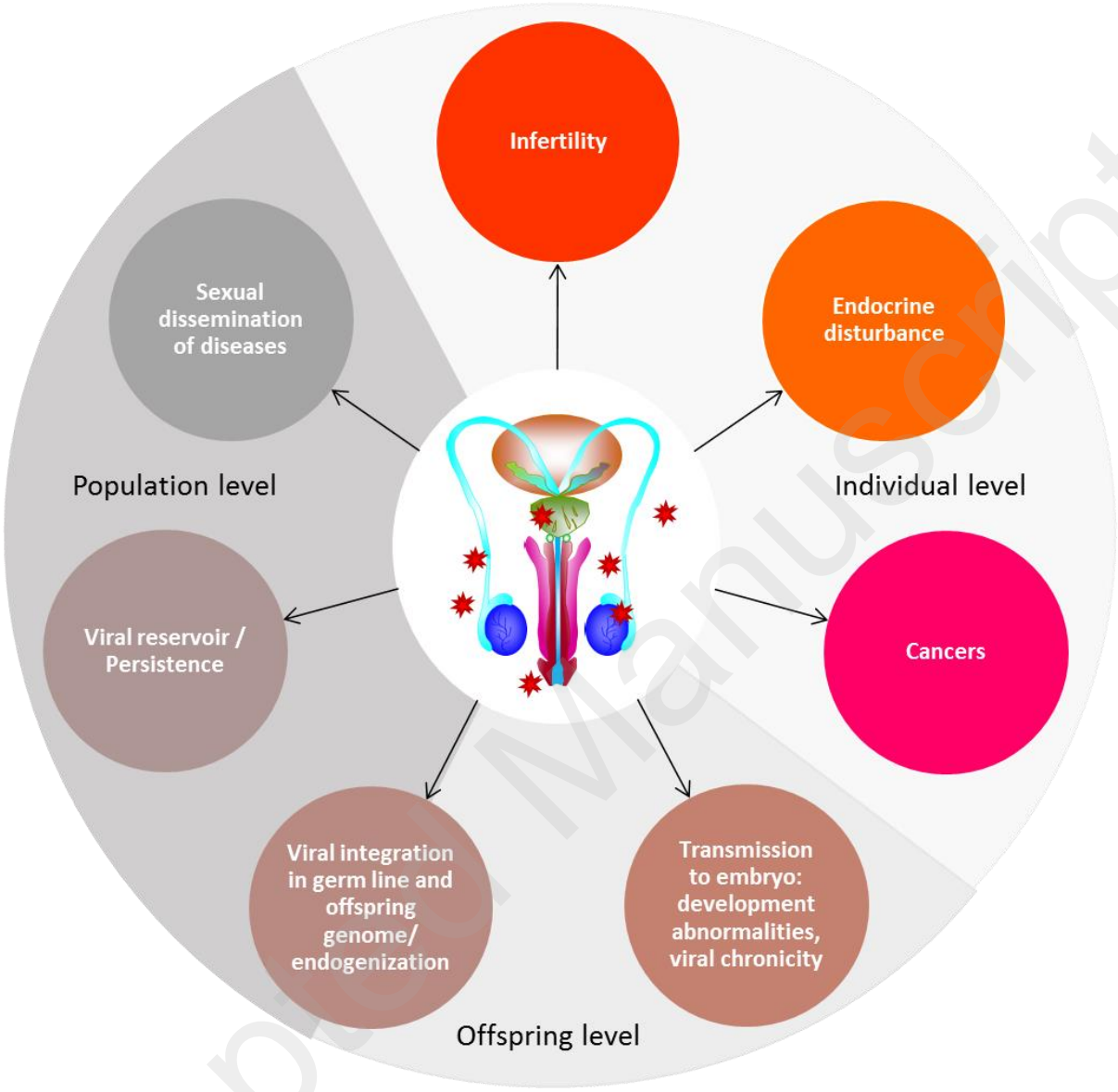
Abstract

The male genital tract (MGT) is the target of a number of viral infections that can have deleterious consequences at the individual, offspring and population levels. These consequences include infertility, cancers of male organs, transmission to the embryo/fetal development abnormalities and sexual dissemination of major viral pathogens such as human immunodeficiency virus (HIV) and hepatitis B virus (HBV). Lately, two emerging viruses, Zika and Ebola, have additionally revealed that the human MGT can constitute a reservoir for viruses cleared from peripheral circulation by the immune system, leading to their sexual transmission by cured men. This represents a concern for future epidemics and further underlines the need for a better understanding of the interplay between viruses and the MGT.
We review here how viruses, from ancient viruses that integrated the germ line during evolution through old viruses (e.g. papillomaviruses originating from Neanderthals) and more modern sexually-transmitted infections (e.g. simian zoonotic HIV) to emerging viruses (e.g. Ebola and Zika) take advantage of genital tract colonization for horizontal dissemination, viral persistence, vertical transmission and endogenization. The MGT immune responses to viruses and the impact of these infections are discussed. We summarize the latest data regarding the sources of viruses in semen and the complex role of this body fluid in sexual transmission. Finally, we introduce key animal findings that are relevant for our understanding of viral infection and persistence in the human MGT and suggest future research directions.

Graphical abstract: Potential consequences of viral infections in the male genital tract



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Introduction

The male genital tract (MGT) is composed of a series of organs and ducts that ensure male gametes production, storage and transport. It is also endowed with endocrine functions necessary for the maintenance of the male body phenotype. Alteration of male organ integrity and functions following viral attack can therefore affect both general and reproductive health. The search for a viral etiology to male infertility has expanded over the last 2 decades with the increase of medically assisted reproduction procedures. In addition to deleterious effects at the individual level, viral infections of the MGT can impact sexual partners and offspring. While the first identification of viruses in human semen and male organs date from the late 1960s-early 1970s (138), concern about the sexual transmission of viruses via semen peaked with the Acquired Immune Deficiency Syndrome (AIDS) pandemic that began in the 1980s and is still ongoing. Lately, emerging viral diseases have renewed the concern about MGT infection, and induced a burst of investigations on the subject. Indeed, the unexpected sexual transmission of Zika and Ebola viruses (ZIKV and EBOV, respectively) by cured men revealed that the MGT constitutes a reservoir for viruses. Back in the early 1970s, two papers in Science (94) and the New England Journal of Medicine (695) indicated that men serve as a reservoir for herpes simplex virus (HSV) and cytomegalovirus (CMV). This "reservoir notion" was, however, little developed until the arrival of human immunodeficiency virus (HIV) and the observation of persistence of this virus in the semen of a subset of men with undetectable viremia under effective antiviral therapy (691). However, because all these viruses establish persistent infection in their host, the existence of viral reservoirs is not unexpected, unlike ZIKV and EBOV that do not establish persistent infection in their host. Evidence is currently building up that a number of other emerging and neglected viruses also have the ability to persist in the MGT. Yet the source of viruses in semen and the nature of the MGT reservoirs are unknown.

Investigations on viral infections of the MGT are at the interface between different fields such as reproductive biology/urology and infectious diseases/virology. In this review, we aimed to cover these diverse but inter-connected aspects in order to highlight research needs and to prompt integrated researches.

After a brief overview on viruses (section I) and a summary of MGT key features (section II), section III details the routes of entry of viruses into the human MGT and compile the data available on their target organs and cells at this level. Section IV outlines the immune specificities of these organs as well as their equipment and responses against viral agents or mimicry in animal models and humans. The viruses that infect the MGT and their consequences are reviewed in section V. We begin with the ancient infections of the germ line in our ancestors, for which we postulate the implication of male germ cells infection. We summarize the data associating viral infections with human male infertility, as well as studies that investigated a viral etiology for cancers of the male organs, and discuss vertical transmission of viruses through semen. Then we outline evidence for the existence of viral reservoirs in the human MGT. Section VI focuses on semen as a vector of viral dissemination and on the latest data regarding the sources of viruses in this body fluid. Finally, section VII presents a selection of findings in animals that might enlighten our understanding of viral infections of the human MGT and help us better prepare for upcoming epidemics. In the conclusion, we highlight research needs and propose questions for future research.

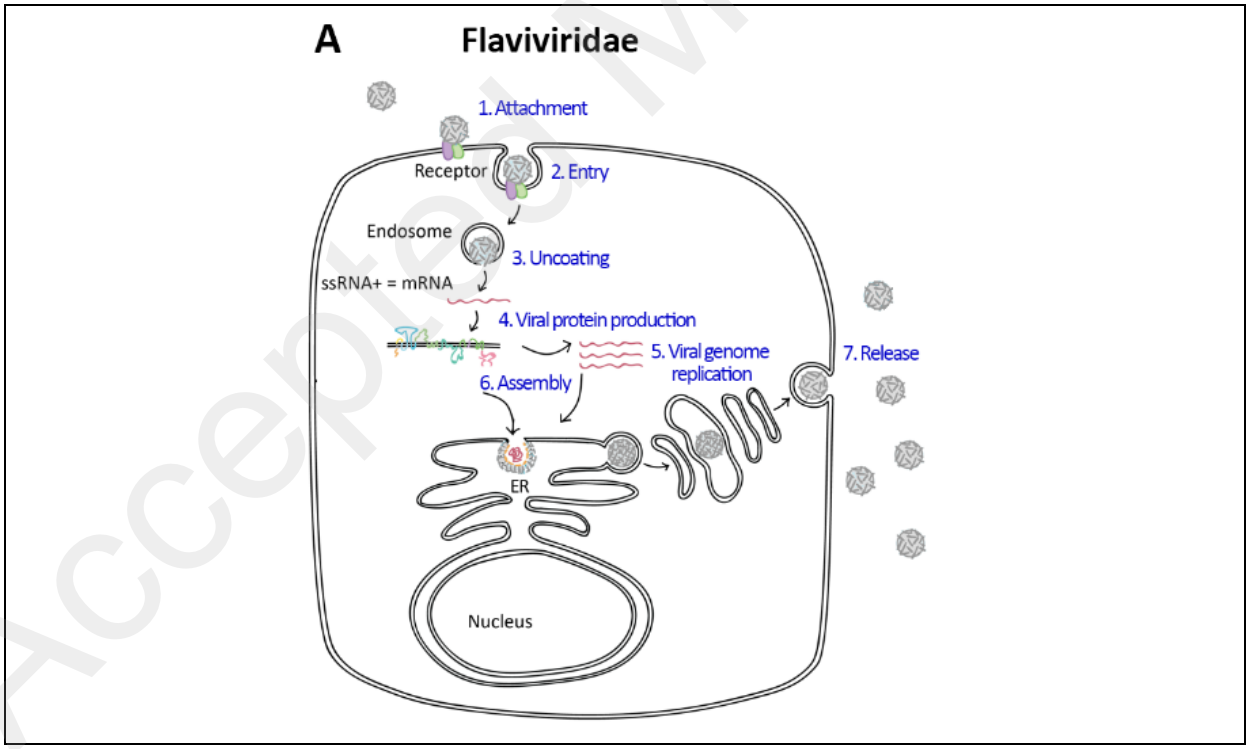
I. Brief overview of viruses: what are they? How do they infect and spread?

Viruses are obligate intracellular organisms with a simple structure consisting of a nucleic acid (DNA or RNA, single or double stranded, segmented or not, positive- negative- or ambi- sense)

contained in a proteic shell, the capsid. An outer lipidic envelope derived from host cell membranes is also present in more complex viruses and includes viral glycoproteins involved in the attachment and entry into the host cell. Based on their type of viral genome and mode of replication, viruses are classified (suffix in brackets) by order (-virales), family (-viridae), subfamily (-virinae), genus (-virus), and species (often take the form of [disease] virus) **(Table 1)**. Three to four new species are found every year (743) and the taxonomy of viruses is regularly updated by the International Committee on Taxonomy of Viruses (https://talk.ictvonline.org/).

The life cycle of a selection of viral families is shown in **Figure 1**. The virus host and cell tropism is defined as its capacity to infect specific species and cells. It depends on both viral and cellular characteristics, such as the presence of cognate receptors for the virus attachment molecules, the cellular differentiation state and expression of antiviral/restriction factors.

In terms of infection outcome, viral infections are classified as either acute or persistent. In acute infections (e.g. ZIKV), the virus is cleared by the host immune response, while in persistent infections, the virus remains in specific host cells/organs. Persistent infections can be latent (infectious virus not produced between episodes of recurrent disease, e.g. HSV, varicella zoster virus VZV), chronic (continued presence of infectious virus following the primary phase, e.g. HBV, HIV) or slow (prolonged incubation period followed by progressive disease). A viral reservoir is a cell type/anatomical site in which replication-competent viruses accumulate and remain over a long period. There are various mechanisms leading to the long-term survival of viruses in the host, but all are based on the ability of the infectious agents to escape from immune system recognition and killing.



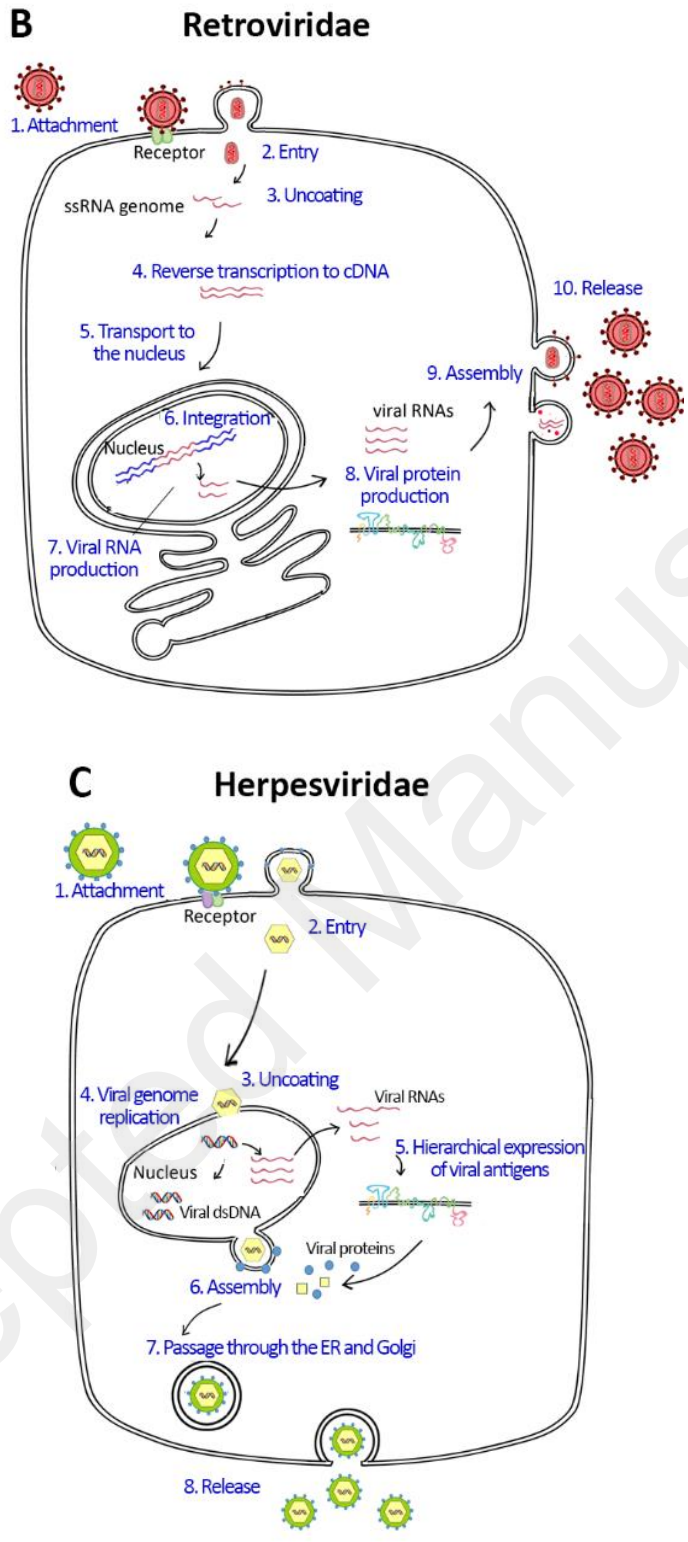
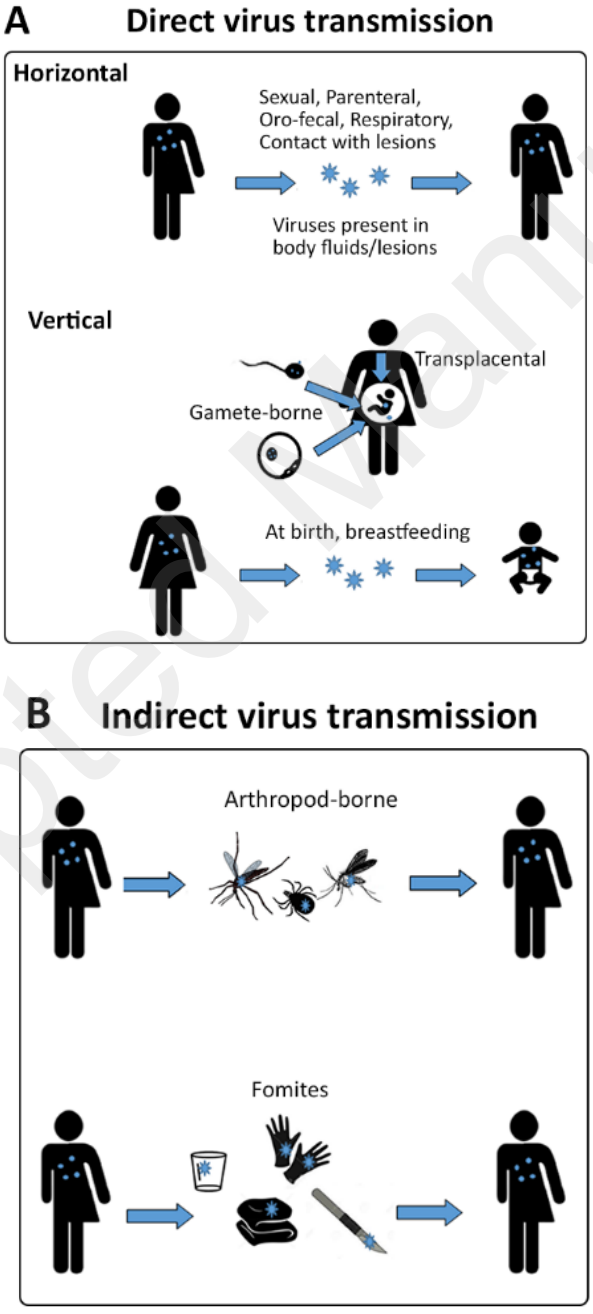


Figure 1: Life cycle of three representative viral families that infect the male genital tract. **(A) Flaviviridae** (e.g. ZIKV, HCV); **(B) Retroviridae** (e.g. HIV-1/2, HTLV-1/2); **(C) Herpesviridae** (e.g. HSV, CMV). At the host cell level, the main common steps of the life cycle of a virus consists of : i) attachment to the cell surface through receptor recognition; ii) cell entry through either endocytosis/pinocytosis (e.g. Flaviviridae) or a fusion process (e.g. Retroviridae, Herpesviridae); iii) uncoating followed by the release of the nucleic acid in the cytoplasm (Flaviviridae, Retroviriae) or in the nucleus (Herpesviridae); iv) expression and replication of viral genome; v) assembly of progeny viral particles; vi) release of newly-formed viral particles (virions) through budding or cell lysis. In a

cell that is susceptible (i.e. in which the virus may enter through receptor binding), the virus may establish: (i) productive infection (cell is fully permissive to viral replication and viral progeny is released, which may lead to cell death resulting in cytolytic infection); ii) restrictive infection (cell is only transiently permissive); iii) latent infection (viral progeny is not produced until active replication is triggered by specific stimuli, as may happen for HSV, VZV, CMV, EBV and HIV); or iv) abortive infection (replication cannot be completed due to a non-permissive host or cell, or because the virus is defective).

Viruses spread among their hosts through horizontal and vertical transmission, through arthropod vectors or fomites or by cross-species infections **(Figure 2)**. Zoonotic infections are those transmitted from animals to humans. More than two thirds of the viruses that are able to infect humans can also infect animals and many have a mammalian or avian origin (743).



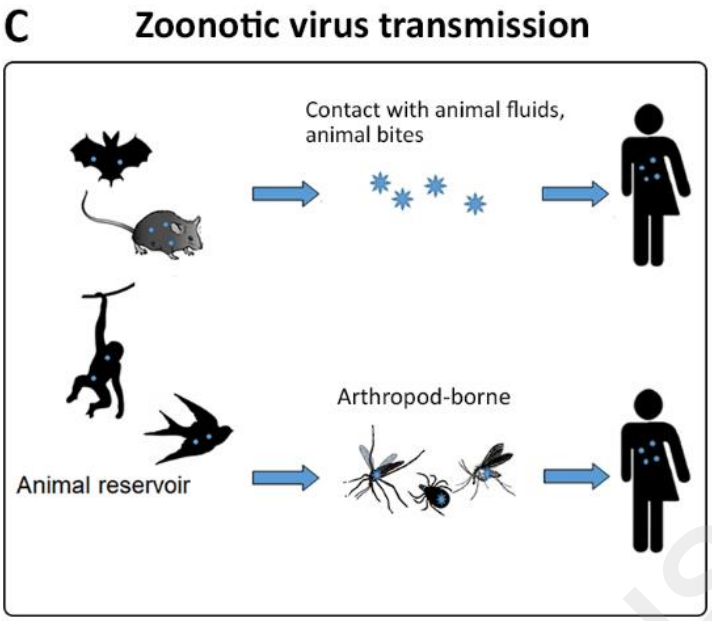


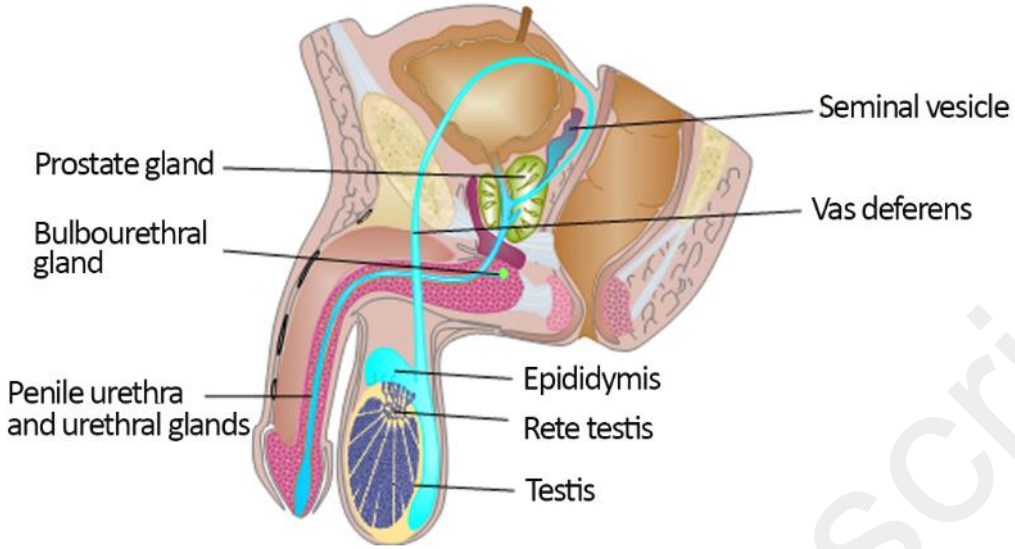
Figure 2: Modes of transmission of viruses. (A) Inter-host direct transmission can be horizontal (i.e. sexual, parenteral, oro-fecal, respiratory or through contact with lesions) **or vertical**, occurring *in utero* (i.e. gametes-borne or transplacental) or transmitted to the new-born (i.e. at birth or through breastfeeding). **(B) Indirect transmission** may be mediated by arthropod vectors (e.g. mosquitoes, ticks, sand flies) or fomites (i.e. inanimate objects able to transmit microbes). **(C) Zoonotic infections** are those transmitted from vertebrates to humans, usually through contact with animal fluids, animal bites or vector transmission. A natural reservoir for a virus is a species in which the pathogen lives and replicates, usually without causing disease.

Emerging infections are defined as infections that have newly appeared in a population, or have existed but are rapidly increasing in incidence or geographic range. Emerging diseases can be caused by previously unknown agents or by agents previously not associated to a specific disease. Re-emerging infections are caused by pathogens whose incidence of disease had significantly declined in the past and has newly appeared in the same or in a different geographical region (349). Several viruses found in the MGT have been termed as emerging (e.g. zoonotic HIV, derived from simian immunodeficiency virus -SIV- in monkeys, and that began to spread in the human population in the 1980s) or re-emerging (e.g. recent large outbreaks of ZIKV and EBOV). While viruses constitute only a small portion of the 1400 human pathogens, they represent more than two-thirds of all new human pathogens (743). Indeed, the ability of viruses to quickly adapt to new hosts makes them the most able to trigger emerging diseases (300).

II. Key features of the human MGT

The functional anatomy of the MGT and the main morphological features of the male genital organs and ducts are summarized in **Figures 3** and **4**, with key differences between human and rodent MGT organs highlighted in **Figure 4C**. **Figure 4** additionally presents the distribution in the human MGT of immune cells, which may have a dual role in viral infections as either targets or defenders.

A



B

	Semen composition
Seminal plasma	• Lipids • Sugars • > 2500 proteins (enzymes, cytokines, chemokines, cell-cell signaling factors)
Seminal cells	• Spermatozoa (>85% of seminal cells, with normally > 39 million per ejaculation) • Exfoliated immature germ cells • Exfoliated epithelial cells • Seminal leukocytes (normally < 1 million/ml, in part coming from epididymis): 50-60% granulocytes 20-30% macrophages 5% T lymphocytes rare dendritic cells in individuals with chronic inflammation of the MGT

Figure 3: Functional anatomy of the human male genital tract. (A) The testis is a highly compartmentalized organ divided into lobules consisting of interstitial tissue and seminiferous tubules, which converge towards the rete testis. Immotile spermatozoa produced in the testis seminiferous tubules during spermatogenesis are expelled through the efferent ducts into the epididymis, where they are matured for 1 to 21 days as they travel through the epididymis head, body and tail and stored. During ejaculation, spermatozoa and epididymis secretions (about 10% of seminal plasma) travel through the vas deferens and mix with secretions from the seminal vesicles (about 70% of seminal plasma), and then through the ejaculatory ducts which rejoin in the prostate that produces about 30% of seminal plasma. Semen then travels through the bulbourethral gland (Cowper's gland) and urethra, where the urethral glands (Littré glands) produce the pre-ejaculatory fluid, and exit through the penis meatus. **(B) Semen composition.** The box recapitulates the composition of semen, which comprises spermatozoa, seminal leukocytes, exfoliated epithelial cells and immature germ cells, all bathing in seminal plasma. This dynamic fluid helps the transport and survival of spermatozoa, preserves their fertilizing abilities and primes an adaptive immune response in the female reproductive tract. Seminal plasma has been shown to directly and indirectly interact with viruses (see part VI.4.).

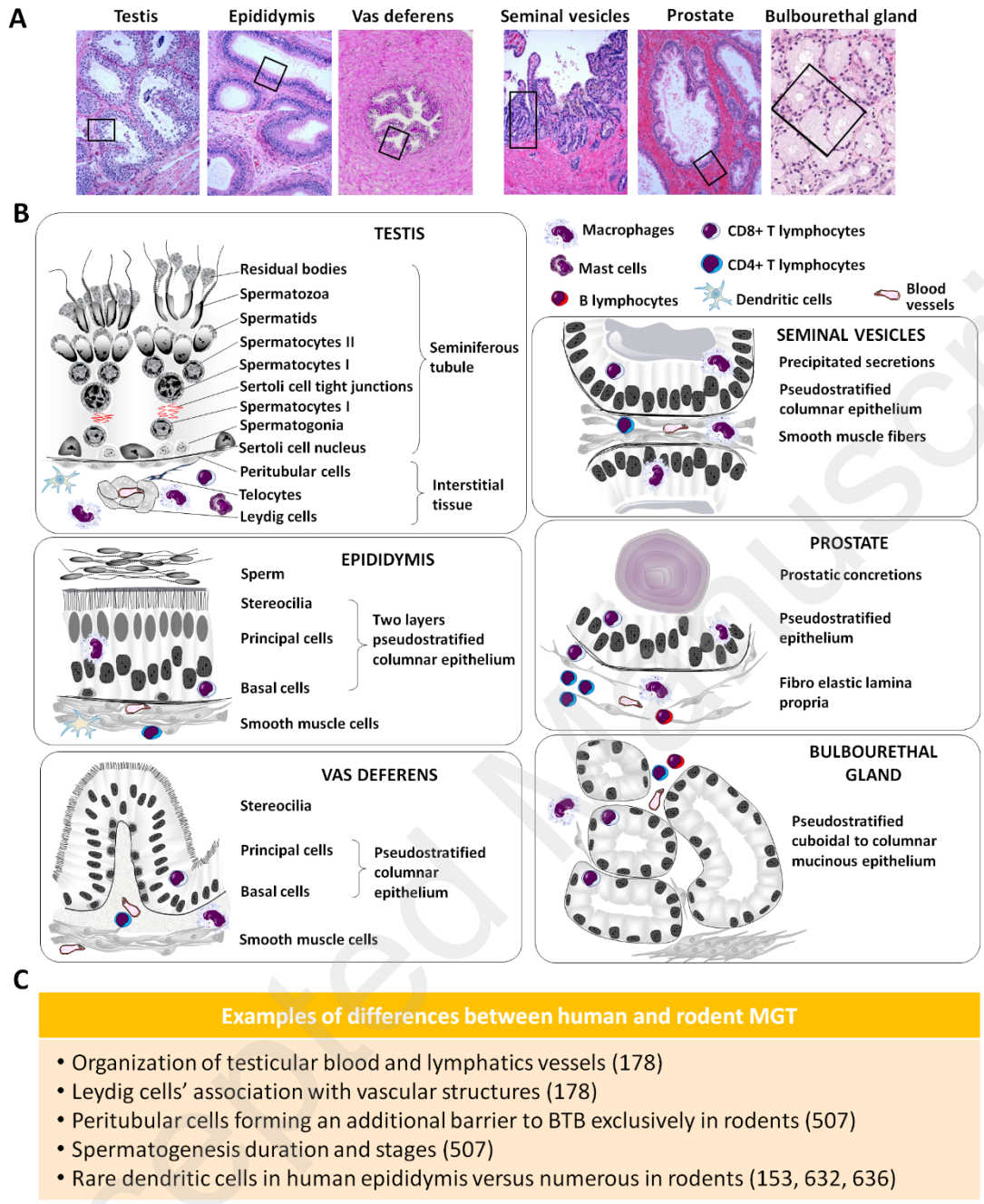


Figure 4: Morphological specificities of human MGT organs and immune cell distribution: (A) histological sections, (B) schematics, (C) main morphological differences between human and rodents. The interstitial tissue of the **testis** primarily contains Leydig cells, along with blood vessels, immune cells, telocytes (428), fibroblasts and nerve cells. Leydig cells produce testosterone under the control of the pituitary luteinizing hormone (LH) and also play important paracrine roles for testis functions (508). The seminiferous tubules contain the germ cell-nursing Sertoli cells, the basal tight junctions of which form the blood testis barrier (BTB). The production of spermatozoa from spermatogonia through meiosis (i.e. spermatogenesis) lasts about 74 days in human. Differentiating spermatogonia are generated every 16 days from stem spermatogonia, which also proliferate by mitosis to regenerate stem cells (508). Importantly, stem spermatogonia and primary spermatocytes up to pre-leptotene stage are not physically protected by the BTB from pathogens entering the interstitial tissue through blood vessels, since they are located in the outer wall of the tubule. The BTB opens in a tightly regulated manner to let germ cells progress towards the seminal lumen. Meiotic spermatocytes, post-meiotic spermatids and spermatozoa located in the adluminal compartment are segregated by the BTB

from interstitial components (e.g. viruses, immune cells and antibodies). Sertoli cells phagocyte degenerated germ cells and residual bodies (remnants of spermatozoa cytoplasm) and play a key role for paracrine and endocrine regulations (e.g. inhibin synthesis), the latter under the control of pituitary follicle stimulating hormone (FSH) (145). Each seminiferous tubule is lined with myoid peritubular cells, which contractions help the release of spermatozoa in the tubule lumen. **The epididymis** is a single convoluted tubule (about 5-7 m long in humans) structurally divided in three parts, head (caput), body (corpus) and tail (cauda), with distinct functions (e.g. absorption of testicular fluid and expulsion of spermatozoa during ejaculation). Only spermatozoa that have passed through the epididymis are mature enough to be capable of motility. Macrophages located in the lamina propria and in between the epithelial cells are the predominant epididymal immune cell types. Stromal T cells are mainly CD4+, whereas intra-epithelial T lymphocytes are primarily CD8+. In humans, a small number of dendritic cells (DCs) are located mainly in the interstitial compartment of the epididymis head (153). **The vas deferens** is a narrow tube (about 30 cm long in humans) which layers of smooth muscles provide most of the propulsive force for ejaculation. Its distal part enlarges to form an ampulla, acting as a storage chamber. The vas deferens epithelium contains CD8+ T lymphocytes while CD4+ T lymphocytes and macrophages are found in the lamina propria (165). **Each seminal vesicle** consists of a single tube folded and coiled on itself. The seminal vesicles secrete a viscous alkaline fluid that provides nutrition for the sperm. The development, maintenance and exocrine function of the seminal vesicles is highly dependent on testis-secreted androgens. The seminal vesicles contains stromal and intra-epithelial macrophages, and to a lesser extent CD4+ (mainly in stroma) and CD8+ T cells (mainly within the epithelium). B lymphocytes are rare or absent (22, 141, 165). **The prostate** is a spherical tubuloalveolar exocrine gland regulated by male androgens and composed of complex branching glands in a fibromuscular lamina propria. The main function of the prostate is to secrete a slightly alkaline fluid that nourishes and protects the sperm, and contains proteolytic enzymes (e.g. prostatic acid phosphatase, prostate-specific antigen) involved in liquefying the ejaculate. **The prostate** gland encompasses numerous immunocompetent cells including scattered T and B lymphocytes, macrophages, mast cells and occasionally DCs in the stroma and epithelium. Foci of CD4+T lymphocytes are frequent (22, 660, 683). The **bulbourethral gland**, also known as Cowper's gland are small tubuloalveolar glands which secretions lubricate the ejaculate. A small population of scattered CD4+ T and B lymphocytes and macrophages are present in the connective tissue (464) and infiltrating CD8+ T cells are embedded in its epithelium.

III. Viruses detected in the MGT: routes of infections and target organs and cells

The viruses that infect the MGT include both sexually acquired viruses responsible for localized genital infections, and systemic viruses present in multiple organs and body fluids, which may or not be sexually transmitted. For sexually acquired viruses leading to localized genital infections such as HSV and human papillomavirus (HPV), the penile mucosa is the main mode of entry into the MGT. Sexually transmitted viruses responsible for systemic infections such as HIV, HBV and human T-lymphotropic virus (HTLV) can also infect men through the penile mucosa, which represent a major female-to-male mode of acquisition. However, their dissemination to internal MGT organs is believed to occur mainly through hematogenous spread, similar to other systemic viruses that are not transmitted through the penis, like ZIKV and EBOV.

There follow details of the routes to infection of the MGT used by a range of human viruses, and a summary of the organs and cells they infect.

1. Sexually transmitted viruses that infect the penile mucosa

The different penile mucosal epithelia (foreskin, shaft, glans, meatus, fossa navicularis and penile urethra) represent a range of entryways for sexually transmitted viruses **(Figure 5).** Viruses can either infect the epithelial cells of the penile mucosa (e.g. HSV, HPV) or cross the penile epithelial barrier through a range of mechanisms that have been described *in vitro* (196)

and partially *in vivo* (146, 206). These mechanisms, as for the ones occurring in the female tract, are detailed in **Figure 11**. The influence of hormones, microbiota and genital fluids, described for viral infections of the female mucosa (81), are likely to modulate penile infection but there are no studies on this.

Of the 30-plus bacteria, parasites and viruses responsible for sexually transmitted infections (STIs), the most common viruses that can be sexually acquired by men through penile infection are HPV, HSV, HBV, HIV, HTLV-1, and hepatitis D virus (HDV) **(Table 2)**. Molluscum contagiosum virus (MCV), a viral skin infection often affecting the genital area, should also be included**.** Male acquisition of other hepatitis and herpes viruses upon sexual intercourse also occurs but is less frequent, and evidence of acquisition through the penis is either scarce (CMV, hepatitis C virus HCV, Epstein-Barr virus EBV, and Kaposi's sarcoma associated herpesvirus KSHV) or non-existent (hepatitis A virus HAV and hepatitis E virus HEV). The transmission of emerging sexually transmissible EBOV and ZIKV through the penile mucosa is theoretically possible since they have been detected in cervico-vaginal secretions (475, 711), but never demonstrated.

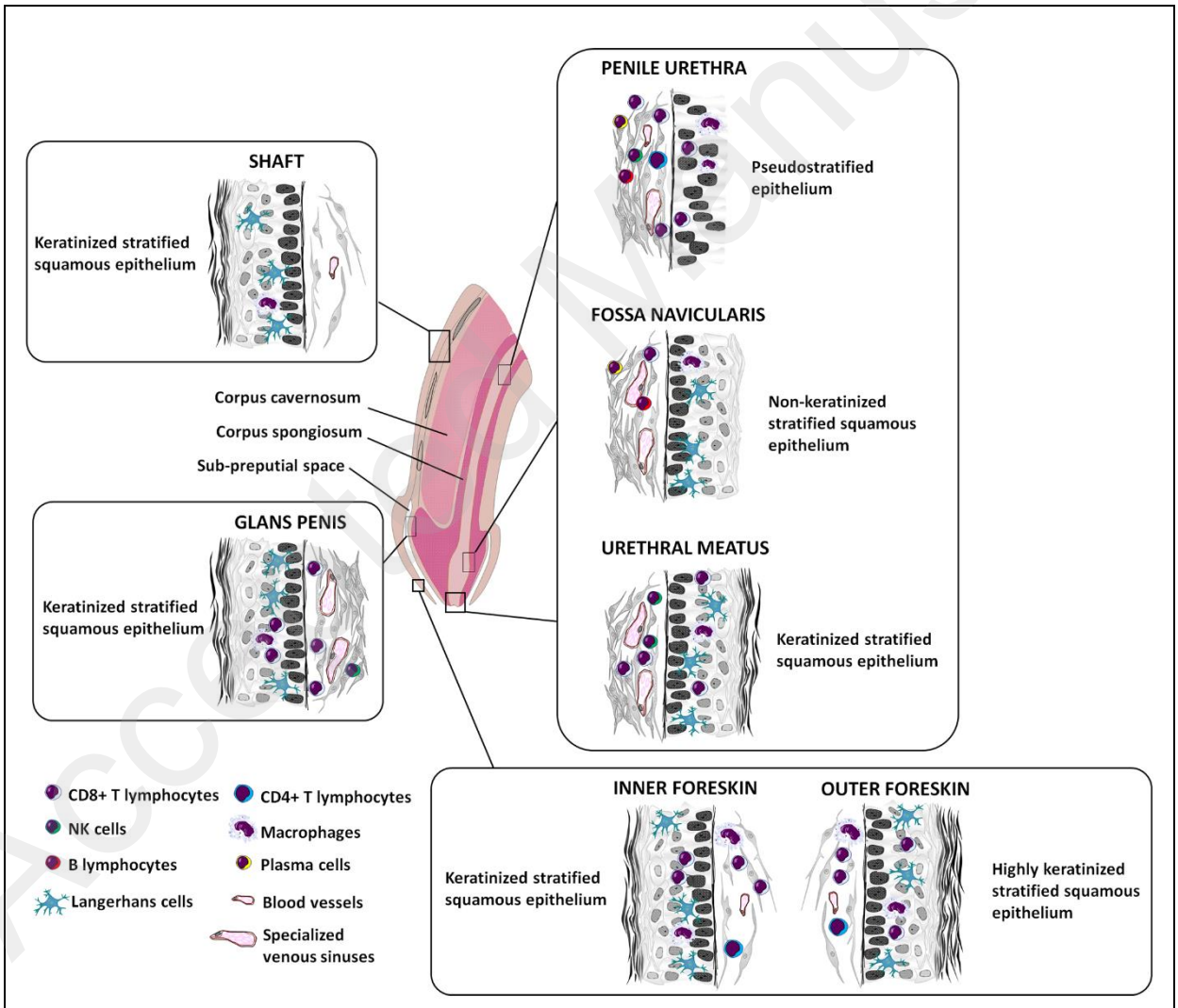


Figure 5: Anatomy of the human penis and immune cell distribution. The level of keratinization and thickness of the epithelia vary between the different penile mucosa (shaft, glans, inner and outer foreskin, urethral meatus, fossa navicularis) (19) and, along with mucus, constitute the first line of defense to viral invasions potentially transmitted during sexual intercourse. In circumcised men (where

the foreskin is completely removed; about 30% of the male population worldwide (481), the "wet" keratinized epithelium of the glans formerly covered by the foreskin becomes a dry epithelium, and is believed to be more resistant to microabrasion during sexual intercourse, which in turn may limit viral exposure of target cells located within and below the epithelium layers. Multiple small urethral glands (called Littré glands) bud all along the epithelium of the penile urethra and secrete a mucous as a pre-ejaculatory emission, a lubricant thought to form an immunological barrier against invading pathogens due to the presence of secreted immunoglobulin A (IgA). Throughout the stratified squamous epithelia of the penis, there are numerous Langerhans cells (epidermal DCs) but few macrophages. T lymphocytes, in majority CD8+ cells, are found in the epithelia of the glans, foreskin and meatus (188, 202, 444). In contrast to other parts of the penis, there are no DCs in the columnar urethra mucosa but many macrophages, as well as CD8+ T lymphocytes. The lamina propria of the **foreskin** encompasses predominantly macrophages, as well as memory CD8+ and a few CD4+ T lymphocytes including T helper 17 cells (19, 320, 555). The lamina propria of the penile **urethra** contains numerous T lymphocytes, essentially memory CD8+ T cells with a few CD4+ naïve and memory T cells (most CD103+), natural killer (NK), memory B, and IgA and IgM producing plasma cells, but only a few macrophages (19, 618). In addition to the urethra, memory B cells and IgA and J chain + plasma cells are found in the glans and fossa navicularis mucosa, but are rare in the meatus (19, 505, 618). Compared to the urethra and fossa, the glans contains a higher number of NK cells that are more activated, as well as a higher number of effector CD8+ cells (618).

1.1. Viruses responsible for localized genital infection

Human papillomaviruses

Over 40 types of HPV are sexually transmitted and infect the genitals or anus. HPV is the most common infection of the reproductive tract, with over 80% of sexually-active adults infected by one HPV at least once in their lifetime (105). HPV infections are usually cleared by the immune system within a few months of acquisition. However, a small proportion of infections with certain types of HPV can persist and progress to cancer, including cervical cancer (the most prevalent) and penile cancer. HPVs are classified as either high risk (at least 14 types, e.g. HPV 16, 18, etc.) or low risk (e.g. HPV 6, 11 and others) based on their presence or absence in cervical cancer. Interestingly, two oncogenic HPV lineages were introduced in our modern ancestors through sexual intercourse with infected Neanderthals/Denisovan populations (102, 546).

HPV infects the basal cells of stratified epithelium, the only tissue in which it replicates, through breaks in the epithelial barrier integrity, such as micro-abrasions caused by sexual intercourse (655). Virions enter the cells by endocytosis after binding to putative receptors (α integrins, laminins, and annexin A2) on the basement membrane (567). Antibodies play a key role in neutralizing the virus whilst it resides on the basement membrane. HPV does not kill the infected cell and remains as a chronic asymptomatic infection, with episomal copies of its genome in the cell nucleus. Viral particles are released with desquamating cells. Although the virus is transmissible as soon as it infects the basal epithelial cells, it takes months or years before squamous intraepithelial lesions develop and can be clinically detected. HPV has been found on the scrotum and external parts of the penis (glans, shaft, foreskin), and with a lower prevalence in the urethra, ductus deferens, epididymis and testis (158). In a cohort of Japanese men with urethritis, HPV prevalence was similar to that in the glans (20% as opposed to 31%) (630), possibly due to increased acquisition through the already damaged urethral epithelium, or to enhanced detection because of the increased exfoliation of infected cells. Male circumcision decreases the prevalence of HPV in men, including high-risk (782), and has been associated with reduced acquisition of the virus (when scrotum and penis shaft sampling were excluded) (9, 253) as well as with increased viral clearance (253, 286, 686). Overall, this data suggests that the foreskin constitutes a favorable environment for HPV infection.

Herpes Simplex viruses

HSV-1 and -2 induce lifelong infection in humans. HSV-1 is mostly transmitted by oral-to-oral contact, causing oral herpes, but can also be transmitted by sex and cause genital herpes. In the last decade, an increasing proportion of genital herpes has been attributed to HSV-1 in developed countries, probably arising from improvements in hygienic standards. This is evidenced by the acquisition of the HSV-1 infection later in the life, during the initiation of sexual activity, rather than in childhood (753). Moreover, the increasing acceptability of oral-genital sex favors the acquisition of genital HSV-1 (579). Genital HSV-1 is most prevalent in America, Europe and the Western Pacific. Globally, 140 million adults (about 25% of the people infested with HSV-1) were estimated to have genital HSV-1 infection in 2012, but prevalence varied substantially by region (744). HSV-2, which infects an estimated 471 million people under the age of 50 worldwide (64% women), is the main agent of genital herpes and is transmitted almost exclusively via vaginal and anal sex. Similar to other pathogens such as HTLV-1 and HIV, HSV-2 is more efficiently transmitted from men to women than from women to men (744). Risk factors for HSV-2 acquisition in men include HIV infection (2.5 and > 3-fold increase in 2 trials) (455, 647), genital ulcer disease and penile epithelial trauma (455). How HIV infection facilitates HSV-2 acquisition is unclear, but might involve modification of the genital immune protection against HSV-2 caused by HIV, or shared risky behavior.

HSV (either 1 or 2) first replicates in keratinocytes in mucosal surfaces and subsequently infects nerve cells via nearby nerve endings and retrograde axonal transport, where it establishes latent infection. Upon reactivation, HSV is transported back to the epithelium, creating lesions due to virus-induced cell death (676). The cell surface, heparan sulphate proteoglycans, widely expressed by epithelial cells, are involved in the attachment of HSV to the target cells, but viral entry only occurs upon recognition of specific cellular co-receptors (654). The co-receptor(s) used by HSV to infect the penis mucosa are unknown. In the foreskin, HSV-2 did not co-localize with nectin-1 (607), one of the most frequently-studied HSV receptors. In two trials conducted in Africa involving about 3,000 men each, medical male circumcision resulted in a moderate reduction (28-30% (647, 687) in male HSV-2 acquisition, while in a third african trial involving about 2000 men, no reduction was observed, even at a six-year follow-up (455, 456). The results of these trials suggest that the foreskin does not represent the main entryway for HSV. *In vitro* studies on reconstructed foreskin epithelial layers and monolayers of polarized keratinocytes showed that HSV-1 preferentially infects the basal layer of the epithelium (607, 715), and requires accessibility of cellular basolateral membranes to infect, whereas cells that only expose the apical surface are resistant to viral entry (607). This explains why damage to the genital epithelium integrity caused by ulcers or trauma (e.g. micro-abrasions occurring during sexual intercourse) favor HSV acquisition, whereas an intact epithelium offers relative protection.

The occurrence of urethritis in HSV-1 infected men suggests that the urethra might represent a site of entry for HSV-1 (70). In addition to epithelial cells, HSV-1 and HSV-2 infect human dendritic cells (DCs) (64). Opsonization by blood-derived DCs of HSV-2 particles coated with complement molecules that are naturally present in genital secretions enhanced the productive infection (124). Infection of DCs might represent an alternative mechanism of HSV penetration into the penile mucosa, and a way for the virus to escape immune recognition. The activation of virus-specific cytotoxic T lymphocytes is central to the immune control of HSV (217, 392, 631, 778), and requires presentation of viral antigens by DCs in secondary lymphoid organs. Infection of DCs by HSV in mucosal tissues might impair their ability to migrate to lymphoid organs and present viral antigens to T cells, as shown for HSV-1 in the skin (260). In addition, the cell-to-cell spread of HSV through viral synapses (260) allows the virus to hide from

neutralizing antibodies (603) and may contribute to penile infection. Genital ulcerative disease caused by HSV is associated with increased risk of HIV acquisition (606, 685).

1.2. Viruses responsible for systemic infections

Human hepatitis B virus

Sexual intercourse is the most common way that HBV is disseminated in areas of low to intermediate prevalence of infection (314). Sexual transmission is most common in MSM (men having sex with men) but HBV is also readily transmitted through heterosexual intercourse. One study identified insertive rather than receptive anal intercourse as the major risk factor for HBV seroconversion, suggesting that penile acquisition is a particularly efficient mode of transmission (357). Male circumcision decreases the risk of HBV acquisition, while HIV-1 seropositive status is a risk factor (530, 720). The main target cells for HBV are the hepatocytes, but the virus also infects lymphoid cells (663), detected in early studies it was detected in the testis and other organs (438). Despite its transmission being much more efficient than that of HIV (357), the acquisition mechanisms for HBV through the genital mucosa have not been investigated, mainly due to the lack of robust cell culture systems for this virus (710). Similarly, the transmission mechanisms for HDV, which requires HBV for replication and is acquired through the same transmission routes, is unknown.

Human Immunodeficiency Virus

Most cases of HIV infection worldwide (about 2 million new infections each year) are the result of sexual transmission, with greater risk for male-to-male than heterosexual transmission (593). Indeed, receptive and insertive vaginal intercourse risk of HIV acquisition is estimated around 8 and 4 infections per 10 000 exposures, respectively. Risk of penile acquisition of HIV by insertive anal sex is around 11 infections per 10 000 exposures. The highest risk occurs in people practicing receptive anal intercourse (138 infections per 10 000 exposures) (534). The main cellular targets for HIV are the cells of the immune system, namely CD4+ T lymphocytes, cells of the macrophage lineage and some population of DCs. The receptor for viral entry is the CD4 molecule, and the C-C and C-X-C motif chemokine receptors CCR5 and CXCR4 function as main co-receptors. The foreskin represents an important entry route for HIV, as demonstrated in clinical trials by lower incidence/prevalence following circumcision (a reduction of 56–61%) and epidemiological studies (19, 34, 36, 174, 252). As a result of these reports, the World Health Organization (WHO) recommended male medical circumcision as an important element in HIV prevention programs (731). Although these studies point at the foreskin as a highly susceptible site of infection, they also indicate that HIV can access the MGT, and in turn the systemic circulation, through the infection of other penile mucosal epithelia. Studies on HIV infection of various penile sites has demonstrated that explants of inner foreskin, glans meatus and urethra were all susceptible to HIV-1 infection (188, 202, 535). When a polarized model of foreskin explant was developed to more closely mimic the physiological exposure of the apical side of the epithelium to incoming virus, efficient HIV-1 transmission occurred in the inner foreskin but not the outer foreskin following exposure to infected cells, whereas cell-free virus did not infect. Cell-mediated infection required the formation of viral synapses between mononuclear infected cells and apical foreskin epithelial cells, internalization of HIV-1 by epidermal Langerhans cells, and transfer of the virus to T-cells by Langerhans cells (202). Exposure of the inner foreskin to HIV-1 infected cells resulted in RANTES-mediated recruitment of T-cells into the epidermis (RANTES being Regulated on activation, normal T cell expressed and secreted or chemokine (C-C motif) ligand 5 (CCL5)), and CCL20-mediated trafficking of Langerhans cells (776). In *ex vivo* exposed glans and foreskin tissue, more viral particles entered the glans penis as compared to foreskin tissue, and to greater depths (146). However, after 24 hours of culture, HIV particles were primarily visualized in the inner side of the foreskin,

similar to observations *in vivo* in Rhesus macaque upon penile inoculation of SIV (146). Polarized human urethral explants demonstrated that CCR5+/CD4+ macrophages were the initial target of HIV-1 upon exposure of penile tissue to infected cells, while exposure to cell free virus, again, did not result in infection. The fossa navicularis and glans appeared relatively resistant to HIV-1 (201). A study in Rhesus monkeys showed that the T cells, macrophages and DCs of the glans, foreskin, and coronal sulcus are the primary targets of SIV, after penile inoculation of the virus. SIV next reached the genital lymph nodes and disseminated to the bloodstream and lymphoid system within one week. After 14 days SIV had contaminated all the tested tissues (411). A model of repeated SHIV (a chimeric simian-human immunodeficiency virus containing HIV envelope gene) penile exposure of Rhesus macaques further suggested that the urethra is more susceptible to HIV acquisition than is the inner foreskin or glans tissue (206). As with other STIs, the mucosal acquisition of HIV/SIV is influenced by the genital microbiota (174), immune response (505) and host genetic factors (399, 651, 759). In addition, the risk of HIV acquisition is increased by other STIs such as HSV-2 (approx. 3-fold increase), most likely due to disrupted genital mucosae as a result of ulcerative STIs, and the inflammation-driven recruitment and activation of HIV target cells residing in the penile tissues (174).

Human T-lymphotropic virus type 1/2

Sexual acquisition is the second most common mode of transmission of HTLV-1 in endemic areas. Like HIV, HTLV-1 is transmitted more efficiently from males to females than from females to males (526). The mechanism of HTLV penile transmission is unknown. Considering the exclusive tropism of HTLV-1 for T lymphocytes and the requirement of cell-to-cell contact for infection (198), it may involve direct contact between infected T cells in female genital secretions and T cells present in the penile mucosa and/or internalization of cell-free particles by DCs and subsequent transfer to lymphocytes by cell-to-cell contact (327). Female-to-male transmission is higher in men with syphilis or a history of penile sores or ulcers (491), consistent with the concept that disrupting the genital epithelium increases viral transmission. A closely related virus is HTLV-2, distributed mainly among native American population (589). The mode of transmission and the target cells (T lymphocytes) of HTLV-2 resemble that for HTLV-1, but is generally asymptomatic.

2. Viral infections of internal male genital organs

2.1. Hematogenous and non-hematogenous routes of infection

For systemic viruses that generate high viremia, e.g. during the acute stage of infection of HIV, EBOV and ZIKV, hematogenous spread probably represents the main entry portal into the MGT. Viruses may then enter the lamina propria and testis interstitium through either passive diffusion of viral particles across the vessels, endothelial cell infection, or active passage of infected cells. The biphasic infection process observed for ZIKV within the mouse testis and epididymis, i.e. infection of cells located close to blood and lymphatic vessels before seminiferous tubules and epididymal epithelial cell spreading, suggest partial protection of these compartments by the myoid cells and extracellular matrix layers (441, 696). Of note is that the barrier represented by the myoid peritubular cell layers in rodents'testis does not exist in humans.

Virus transfer between the testis and epididymis has been recently suggested by phylogenetic analysis of viral strains in SIV-infected macaques (299) and by micro-RNA targeted viral clones for ZIKV in immune-deficient mice (696). Migration to the epididymis of infected cells such as germ cells, rete testis macrophages, and/or connected vasculature could be involved. In addition, downstream MGT ducts and glands might be infected by the viral particles or infected

cells carried by the excurrent flow during ejaculation; phylogenetic analyses in SIV-infected macaques suggested that urethral viruses originated partly from viruses present in semen. Reinfection of the urethra by seminal viruses might be facilitated by the stagnation of residual semen in the penile urethra post-ejaculation (299).

2.2. Targeted cells and tissues

Viruses belonging to a broad range of families have been found in the organs of mammalian MGTs, including humans **(figure 6)**, by means of polymerase chain reaction, in situ hybridization, electron microscopy , immuno-detection of viral antigens and viral isolation (135, 138). **Tables 3 and 4** present an updated list of the viruses detected in the male genital organs and cells. Depending on virus tropism, various cellular populations of the male organs are targeted, including epithelial cells (e.g. HPV), endothelial cells (e.g. EBOV), fibroblasts (e.g. CMV), immune cells (e.g. HIV, CMV), Leydig cells (e.g. mumps virus (MuV)), Sertoli cells (e.g. Marburg virus (MARV) and ZIKV) and germ cells (e.g. ZIKV, human herpes virus 6 (HHV-6)). Although the tight junctions of Sertoli cell protect the testicular meiotic and post-meiotic germ cells from pathogens in the interstitium, several viruses have evolved mechanisms to hijack tight junction proteins by either using them as receptors or co-receptors for cell entry, or by opening them to facilitate dissemination (501, 689). In addition, as suspected for ZIKV, viruses can bypass the testicular Sertoli cell barrier through a variety of mechanisms, including: (i) direct infection of Sertoli cells (441); (ii) viral transcytosis (i.e. passage through the cell cytoplasm without infection) from the Sertoli cell basal to apical pole (634); (iii) disruption of the epithelial barrier induced by inflammatory mediators released by infected cells in the vicinity (634, 665).

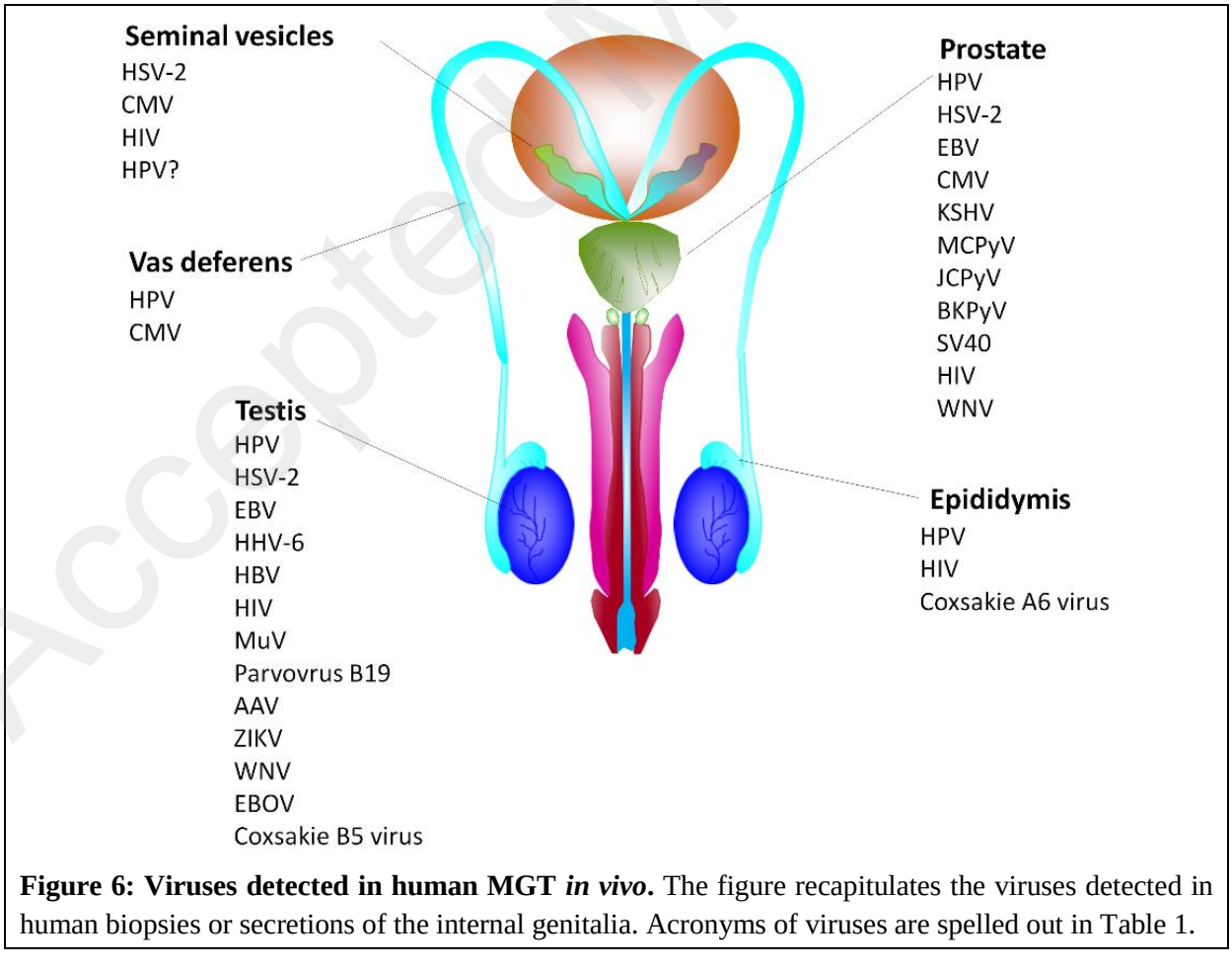


Figure 6: Viruses detected in human MGT *in vivo*. The figure recapitulates the viruses detected in human biopsies or secretions of the internal genitalia. Acronyms of viruses are spelled out in Table 1.

IV. MGT sentinels, weapons and Achilles heel in relation to viral attacks

There follows a review of the little data that is available on humans and the bulk of studies on rodents relating to the immune specificities of male genital organs and their ability to respond to viral attacks. **Figures 4, 5 and 7** show the localization of specialized immune cell types in MGT organs, and **Table 5** shows the expression of pathogen sensors throughout the MGT.

1. The testis

1.1. An immune privileged organ

The testis possesses specific immunity characteristics to prevent immune rejection of the developing germ cells and spermatozoa that appear during puberty, following the establishment of systemic self-tolerance, and which carry high surface antigen load. The initial discovery of the testis as an immune privileged site came from the observation that allografts in rat testis enabled prolonged survival (342). However, allografts in the testis from larger animals, including non-human primates (NHPs), showed a wide variation in immune protection duration (342), suggesting species-specific characteristics. Rodent studies showed that immune privilege in the testis is dependent on: (i) physical segregation by the blood-testis barrier (BTB) of the post-meiotic spermatids and meiotic spermatocytes localized in the adluminal compartment of the seminiferous tubules; (ii) an active local immunosuppressive and tolerogenic environment (27, 100, 771). Indeed, the BTB is insufficient to sequester all germ cell autoantigens, since some of the meiotic germ cells (i.e. primary spermatocytes up to the preleptotene stage) are located in the basal compartment of the seminiferous epithelium, in reach of immune components. Below is a summary of the cellular and molecular basis for the testis immune privilege, mostly established in rodents, along with data for human and NHP **(Figure 7)**.

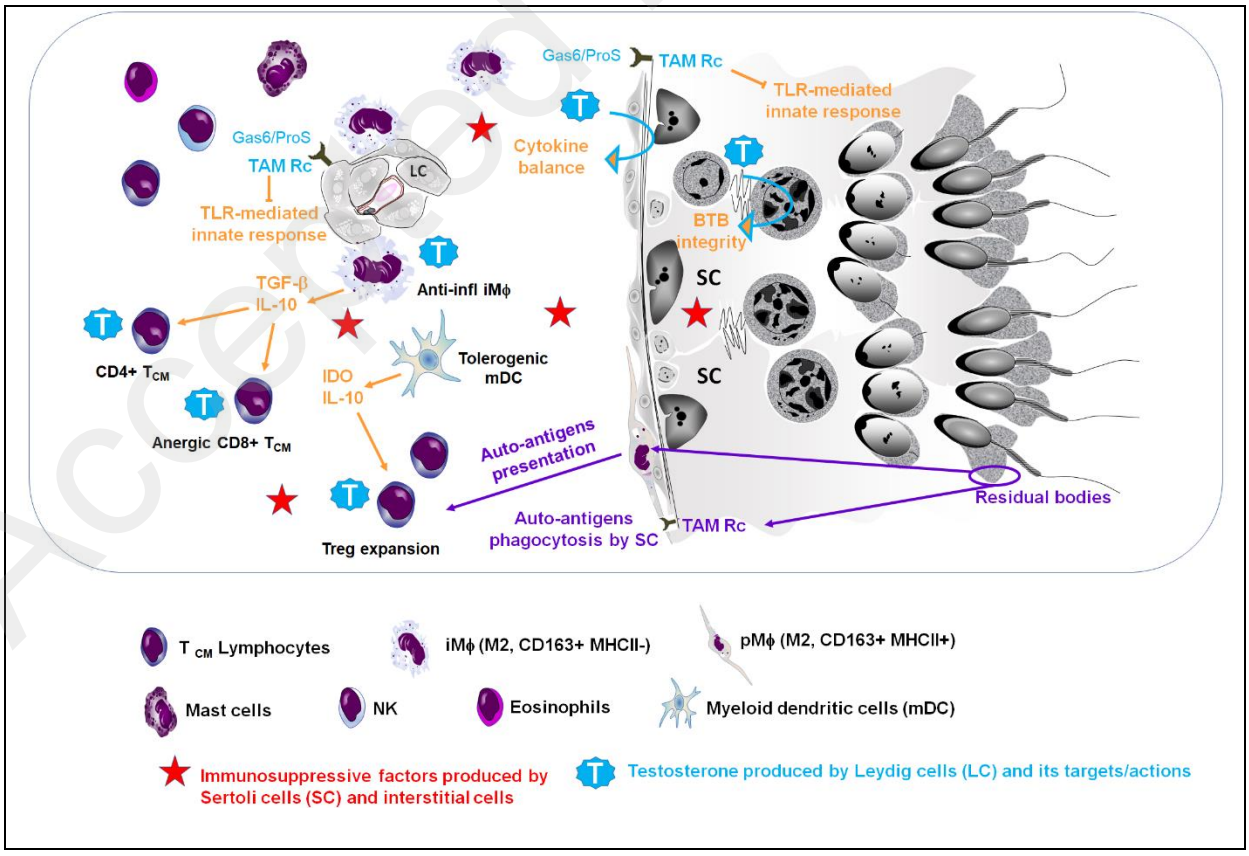


Figure 7: Immune privilege in the testis. Interstitial resident macrophages are the main immune cell population in the testis. A few T lymphocytes (mostly central memory CD8+, regulatory and natural killer T cells), myeloid dendritic cells (mDC), mast cells, natural killer (NK) cells and eosinophils are also naturally present in the interstitial tissue, whereas B lymphocytes and neutrophils are absent (322, 550, 771). Interstitial testicular macrophages are closely associated physically and chemically with Leydig cells and play an important role in their development and regeneration and in testosterone production (55, 485). In the rat testis, a subpopulation of testicular macrophages of embryonic origin closely associated with seminiferous tubules (so-called peritubular macrophages) was characterized (134, 484). Besides the Sertoli cell tight junctions forming the BTB, the immune privilege of the testis is maintained by immunosuppressive factors secreted by Sertoli cells (SIF), interstitial macrophages, mDCs and T lymphocytes (e.g. TGF-b, IL-10, Activin A, IDO, Galectin-1), which suppress T cell activation and favor Treg expansion. Gas6/ProS signaling through TAM receptors inhibits the TLR-initiated innate immune response in Sertoli and Leydig cells. Testosterone secretion by Leydig cells regulates cytokine expression in Sertoli and peritubular cells, consolidates Sertoli cell tight junctions and controls the proportion of testicular leukocytes. Germ cell autoantigens arising from apoptotic germ cells/residual bodies are either phagocytosed by Sertoli cells under TAM receptor regulation, or presented by peritubular macrophages to Treg, in turn preventing inflammatory responses. Treg: regulatory T cells; SC: Sertoli cells; LC: Leydig cells; P: peritubular cells; iMϕ: interstitial macrophage; pMϕ: peritubular macrophage; CM T lymphocyte: central memory T lymphocyte; IDO: indoleamine-pyrrole 2,3-dioxygenase; Gas6: growth arrest-specific gene 6; ProS: protein S; TGF-b: transforming growth factor b. TAM-Rc: TAM receptors.

1.1.1. The role of resident immune cells in the immune privilege of the testis

In both rodents and humans, **macrophages** represent the largest population of immune cells in the testis and play a key role in maintaining testis immune privilege (457, 485).

Rodent and primate testis macrophages display an M2-like phenotype. In this regard, they express the scavenger receptor CD163 (550, 586, 739), secrete high levels of immune-suppressive interleukin-10 (IL-10) and transforming growth factor β (TGFβ), and low levels of pro-inflammatory tumor necrosis factor α (TNFα) (586, 739). In response to infection or inflammatory stimuli, rodent testis macrophages exhibit relatively low inflammatory responses and high immunosuppressive properties compared with macrophages located in others tissues (reviewed in (457)), which confer upon them a unique immune-tolerant role against meiotic germ cells antigens that egress from seminiferous tubules.

Blocked NF-kB signaling pathway and basal corticosterone production in rat testicular macrophages is associated with reduced pro-inflammatory capacities (457). In the mouse, interstitial embryo-derived macrophages have more potent immune suppressive properties than peritubular macrophages, which are derived from the bone marrow after birth (484). Rodent and human testis interstitium contains a small population of **DC**, mostly of myeloid phenotype (538, 550), which in rats are unable to induce T cell proliferation under physiological conditions. They release anti-inflammatory cytokines (e.g. IL-10, indoleamine 2,3-dioxygenase (IDO)) and induce T regulatory cells (Tregs) instead of auto-reactive T cells following antigenic presentation (263, 723). Low numbers of T **lymphocytes,** essentially central memory, are present in human and animal testis (CD8+ T cells mainly, with a few CD4+ T cells, Tregs, and natural killer T cells) (586, 688). Their response to foreign antigens tends to be inhibited (586), probably because of local immunosuppressive factors (e.g. IL-10, TGFβ, activin A, lyso-glycerophosphocholine) (193, 282). Immunosuppressive purinergic signaling was reported in human testicular Tregs and memory CD8+ T cells (322). Egress of spermatid fragment antigens during spermiation contributes to mouse testis immune tolerance (698), possibly through the presentation of autoantigens to Tregs by major histocompatibility complex II (MHC II) positive peritubular macrophages (485).

1.1.2. The role of non-immune testicular cells

The testosterone produced by **Leydig cells** balances pro- and anti-inflammatory cytokine expression in Sertoli cells and peritubular cells (184), regulates testicular macrophage and lymphocyte numbers and pro-inflammatory properties, and stimulates Tregs expansion (184, 186). Androgen signaling in Sertoli cells is also essential for BTB integrity (459, 460). Leydig cells also produce growth arrest-specific gene 6 (Gas6)/ProS, which inhibits innate immune response in DC, macrophages and Sertoli cells (620). Rodent and human **Sertoli cells** express several immunoregulatory factors (TGFβ, IDO, Galectin-1, Activin A) that induce Treg and tolerogenic DC (205, 343). The co-transplantation of Sertoli cells with tissue in mice and NHP prolonged graft survival (404). Phagocytosis of apoptotic germ cells and residual bodies by Sertoli cells under TAM receptor regulation avoids inflammatory responses to damaged germ cell auto-antigens (751). Fas ligand (FasL), originally described on Sertoli cells, was subsequently found on germ cells and might induce T cell apoptosis (47, 128). The programmed death-1 (PD-1)/PD-1 ligand (PDL-1), expressed by spermatocytes and spermatids system, which promotes the development and function of Tregs and suppresses effector T cell-mediated immune response, is also suspected of contributing to testis immune suppression (103).

1.2. Testicular immune responses to invading virus

The sensing of a pathogen by pattern recognition receptors (PRRs) **(Table 5)** expressed by both immune and non-immune cells is key in initiating antiviral responses. Upon activation, these sentinels send intracellular signals that lead to the expression of innate immune mediators such as antiviral interferons (IFNs) and pro-inflammatory cytokines. Additionally, PRR-triggered cell-signaling induces several non-transcriptional processes such as phagocytosis, autophagy, cell death and inflammasome/cytokine processing. In short, the innate immune system can counteract the infection through: (i) the elimination of virus-infected cells by macrophages, neutrophils and natural killer cells, or by apoptosis; (ii) the production of proteins with antiviral activity. Upon binding to their receptor, IFNs induce the synthesis of hundreds of interferon-stimulated genes (ISGs) that inhibit different steps of viral replication (611); (iii) the mobilization of adaptive immune response through pro-inflammatory cytokine/chemokine production.

1.2.1. Rodent models

Rodent somatic testicular cells appear well-equipped to defend against viral attacks. Rat Leydig cells and Sertoli cells produced large amounts of type I IFN, ISGs and pro-inflammatory cytokines when exposed *in vitro* to Sendai virus, an RNA virus from the same viral family as MuV (136, 137, 139, 243, 458). MuV induced antiviral responses in mouse Sertoli and Leydig cells through Toll-like receptor 2 (TLR2) and retinoic-acid inducible gene I (RIG-I) signaling (746). Sertoli cells also expressed functional TLR3 and TLR4 (572, 656, 747). However, TLR-initiated innate immune response in Sertoli and Leydig cells were negatively regulated by Gas6/ProS-TAM signaling, which may prevent a sustained inflammatory response (620, 667). PolyIC, an agonist of the RNA virus sensors TLR3, RIG-1 and Melanoma Differentiation-Associated protein 5 (MDA5), disturbed testosterone secretion by Leydig cells, whereas HSV-60, an agonist of the cytosolic DNA sensor p204, had no effect, despite p204 expression (620, 779, 780). Exogenous type I IFN induced ISGs and inhibited MuV replication in Leydig cells, macrophages and Sertoli cells (748), demonstrating effective IFN signaling cascade. MuV-exposed Sertoli cells secreted high levels of pro-inflammatory cytokines, among which chemokine (C-X-C motif) ligand 10 (CXCL10) triggered germ cell apoptosis (325), suggesting that Sertoli cells might play a key role in MuV-induced inflammation and germ cell damage in the testis (746).

Rat testicular macrophages expressed lower levels of TLR4 receptors than peritoneal macrophages (56) as well as low basal expression of TLR-signaling pathway genes (e.g. CD14,

TRIF, TRAF6, IRAK1, TAK1 etc.), whilst the negative regulation of TLR-signaling pathways such as IkBα, SARM and RP105 were highly expressed (56). Nevertheless, testicular macrophages were able to display IFN, ISGs and pro-inflammatory cytokine production following Sendai virus exposure (139, 140, 243).

In contrast, Sendai virus (SeV) (136), MuV (746) and ZIKV (581) infection did not trigger an IFN-based antiviral response in differentiating rat and mouse germ cells. Nevertheless, poly IC induced the production of pro-inflammatory cytokines and type I IFN through TLR3 and MDA5 signaling in mouse germ cells, but to a much lower level than in Leydig cells (302, 724). Exogenous IFN stimulation failed to induce a strong upregulation of ISGs in differentiating testicular germ cells, which is in line with the lack of functional type I IFN receptor expression in meiotic and post-meiotic mouse germ cells (136, 581, 602). However, male germ cells are equipped with autophagic machinery (621), and autophagy contributed to blocking MuV replication in mouse germ cells and testicular macrophages (748). Additionally, the stem germ cell spermatogonia differed from their daughter cells in that they expressed both subunits of the type I IFN receptor and produced low levels of ISGs upon viral stimulation (136, 602). Interestingly, over-expression of type I IFN in mouse testis triggered germ cell apoptosis and induced sterility. This effect might be mediated by IFN-induced alterations in Sertoli cells or spermatogonia (602).

1.2.2. Humans and NHPs

In contrast to their rodent counterparts, human Leydig cells infected by the MuV or stimulated by poly IC *in vitro* did not upregulate type I or II IFNs and only slightly upregulated ISG expression, whereas pro-inflammatory CXCL10 was highly expressed (244, 692). Acute infection of a human Sertoli cell line by ZIKV induced an upregulation of genes implicated in innate immune response and IFN signaling, but this response was downregulated after prolonged infection (634, 665). In human testis tissue exposed to ZIKV *ex vivo*, the virus infected a broad range of somatic and germ cell types and triggered the transcription of a number of ISGs, but surprisingly did not stimulate type I, II or III IFN transcripts or proteins. Additionally, the pro-inflammatory response was restricted to CXCL10 upregulation (441). This muted innate response is unlike that observed in mouse testis infected with ZIKV *in vivo* (441, 657). It might explain the absence of orchitis in ZIKV-infected men and contribute to viral persistence in the human testis (see part V.3.). The apparent lack of IFN upregulation in the infected human testis requests further investigation. As for human peritubular cells, they produced IL6 and monocyte chemoattractant protein 1 (MCP-1) upon activation of TLR2 (442). In MARV-infected NHP, the persistent infection of Sertoli cells was associated with BTB disruption, germ cell depletion and leukocyte infiltration with numerous Tregs, the latter postulated to prevent virus clearance (111). Similarly, testis inflammation and lesions, along with testis pain and orchitis, were observed in MARV-infected patients (609). In contrast, EBOV, another filovirus with testicular tropism, did not induce any apparent damage in human and NHP testis (609). Differences in the infected cell types and in the PRRs activated by viruses in the testis most probably have a strong influence on the testicular immune responses and infection outcome.

In SIV-infected macaques, testis infection did not lead to leukocyte infiltration or elevated cytokine levels, unlike prostate infection (625, 693, 740). Although an increase in the relative proportion of effector memory CD8+ T cells was detected in the testis of SIV-infected pigtailed macaques, these cells had suppressed cytokine responses to mitogen activation (740). In the testis of HIV-infected individuals, elevated CD4+ and CD8+ T cell immune activation was postulated to favor HIV replication (322). These results suggest that immunosuppression in the testis may be restricting the ability of T cells to respond to SIV/HIV infection and allow virus persistence in this organ.

Overall, the immune-suppressive environment necessary to the testis homeostasis represents an Achilles heel when it comes to viral infections; activation of the acquired immune system is normally repressed in the testis, creating a shelter for viruses. In addition, inflammatory responses have negative consequences for the testis that can lead to sterility. In the human testis, weak antiviral innate responses, as observed following MuV and ZIKV infection *in vitro* and *ex vivo*, represent additional weaknesses that might promote viral persistence.

2. The epididymis and vas deferens

2.1. Immune characteristics

Although autoantigenic spermatozoa accumulate in the epididymal ducts, transplantation experiments in rat epididymis and injection of spermatozoa in the stroma indicated limited immune protection compared with the testis (281, 317, 469). The epididymal epithelial barrier composed of apical tight junctional complexes is penetrable by macrophages, most lacking MHC class II (281, 463, 469), and by CD8+ T lymphocytes, both in elevated proportion in proximal regions of the epididymis (496, 497). DCs, present underneath and through the rodent epididymal epithelium (633, 637), are thought to be involved in the elimination of abnormal sperm cells and non-self-ascending pathogens (264). The fewer DCs present in normal human epididymis are located exclusively in the stroma (153). Immunoregulatory IDO, Activin A and TGFβ are highly expressed in rodent caput epididymis and may promote tolerance to sperm antigens (463).

2.2. Innate immune defenses

Epithelial cells from rodent epididymis express a wide range of PRR **(Table 5)**. Activation of TLR3 and RIG-1 induced the expression of type I IFNs, ISGs and pro-inflammatory cytokines, while DNA sensor ligand HSV-60 only induced the expression of IFNs and ISGs (781). Interestingly, an inverse gradient of expression of immunoregulatory genes (e.g. IDO and activin A) and PRR was observed along the length of the human epididymal duct (77, 78). This may lead to a tolerogenic-orientated environment in the regions proximal to the testis, and to a more vigorous antigen-specific immunity in the cauda, consistent with the need to protect sperm emerging from the testis without compromising the ability to respond to ascending infections. Rodent and human epididymis are major sites of production of β-defensins, a number of which are specific to this organ and display segment-selective expression along the length of the epididymis (321, 755). These small cationic peptides, essential for sperm maturation (768, 774), possess potent antimicrobial activity, including antiviral (291). The epididymis also secretes antimicrobial lysozyme and lactoferrin (275). In the vas deferens, TLRs 1-9 and 11 are constitutively expressed (527) and TLR2, 3, 4 and 9 agonists stimulated the secretion of CXCL1 (413).

3. The seminal vesicles and prostate

3.1. Immune characteristics

The prostate is the male organ in which infectious and inflammatory occurrences are the most frequent, whereas pathologies of the seminal vesicles are rarely reported. Infections and inflammation also occur in this organ, however, but may be more silent. The continuous line of basal cells joined by tight junction at the basement of the prostatic epithelium, together with the expression of P-glycoprotein at the apical pole of prostatic epithelial cells, contribute to restricting leukocyte passage and molecular movement through the prostatic epithelium (344). Like the seminal vesicles, the prostate is a strictly androgen-dependent organ. Testosterone possesses immunosuppressive properties and influences the innate immune responses as well

as the outcome of infections and inflammation in the prostate (564). Thus, in rodents and other animals, castration is efficient at eliminating bacterial pathogens and dampening infection-related inflammation of the prostate (564). Little is known about the specific effects of androgens on host defense. In rat prostatic cells, testosterone negatively modulated the TLR4 pathway (563, 565). Also, testosterone maintained high levels of immunomodulatory factors in the prostate, such as galectin-1 (564). Nevertheless, the prostate is an immunocompetent organ. The numerous intraepithelial CD8+ T cells constitute a first line of defense against foreign agents reaching the prostate through retrograde flow (65). Even in the absence of pathology, most adult prostate tissues contain inflammatory infiltrates composed of T cells and macrophages (436, 507, 694).

3.2. Innate immune defenses

The prostate epithelial cells secrete an antimicrobial substance with potent antibacterial and antiviral actions such as defensins (563), protease inhibitors (e.g. Secretory leukocyte protease inhibitor or SLPI) and collectin proteins (512, 513), while seminal vesicle epithelial cells secrete high levels of lactoferrin (736). Surprisingly, TLR 2-9 proteins were undetectable in human seminal vesicles (559), whereas mouse seminal vesicles cells in primary culture produced CXCL1 in response to TLR2, 3, 4 and 9 stimulation, although to a lower level than prostate and epididymis/vas deferens cells (413). Stromal cells isolated from patients with benign prostate hyperplasia (BHP) acted as antigen-presenting cells and responded to TLR agonists by producing pro-inflammatory cytokines/chemokines, except TLR9 (537). Mixed cell culture of normal rodent prostate responded to TLR2, 3, 4 and 9 agonists with the secretion of pro-inflammatory mediators and upregulation of TLR genes (215, 413, 414). These reports suggest that prostatic epithelial cells are equipped to resist infection, but their response to viral infections has never been studied. Additional studies are required regarding the immunity of primate seminal vesicles. This organ has been largely ignored and was recently found to seed virus and infected cells into semen (299).

4. The penis

4.1. Immune characteristics

The penis is a major portal of entry for many pathogens and an immunologically active site. The immunity of the penis has been reviewed in detail elsewhere (558, 618) and only a few relevant key aspects are presented here. While the urethra displays classic mucosal effector features, the glans has even more activated natural killer (NK) cells and terminally-differentiated effector CD8+ T cells (618). The penile urethra contains numerous polymeric immunoglobulin A (IgA) and IgM producing plasma cells (558). In addition, the urethral glands (Littré glands) secrete IgA that coats the urethral epithelial surface to form an immunological barrier against invading pathogens (558). Urethral swabs from HIV-highly exposed uninfected men contained HIV-1 specific IgA (86), suggesting effective responses that could be used for vaccination strategies. The penile foreskin is also able to mount a specific humoral response: exposing rhesus macaque foreskin to SIV induced SIV-specific IgG antibody and cytokine-secreting SIV-specific CD8+ T cells (588). The inner foreskin produces high levels of pro-inflammatory cytokines, a feature of inflamed epidermal barrier (385, 555) that is probably favored by the microbial community of the sub-preputial space (553).

4.2. Innate immune defenses

Both the foreskin and the urethral epithelial surface are coated with a mucus layer consisting of membrane-associated mucins, which in addition to lubrication play an important role in first-line immune defense by trapping microbes before they reach the epithelial surface (19, 596). Antimicrobial peptides are widely expressed all along the human penile mucosa: α defensin-5 is present in urethral secretions (551) and lysozyme in the urethral glands (Littré glands) (558) and foreskin (19); lactoferrin is expressed by urethral epithelial cells (558) and detected in the foreskin lamina propria (19), while SLPI is expressed abundantly by urethral epithelial cells and urethral glands (275, 517, 558). IFN beta is constitutively expressed in the foreskin epithelium and lamina propria, and by basal epithelial cells in the fossa navicularis (558). Highly localized IFN alpha expression was noticed in the urethral epithelium of patients in the presence of high levels of TLR9 (558). *Ex vivo* infection of the inner foreskin with HIV increased the secretion of CCL5/RANTES, which mediated T-cell recruitment into the epidermis, while decreasing the secretion of CCL20/macrophage inflammatory protein 3 alpha (MIP-3 alpha), enabling Langerhans cells to travel deeper into the tissue (776). HIV-1 infected CD4+ T cells formed viral synapses with foreskin keratinocytes and activated the MyD88-independent TLR-4-nuclear factor NFκB signaling pathway, leading to pro-inflammatory cytokine secretion, epidermal redistribution of Langerhans cells and the formation of conjugates with T-cells (777).

V. Consequences of viral invasion of the MGT: from ancient to emerging infections

1. Viruses as enriching colonizers: the benefits of ancient infections

Several viruses that infect somatic cells can persist lifelong in humans (e.g. EBV, HSV, HIV). However, the smartest way for a virus to permanently colonize a host is to integrate its DNA into the germ line (i.e. the gametes and their progeny up to the early embryo) in order to be passed on vertically to future generations, invading every somatic and germ cell of the offspring. A number of viruses, mostly ancient but some contemporary ones such as HHV-6, have attempted this, leading to the integration of viral sequences into our ancestors' genome which, if not detrimental, eventually became fixed (endogenous) in the population (183). This colonization of the germ line has strongly shaped our evolution, adding new functions, and is still ongoing nowadays in mammals. Our review of the range of viruses, processes and benefits associated with germ line infection, along with elements suggesting initial male germ cell infection appears below **(Figure 8)**.

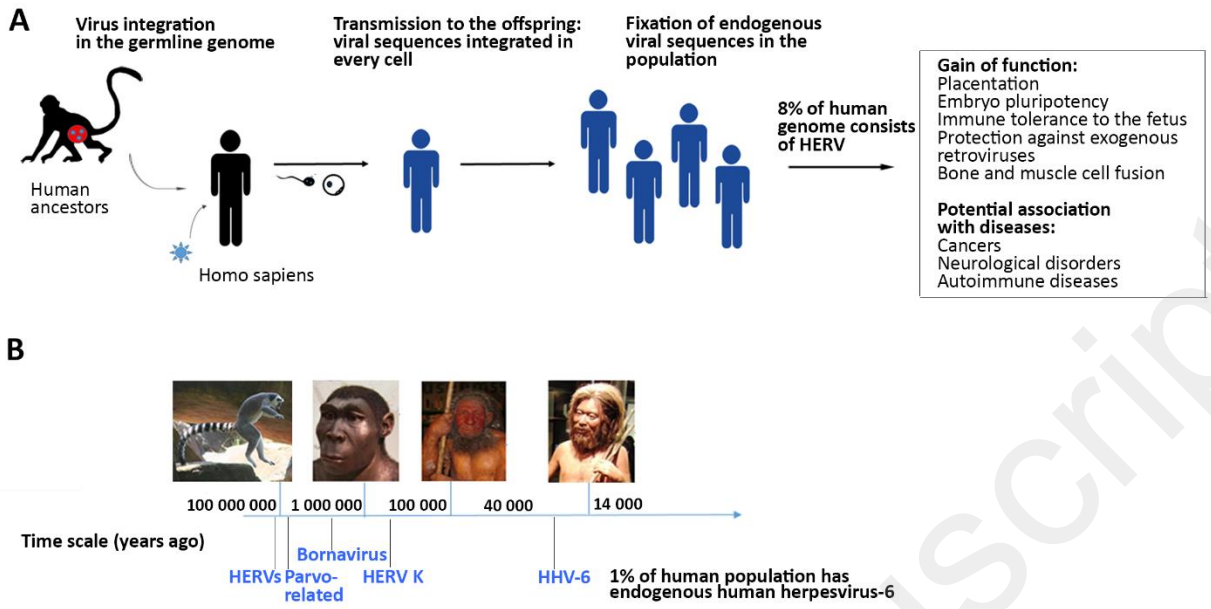


Figure 8: Integration of viruses in the germ line and its consequences. (A) Pathway to endogenization and fixation of viral sequences in the human population and their benefic effects. The integration of viral elements may nevertheless carry their burden of negative consequences: the reactivation of human endogenous retroelements (HERVs), when permitted by the innate and acquired immunity, has been incriminated in the development of inflammatory, autoimmune and neoplastic diseases, although proofs of causality are currently lacking (337, 338, 462, 717). **(B)** Estimated timeline of viral endogenizations in human ancestors.

1.1. Endogenous retroviruses

Sequencing of the human genome has provided proof of the enormous scale of viral infections that have led to the integration of viral genes into the chromosomes of the host germline, and transmitted vertically by Mendelian inheritance to become endogenous during evolution (258). Thus, about 8% of the human genome consists of endogenous retroviral elements (ERVs), the remnants of ancient exogenous retroviruses that infected germ cells (258). More than 31 viral families of human ERVs (HERVs) have been characterized in the human genome (HERV K, W, H etc.), with over 100,000 copies of retroviral elements representing several amplifications (duplications, transpositions, etc.) and reinfection events during evolution (48, 340, 412, 525). Nearly all HERVs were integrated up to 100 million years ago (172), with the most recent integration episode (HERV K family members) estimated at between 100,000 years and 1 million years ago (39, 737). ERVs have been found in all vertebrate genome sequences to date (48, 754) and endogenization of viral sequences is still ongoing, as showed in koalas (674).

1.1.1. Male germ line infection

Several ERVs are located on the male Y chromosomes of human and NHPs (360, 638, 639), providing evidence of their transmission through the male gametes in these species. Specific characteristics of the Y chromosome, such as reduced recombination and low number of functional genes, may have prevented the loss of integrated sequences and allowed integration with no deleterious effect (360), thus favoring viral endogenization. While it is unknown whether male or female gametes or early embryos were preferentially targeted for initial infection, we speculate that in addition to Y chromosome integration, infection of the male

germ cells might offer a selective advantage for viral dissemination compared with infection of the female gametes. Unlike female germ cells, the male stem germ line continues to divide in adulthood and gives rise to an indefinite number of sperm cells, allowing numerous vertical transmissions of integrated sequences with endogenization potential.

1.1.2. Ancient and contemporary lentiviruses

While integration into the germline is commonplace in many retroviral genera and hosts, it was thought until relatively recently that lentiviruses (the group of retroviruses to which HIV belongs) were entirely exogenous. This was proven wrong by the discovery of ancient endogenous lentiviruses in different mammals (231, 232, 341, 346). The finding of endogenous prosimian SIV in lemurs raises the possibility that contemporary HIV and its simian counterpart SIV might one day also become endogenous. The detection of HIV DNA within isolated testicular germ cells and spermatozoa from patients (691, 722) has been controverted. Interestingly, results from our laboratory show that HIV can bind, enter and integrate its genome into the male germ cell genome *in vitro,* albeit inefficiently (unpublished data). Although primates have evolved a variety of cellular factors to block viral infection, viruses evolve much more quickly than their host and can counteract these innate immune factors (155). The repertoire of antiviral factors expressed by human male germ cells, and in turn their ability to block integration of contemporary viruses, is currently unknown.

1.1.3. Host virus interaction and added functions

ERVs are usually inactivated by genetic mechanisms (e.g. deletions, inversions or point mutations in the open reading frames of viral proteins under the pressure of host innate factors such as apolipoprotein B mRNA editing enzyme catalytic polypeptide-like (APOBEC)) and epigenetic mechanisms (323), and therefore cannot produce infectious viral particles, with a few exceptions (592). Interestingly, it was recently demonstrated in the Koala that older endogenous retroelements recombine and degrade the new colonizing retrovirus genome, thus contributing to their inactivation (401). Nevertheless, several integrated retroviral DNA copies are still transcribed and encode original or truncated viral proteins (e.g. HERV-K copies during embryogenesis) which can add functions to the host. In addition, the ability of ERVs to recombine and transpose into the host genome and to modify the nearby gene expression through their own sequences (e.g. the long terminal repeat (LTR) promoter *and* enhancer element in retroviruses) is an important source of genomic and regulatory variability (338). Understandably, the activity of ERVs is under tight complex regulation by the host, especially in the germ cells and during early embryo development, where ERVs are sequentially and specifically expressed or silenced to protect them from excessive re-infection or transposition (592).

a. Role in reproduction

The best known benefic impact of retrovirus insertions identified to date is on the acquisition of **viviparity** through the development of effective placentation. Retrovirus envelope genes encode glycoproteins with fusogenic properties, a function necessary for virus entry. The envelope protein from HERV-W (endogenized in our primate ancestors 25 million years ago) was purloined to drive cell fusion in the placenta to form the syncytiotrophoblast, and was hence renamed syncytin-1. Syncytin 2, an envelope protein highly expressed in the placenta, also derives from an ERV (HERV-FRD) (160, 270). A similar process has occurred in various mammals (159), suggesting a non-random pattern of co-option (i.e. usage of a function that is not the original one). The syncitiotrophoblast is essential not only for invasive placental development but also for prevention of immune rejection of the fetus. Interestingly, syncytin 2

also suppresses immune recognition, and could thus contribute to the mother's immune tolerance of the fetus (160, 308). A role for syncytins in the cell fusion of osteoclasts (648) and muscle cells (570) was also evidenced. Other ERV elements play immunoregulatory roles in the placenta. For instance, the tissue-specific expression in human trophoblasts of HLA-G, central to immune tolerance during pregnancy through the inhibition of NK cell mediated cytotoxicity, is controlled by the LTR of human ERV1 (182). Further critical roles for HERVs in human reproduction were recently discovered. A number of converging elements indicate that HERVs actively contribute to the **maintenance of pluripotency** in early embryos (462). In male germ cells, the strong promotor activity of the ERV9 LTR controls the expression of unique isoforms of p63 that preserve genetic integrity by suppressing cell proliferation and inducing apoptosis upon DNA damage (52). The exclusive expression in human testis tissue of a number of HERV transcripts has been reported (639), suggesting other roles for HERVs.
Overall, several of the ERVs which colonized the germline of our ancestors can be considered as the initiators (e.g. role in placentation) and/or the guardians (e.g. role in maintaining genetic integrity in germ cells and pluripotency in the embryo) of human reproduction.

b. Protective role against infections and pathological processes

The impact of ERVs on humans extends beyond reproductive functions. One well-identified positive effect of ERVs is the induction of direct **protection against exogenous viruses** by interacting with different steps of their life cycle, a "fighting fire with fire" process. For instance, competitive binding to the cellular receptor mediating viral entry can occur between the envelope proteins of exogenous virus particles and that encoded by ERVs, as found in mice, sheep and cats (32, 421). Among other protection mechanisms is the association, during assembly, of particles newly released from the exogenous virus of defective viral components encoded by the ERVs, a phenomenon observed for JRSV in sheep (32) and suggested for HERV-K gag protein during normal embryogenesis (262). Finally, ERVs can **boost innate and acquired immune functions**. Only a couple of examples are presented here (for a complete review, see (338)). A number of ERV LTRs contain interferon-stimulated response elements (ISREs) which, after IFN stimulation, can enhance adjacent genes critical for antiviral and pro-inflammatory responses. The HERV-K protein Rec can inhibit exogenous viral infections in human pluripotent cells by increasing the innate antiviral response, and it is suspected that it plays an immune-protective role during early embryonic development. In transformed cells, the expression of endogenous retroviral elements is no longer silenced and can induce innate and acquired immunity to target non-healthy, ERV-producing cells, facilitating their elimination. Endogenous retrovirus proteins are part of the so-called "cancer testis antigens", a set of "self" proteins not expressed in healthy cells other than testicular germ cells, where they are protected from immune recognition by the immunosuppressive testis environment.

In summary, ERVs greatly contributed a range of functions in their hosts. However, in specific conditions, they may be implicated in the development of human diseases. Indeed, when permitted by the immune system, the reactivation of HERV has been associated with a plethora of syndromes affecting a wide range of organs. These include solid and blood tumors (417), neurological disorders (e.g. schizophrenia, autism) (374, 468) and autoimmune diseases (e.g. rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis) (249). In both human prostate and testicular cancers, epigenetically-driven differential and specific expression patterns of the HERV-K (HML-2) loci were observed and associated with cancer establishment (152, 241, 242, 278, 610, 658). Nevertheless, formal proofs of ERVs implication in diseases causality are currently lacking.

1.2. Germ line integration of non-retroviral viruses

Additional endogenous viral elements that do not belong to the retrovirus family have been discovered in the genome of a variety of organisms (6, 292, 339). In vertebrates, a range of DNA viruses is involved, including Herpesviridae (in humans with HHV-6, and in prosimian Tarsier), Parvoviridae (in eutherians, marsupials and birds), Circoviridae (in eutherians, marsupials and amphibians), and Hepadnaviridae (in birds). Two families of RNA virus have also been endogenized: Bornaviridae (in mammals including humans, and in marsupials) and Filoviridae (in marsupials and several mammals, such as bats) (6). In fact, it is becoming increasingly clear that virtually any type of virus can be endogenized.

1.2.1. Mechanisms of integration

The mechanisms by which non-retroviral viruses integrated the germ line and became endogenous are not yet fully understood. Albeit less often than with retroviruses, some DNA viruses can undergo integration through homologous mechanisms (e.g. herpesviruses (480)) or non-homologous mechanisms (e.g. hepadnaviruses, adeno-associated viruses which are parvoviridae dependovirus (333)) of recombination. As for non-retroviral RNA viruses, these need to undergo processes that are unusual and do not normally occur in their life cycle, such as reverse transcription of viral RNA to DNA, entry into the nucleus and integration. The integration of DNA sequences complementary to non-retroviral RNA viruses into the DNA of *in vitro* infected mammalian cells has been reported (362, 772). Interestingly, in relation to the infection of human male germ cells with ZIKV (441, 581), an arbovirus of the Flaviviridae family, chromosome integration was reported for another arbovirus (Sindbis virus) (773) and for animal Flaviviridae HCV (636). The mechanisms for such integrations could involve endogenous reverse-transcriptase activity, revealing interaction between endogenous retroelements and exogenous RNA viruses (362).

1.2.2. Elements in favor of viral integration into male gametes

Epididymal spermatozoa may represent a preferential target for the transmission of non-retroviral viral sequences: Spadafora *et al.* demonstrated that mammalian spermatozoa can take up foreign DNA and RNA *in vitro*, transfer them into their nuclei and reverse-transcribe RNA into cDNA fragments, due to the endogenous reverse-transcriptase activity stored in sperm nucleus and encoded by LINE-1 retrotransposons (234). The capture of foreign nucleic acids is inhibited by seminal fluid and may therefore not happen in ejaculated spermatozoa. Endogenous RT expression, normally repressed in differentiated non-pathological tissues, is increased in germ cells and early embryos (615). Reverse-transcription and integration of poliovirus RNA into the sperm nucleus was demonstrated (234). The authors speculated that the viral cDNAs produced were amplified by a DNA-dependent RNA polymerase, released from the spermatozoa, and taken up again by further spermatozoa, thus spreading foreign nucleic acids among the sperm (653). In mouse models, foreign nucleic acids within spermatozoa nuclei were transmitted to oocytes as low-copy number, extrachromosomal sequences transcriptionally competent, and were mosaic propagated in tissues from the offspring, introducing new genetic traits in a non-Mendelian fashion (653). Alternatively, early embryos could support integration of viral cDNA sequences, leading to their endogenization. Interestingly, fragments of foreign DNA were integrated in the mouse sperm genome following recombination with chromosomal DNA at preferential sites (418, 783), suggesting another potential endogenization mechanism for non-retroviral viruses. However, a sperm endonuclease cleaves foreign DNA, and when potently activated degrades the host DNA, leading to cell death (420), probably controlling the integration processes.

Non-retroviral viruses endogenized in humans or with potential for germ line integration are presented in **Table 6**, along with demonstrated or putative effects.

2. Viruses as aggressors: deleterious effect of contemporary viruses on the MGT and offspring

Figure 9 details the negative effects on the MGT of a range of viruses.

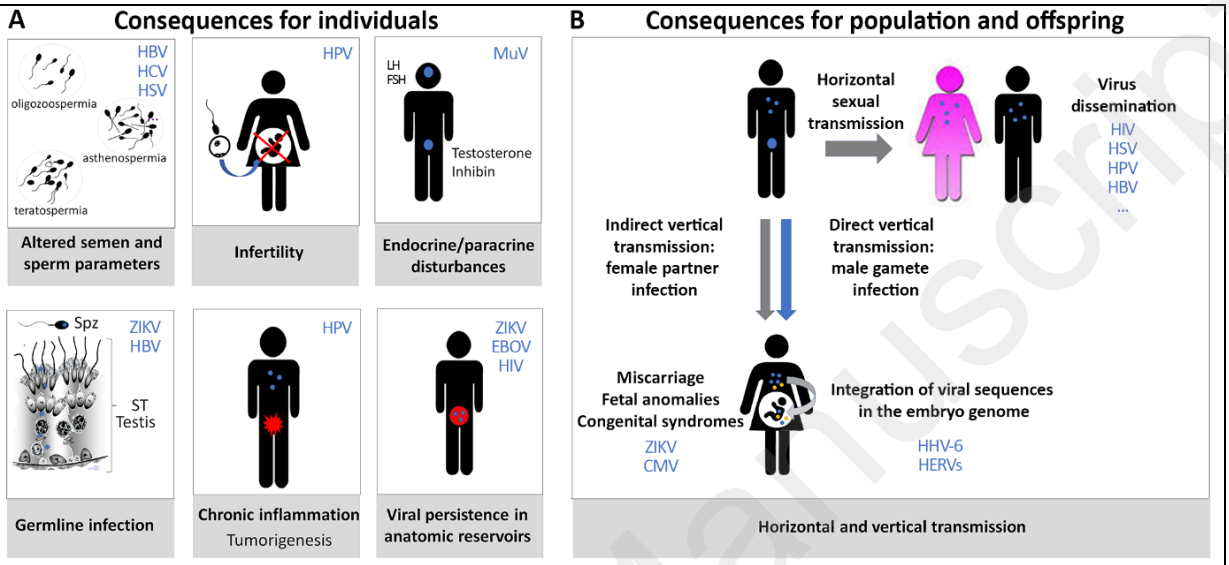


Figure 9: Deleterious consequences of viral infections of the human MGT at the individual (A) and population and offspring levels (B). Examples of viruses associated with these consequences are shown. **(A)** Viral infections of the MGT may have transient or prolonged negative effects on semen and sperm parameters, and induce infertility and endocrine disturbances linked to modifications of testicular hormone secretion. These alterations can derive from a direct or indirect effect of the infection on the testis (see Figure 10) or from the infection and inflammation of the accessory glands, leading to impaired sperm maturation, gametotoxic effect or ductal obstruction. Spermatozoa and their testicular germ cell progenitors can be targeted by viruses, thus presenting a risk for vertical transmission. Viral invasion of male genital organs also increases the risk of tumorigenesis (e.g. penile cancer) that might be initiated through complex virus-host interactions including inflammatory mechanisms. Viral etiology in prostate and testicular cancers, however, is currently unproven. The MGT can allow viral persistence and constitute a pharmacological sanctuary in patients under therapy. **(B)** The presence and persistence of virus in the MGT may lead to viral excretion in semen, contributing to horizontal viral dissemination and indirect vertical transmission, the latter potentially inducing congenital disorders such as miscarriage and fetal malformation (e.g. ZIKV, CMV). Direct infection of the embryo may derive from infected or virus-bound fertilizing spermatozoa. Successful germline infection with viral integration in our ancestors has led to viral sequence transmission through gametes and endogenization at the population level (e.g. HERVs, HHV-6). In the case of HHV-6, it is unclear whether this process is still ongoing. Damaging effects of viral infections on sperm and natural barriers protecting the oocytes might restrict such transmission, only reported *in vitro*. Acronyms of viruses are spelled out in table 1.

2.1. Viral infections and infertility

Male infertility currently affects 20 to 50% of couples seeking medical assistance for procreation, of which 6 to 15% are attributable to infections (185, 624). Infertility is defined as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (765). In addition to identified factors such as varicocele, cryptorchidism, endocrine and genetic disorders, male infertility is considered idiopathic (i.e. of unknown origin) in a large

number of cases. The chemical and biological environment that includes pathogen exposure is increasingly acknowledged as a putative cause of infertility (233, 616, 728). Following viral infection, sperm parameters (e.g. sperm count, motility, number of abnormal spermatozoa, etc.) and/or semen parameters (e.g. volume of seminal plasma, viscosity, pH, enzyme concentrations, etc.) can be transiently or, more rarely, permanently altered to various degrees (see below). In cases of severe defects, this may lead to infertility. While there is no established semen parameter cut-off to predict loss of fertility, apart from azoospermia (absence of spermatozoa in semen), infertility is commonly associated with sperm alterations such as oligozoospermia (low sperm count below 39.10^6 spermatozoa per ejaculation or concentration below 15.10^6 sperm per ml), asthenospermia (percentage of progressively motile sperm below 32%), or teratospermia (percentage of morphologically normal sperm below 4%) (387).
In the context of viral infections, alterations of sperm and semen parameters may result from distinct non-exclusive phenomena:

(i) **MGT tissue inflammation:** while defending against pathogens is critical for controlling invasion and preventing virus-induced damage, high levels of inflammation in the testis (orchitis), epididymis (epididymitis) and prostate (prostatitis) can be deleterious for reproductive functions (16, 185, 713). Orchitis is most commonly induced by a viral infection, and usually involves one testicle only (613). Histologically, orchitis is characterized by multi-focal immune cell infiltrates composed of granulocytes, macrophages and lymphocytes, localized in the interstitial tissue and inside the seminiferous tubules. Orchitis is associated with thickening of the lamina propria bordering the tubules (i.e. peritubular cells and extracellular matrix), and degeneration of the germinal epithelium (185). Dysregulation of the testicular cytokinetic microenvironment disrupts both steroidogenesis (271, 697, 752) and spermatogenesis (53, 325, 602, 681). For instance, during orchitis, infiltrating macrophages and mast cells produce TNFα that induces germ cell apoptosis (681), modifies peritubular cell secretions and induces fibrosis (442). Inflammation of the epididymis and prostate, more commonly induced by bacterial infections but potentially also by viral infections, can also alter sperm parameters or cause irreversible ductal obstruction and fibrotic tissue remodeling, and account for up to 12% of infertility cases (150, 185, 463, 713).

(ii) **Viral replication** within the cells and organs of the MGT may alter their function and integrity, through altered endocrine, paracrine or other biochemical secretions, breakage of the BTB (favoring the induction and leakage of sperm antibodies in the lumen of the MGT and germ cell infection), gametotoxic effect, sperm DNA damage, epigenetic modifications, etc.

(iii) **A systemic effect of the disease**. Febrile episodes in acute infections can alter fertility because the elevated testis temperature impairs spermatogenesis, a temperature of 34°C being necessary to preserve testis homeostasis. In chronic infections, increased levels of oxidative stress, to which spermatozoa are especially sensitive, may damage sperm function. Modifications of the release of the luteinizing hormone (LH) and folliculo-stimulating hormone (FSH) from the pituitary, which control Leydig cell and Sertoli cell endocrine functions respectively, can decrease sperm counts by affecting the secretion of testosterone and inhibin B, which are necessary for spermatogenesis.

The viral infections, classified as either acute or chronic, that have been associated with altered sperm/semen parameters or male infertility, and their postulated mechanisms of action are presented below and in **Figure 10**.

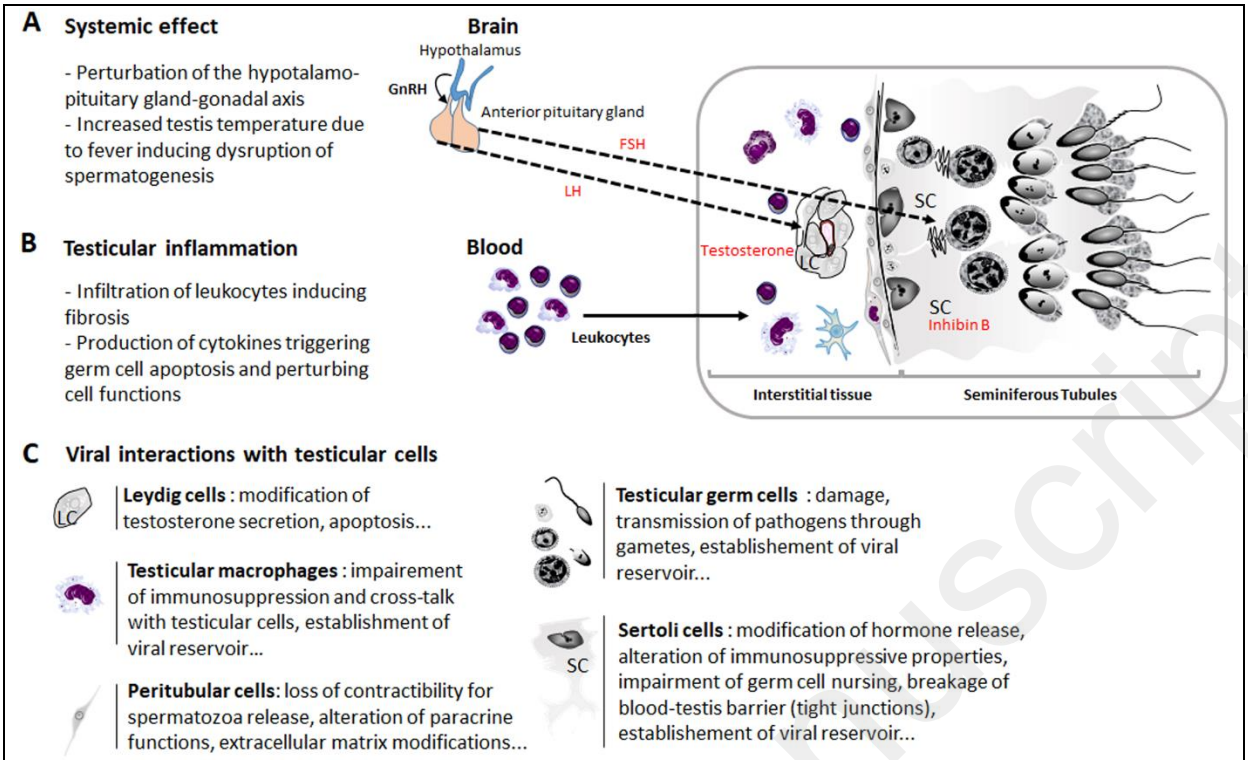


Figure 10: Mechanisms for testis function perturbation caused by viral infections. Viral infections may impact testicular endocrine and exocrine functions through several non-mutually-exclusive mechanisms: **(A)** Viral infections can indirectly perturb testis functions through a systemic effect on the hypothalamic-pituitary-testicular modifying testicular hormone production (e.g. HIV/AIDS) and through fever-induced elevation of testis temperature, which is deleterious for germ cell differentiation (e.g. influenza, chicken pox, pneumonia); **(B)** Testis inflammation (orchitis) can occur following a viral attack of the testis (e.g. MuV) or after systemic infection / generalized inflammation (e.g. influenza virus). This orchitis can transiently or permanently alter testis morphology and functions, leading to sterility if severe and bilateral; **(C)** Viral replication in testicular cell types can damage their function, impair immune-privilege and disrupt the complex inter-cellular and paracrine cross-talks required for steroidogenesis and spermatogenesis (e.g. MuV, MARV). Infection or viral attachment to germ cells and spermatozoa can also result in horizontal and vertical transmission (e.g. HBV, HIV, HPV). Furthermore, testicular cells may constitute a reservoir for viruses (e.g. ZIKV, EBOV and MARV).

2.1.1. Altered sperm parameters/infertility following acute viral infection

Mumps virus

MuV is a well-established etiological agent of orchitis, which occurs in about 10–20% of infected post-pubertal men (437). Consecutive testis atrophy happens in about 50% of these cases and can be associated with low sperm count (oligospermia) and hypofertility, while bilateral atrophy leading to sterility is rare (594). The histology of the testis following MuV infection has been described in detail (138). MuV was rescued from the testis of infected patients (59) but its testicular target cells and the mechanisms underlying germ cell degeneration remain elusive. MuV replicated in human Leydig cells *in vitro* and decreased their testosterone production (244), in line with decreased testoteronemia in patients (4, 7). In a mouse model, MuV also infected primary Leydig cells, as well as Sertoli cells and testicular macrophages, but did not target testicular germ cells (748). Several non-exclusive hypotheses could explain the MuV-induced impaired spermatogenesis in humans: (i) change in testis

temperature due to high fever; (ii) congestion of the seminiferous tubules caused by the interstitial edema (425); (iii) decreased testosterone production by infected Leydig cells (244); (iv) alteration of the paracrine control of spermatogenesis exerted by somatic cells (Sertoli cells, Leydig cells, testicular macrophages) as a result of their infection; (v) germ cell apoptosis triggered by CXCL10 production by infected Sertoli cells, as observed in the mouse (325).

Zika virus

ZIKV infection in men was associated with decreased sperm count and increased sperm abnormalities up to 90 days after the onset of symptoms, along with prolonged viral excretion in semen and the association of infectious viral particles with spermatozoa (307, 326). Relatively mild endocrine perturbations were observed in the early days post-symptoms onset (e.g. lower inhibin β concentration), without any significant modification of testosterone levels (326). The sperm parameters recovered after 4 months (326). Hematospermia (blood in semen, indicative of accessory gland infection/inflammation) and an increased leukocyte count occasionally occurred (307). These anomalies were observed irrespective of virus detection in the semen (307), suggesting either a systemic effect independent of MGT infection or persistence of the damage after viral clearance. We revealed that ZIKV efficiently replicates in human testis explants and targets a wide range of testicular cells including germ cells, which were found to be exfoliated in the semen from ZIKV-positive men (441). No cytopathic effect was observed and the general testis structure was preserved, including tight junction protein ZO-1 expression by Sertoli cells. Basal testosterone and inhibin B levels were unchanged by the infection. Altered sperm parameters could result from: (i) ZIKV replication in Sertoli cells, Leydig cells and testicular macrophages, altering the tight paracrine control of spermatogenesis and consequently the sperm count; (ii) ZIKV replication in peritubular cells, the contractile ability of which is essential for the release of spermatozoa in the testis lumen; (iii) ZIKV infection of immature germ cells, which consequently alters their differentiation; (iv) association of ZIKV with late germ cells/spermatozoa. Semen alterations in ZIKV-infected men could also result from infection of the epididymis/accessory glands or a systemic effect (e.g. fever). Immunodeficient mouse models (e.g. knockout mice for functional type I IFN receptor (IFNAR -/-) or treated with anti-type I IFN antibodies) were developed to study ZIKV infection (483, 657). Wild type mouse strains are normally resistant to the virus, the replication of which is efficiently inhibited by murine type I IFN, whereas in humans, type I IFN signalling is counteracted by ZIKV protein NS5, allowing viral replication. A high level of testis infection was described in mouse models (96, 110, 151, 247, 257, 410, 441, 702) leading to large inflammatory infiltrates and consequently testis atrophy, collapsed testicular hormone levels, breakdown of the BTB, germ cell degeneration and infertility. In addition to testis, high levels of ZIKV replication were consistently detected in mouse epididymis (96, 110, 151, 157, 247, 257, 410, 702), where the virus associated with epithelial cells and/or spermatozoa. Mouse prostate and seminal vesicle infection was not systematic (110, 157, 410, 445). In ZIKV-infected NHPs (287, 364, 390, 524), the virus was occasionnally detected in the testis after day 7-8 post-infection (364, 390, 524), without tissue alteration, and scarcely infected cells were observed in the prostate and seminal vesicles (524), along with low levels of viral RNA similar to other non MGT tissues (287). In 3/6 infected baboons, a marked transient decrease in total and motile sperm count was observed, but these differences did not reach significance (154). Overall, the drastic effect of ZIKV on the MGT in mice significantly differs from that in ZIKV-infected men and NHP, in whom orchitis has never been reported and modifications of sperm parameters appear milder and transient. Higher levels of viral replication and inflammation in immuno-deficient mice are probably responsible for this discrepancy.

Other viruses

A number of systemic acute infections with viruses never detected in semen or MGT organs trigger transient modifications of sperm parameters. Decreased sperm count, motility and altered morphology occurred 8 to 11 weeks after febrile episodes caused by influenza virus (619), chicken pox or pneumonia (415). Sperm DNA integrity was compromised after influenza virus infection (175, 619). In the absence of orchitis and viral material detection in the MGT, transiently altered sperm parameters could result from high fever-induced damage of spermatogenesis, similar to that evidenced after sauna exposure (76). Disturbances of the male endocrine system caused by modifications of the hypothalomo-pituitary-gonadic axis could also be involved.

2.1.2. Altered sperm parameters or infertility associated with chronic viral infections

Hepatitis viruses

A study using a large national insurance data set from the Taiwan health service (5,138 men with HBV versus 25,690 uninfected men) found a significant increase in the incidence of infertility associated with **chronic HBV** infection, after adjusting for a number of covariates (666). Because the majority of HBV infections in Taiwan occur during the neonatal period, the individuals studied had a longer exposure time to HBV than Western populations, who mostly acquire HBV during adulthood. However, several Western and Eastern studies have reported altered sperm parameters and a negative impact on fertilization in men chronically infected with HBV, including decreased sperm count and/or mobility, increased apoptosis, aneuploidy and/or number of abnormal spermatozoa (382, 402, 477, 516). Disease-induced oxidative stress, to which spermatozoa are especially sensitive, is evident in semen from HBV-infected individuals (562). *In vitro*, viral protein S was found to induce sperm mitochondrial dysfunction (331). HBV DNA integrated into the sperm chromosomes of patients (132, 269, 304) and induced chromosomic instability and DNA damage (304, 477).

Chronic infection with HCV has also been linked to modification of semen parameters. Lower sperm mobility and morphology as well as decreased serum levels of inhibin B and testosterone were described in several studies in HCV-infected versus uninfected men (161, 288, 402, 477, 571, 712), except one (213). Antiviral treatment with IFN and ribavirin improved the hormonal pattern but further degraded sperm quality (161, 288). Semen viremia did not correlate with altered semen parameters, suggesting that HCV does not exert a direct negative effect on sperm (67). HCV in the male partner had no negative impact on pregnancy outcome during assisted reproduction procedures (67, 757).

A strikingly high prevalence of HEV in semen from 185 infertile Chinese men was recently reported (28% vs 0.5% in general population) (303). Oligospermia and asthenospermia (i.e. > 65% of immobile spermatozoa) were observed in HEV+ men. Experimental HEV infection of rhesus macaques triggered leukocyte infiltration in the epididymis and testis, damage to the seminiferous tubules and decreased testosterone levels (303). This intriguing data demands further investigations.

Human immunodeficiency virus

In the late stage of HIV infection (AIDS), oligospermia or azoospermia have been frequently reported, together with orchitis and severely-damaged testis morphology with immune cell infiltration (138). Low testosterone levels (which contribute to cachexia) were encountered with AIDS, along with normal or elevated LH and FSH levels, implying primary testicular failure (135). Rather than HIV infection of testicular cells, the systemic debilitating effect of the disease together with generalized inflammation most probably accounts for the orchitis and hypogonadism in AIDS patients. Thus, although HIV-1/SIV infects testicular macrophages and T lymphocytes early on in the primary infection throughout the course of the disease (691),

testicular morphology was preserved in asymptomatic, chronically-infected patients (486), as well as in acutely or chronically-infected macaques (693). No inflammatory infiltrates or elevated cytokine levels were apparent in infected men or macaque testes at the asymptomatic chronic stage (486, 693), unlike in AIDS-deceased patients and macaques (465, 557). Testosterone-producing Leydig cells were not infected *in vivo* or *in vitro* (465, 486, 557, 590, 625, 693, 738). Lymphocytic infiltrations of the testis and interstitial fibrosis in AIDS patients were associated with a decrease in Leydig cell number, which might partly account for the decrease in testosterone (135). IL-1, a pro-inflammatory cytokine released by phagocytic cells, inhibited the human chorionic gonadotropin (hCG)-stimulated steroidogenesis in Leydig cells *in vitro* (83), adding another potential cause for testosterone decrease. The face of HIV disease has dramatically changed with the introduction of combined antiretroviral therapies. The efficient control of blood viral load achieved by lifelong antiretroviral treatments has massively improved the quality of life of infected individuals, allowing an almost normal life span. Most of the 37 million HIV-infected individuals are of reproductive age (745). In many developed countries, HIV-infected men with controlled viral loads have been offered medically-assisted reproduction to avoid transmission to the partner and embryo. Although still controverted (353) natural conception is now additionally proposed in some countries as a relatively safe/low risk alternative when specific conditions are met (e.g. undetectable viral loads in blood and semen for over 6 months) (708). Semen parameters in HIV+ men attending fertility clinics have been extensively studied. Overall, relatively mild alterations were reported, along with modifications to the sperm mitochondrial DNA (324, 691). These alterations, observed in asymptomatic men with controlled viral loads, are believed to occur as a secondary effect of antiretroviral molecules and not as a consequence of the infection itself. Many studies have pointed at a deleterious effect of antiretrovirals (194, 545, 691), and an eloquent demonstration was provided with the longitudinal follow-up of a cohort of men before and after treatment initiation, showing a degradation of sperm parameters during treatment (384).

Human papillomaviruses

HPV positivity in semen was recently associated with a two-fold increased risk of infertility in a meta-analysis of 31 studies comprising 2,122 men from the general population (HPV prevalence of 11.4%) and 3,072 men attending fertility clinics (HPV prevalence of 20.4%) (409). High-risk HPV16 was the most common type in semen in both populations, followed by high-risk HPV56. A previous meta-analysis reported a lower but still elevated HPV prevalence of 10% in the general population versus 16% in men seeking fertility treatment (379). HPV in semen has been associated with decreased sperm motility in some studies (total of 1944 participants), but not in others (total of 1143 participants) (191, 408), and with the presence of anti-sperm antibodies, which may interfere with sperm motility and oocyte binding (211). In addition to its presence in exfoliated epithelial cells in semen, HPV genome was detected on the sperm surface in infertile patients (191). An *in vitro* study described increased DNA fragmentation in sperm transfected with HPV DNA, but these findings were not substantiated in studies on semen from HPV-positive versus HPV-negative fertile patients (118, 335). Lately, HPV vaccination in men with HPV in semen has reduced virus prevalence, improved sperm motility and decreased anti-sperm antibodies, probably through immunity stimulation, while improving pregnancy and live birth rate (190, 212).

Herpes viruses

HSV-2 has been long suspected of being involved in infertility (135) but proofs are still lacking. Several studies across the globe have reported a correlation between HSV-1 and -2 in semen and altered sperm and semen parameters, including low sperm count and motility, as well as reduced seminal volume and concentrations of epididymal (neutral a-glucosidase) and prostatic

(citrate) molecules (53, 334, 373, 471). Together with hematospermia, these biochemical modifications suggest an impact of HSV infection on the epididymis and accessory glands physiology (53, 373). Two studies failed to substantiate the effect of HSV infection on sperm parameters, but their conclusions could have been impaired by the very low number of HSV+ patients tested (n=4) (54, 503) and by assessment of HSV infection through antibodies rather than virus detection (478). HSV-2 bound to human ejaculated sperm *in vitro* and slightly decreased their motility, but HSV-2 binding was impaired by seminal plasma (529). HSV-1 and -2 DNA were reported in spermatogenetic cells from men and guinea pigs using *in situ* hybridization (256, 370). Since all of these studies only investigated infertile men or men seeking fertility evaluation, it would be important to compare the prevalence of HSV-1 and HSV-2 in semen from fertile versus infertile men in large cohorts with similar age, race, geographical and socio-economic criteria (case-control study) to confront the conflicting data on the potential involvement of HSV in male infertility.
The impact of other *Herpesviridae* (CMV, HHV-6 and EBV) on sperm or semen parameters has been investigated and no significant or consistent association has been demonstrated (54, 163, 334, 499, 500, 503, 758).

2.2. Viral infections and cancers of the MGT

Viruses can initiate or favor carcinogenesis through complex interplay with the host genetics, immunity and inflammation (461), and 7 viruses are well recognized as having a transforming or tumorigenic activity in humans (EBV, KSHV, HPV, HBV, HCV, HTLV and Merkel cells polyoma virus or MCPyV) (60).

2.2.1. Penile cancer

Penile cancer accounts for 0.5% of all cancers in men and generally develops after the age of 60, with incidence estimated to be between 0.2 and 2.2 in 100,000 per year (352). High-risk HPVs, mainly HPV-16 followed by HPV-18 and HPV-45, are established risk factors in squamous cell carcinoma of the penis (284).

2.2.2. Prostate cancer

Prostate cancer is the most commonly diagnosed cancer in men worldwide (1.4 million cases in 2016) and the fifth most common cause of cancer death (240). Established risk factors for all prostate cancers include age, race/ethnicity, family history and genetic variants, while lifestyle may influence cancer aggressiveness (540). Chronic prostate inflammation (that could be induced by a viral infection) is thought to increase the risk of prostate cancer (436), and a link between prostate cancer, sexual activity and sexually-transmitted infection was reported in some studies (306). However, despite years of investigations on HPV (3, 35, 301, 675, 756, 760), KSHV, EBV, BK virus, CMV (3, 301), and the "rumor" virus Xenotropic murine leukemia related virus (XMRV) (531) through serology testing or prostate tissue analysis by PCR, in situ hybridization or immunohistochemistry, there is no compelling evidence for a viral etiology of prostate cancer. Nevertheless, a few studies suggested that KSHV and HPV may represent a risk factor for prostate cancer aggressiveness (239, 494, 756). A recent metagenomics study highlighted two viruses not investigated so far, MCV and JC polyomavirus (JCPyV), in a small number of prostate cancer cases (642).

2.2.3. Testis cancer

Testicular cancer generally affects men between the ages of 15 and 35 and accounts for approximatively 1% of male cancers (561). Testicular cancer is considered to primarily stems from developmental abnormalities during fetal life (641), with exposure to various factors

during adolescence and adulthood potentially promoting its development (446). While there is presently no convincing evidence to support an association of any of the viruses tested (EBV, HPV, CMV, parvovirus B19, HIV) with testicular cancer (284, 762), a significant link between testicular cancer and a history of epididymo-orchitis was recently evidenced (332). This finding is in support of a role for pathogen-induced inflammation.

2.3. Vertical transmission of viruses

Viruses present in semen may indirectly contaminate the offspring by infecting the female partner during conception and pregnancy, or be directly transmitted to the oocyte and embryos, for instance through infected spermatozoon.

2.3.1. Indirect transmission through semen

Among the pathogens that induce congenital disorders at various time points during pregnancy (originally grouped under the acronym TORCH for Toxoplasma, Others, Rubella, CMV and HSV, with an expanding list of "others") (97, 121, 283) are a number of viruses present in semen (HSV, CMV, ZIKV, parvovirus B19), all sexually transmissible to women, except parvovirus B19. Other viruses transmissible to women through semen, such as HIV and HBV, are vertically transmitted without inducing congenital defects. *In utero* infection by HBV represents a predisposition to chronicity, possibly due to fetal immune tolerance to foreign antigens (51, 296, 470). Interestingly however, HBV infection during fetal life enhances the ability of the newborn immune cells to respond to unrelated pathogen exposure through a "trained immunity" process (296, 515). A high viral load in the mother is a significant risk factor for vertical transmission (635), which may result, among other routes of infection, from exposure of the mother to infected semen, followed by hematogenous spread and transplacental infection. Importantly, enhanced *in utero* transmission of ZIKV was observed in a mouse model following exposure to infected semen when compared with subcutaneous infection mimicking mosquitoes bite or with intra-vaginal inoculation (156). Sexual transmission increased ZIKV dissemination in the female genital tract and led to ovary infection. Surprisingly, intra-vaginal inoculation of ZIKV did not enhance fetus infection as sexual transmission did, which might be due to differences in virus dose, post-coitum semen deposition directly into the uterus in mice, or semen-induced inflammation in the female tract. Thus, in addition to transplacental hematogenous spread, ascending viral infection of the female tract following semen deposition might constitute a particularly efficient vertical transmission route that deserves further investigation.

2.3.2. Direct transmission through sperm

Viruses that infect or associate with spermatozoa [e.g. HBV (132, 269, 304), ZIKV (326, 427), HPV (191), HSV (370, 529), HIV (298), CMV (499)] have the potential to be transferred to the embryo upon fertilization. While there is no direct evidence of sperm-mediated vertical transmission of non-endogenous viruses in humans, human spermatozoa naturally or experimentally infected with HIV, HBV and HPV transmitted these viruses to hamster zona-free oocytes and early embryo following *in vitro* fertilization (11, 192, 722). However, HBV DNA integration into the sperm genome of patients triggered chromosome instability and DNA damage (304, 477). Spermatozoa transfected with HBV were prone to apoptosis and had reduced fertilization capacity when using human oocytes (305). HIV became attached to ejaculated spermatozoa *in vitro*, essentially through HSPGs (heparan sulfate proteoglycans), but could not enter these cells (88, 691). HIV virions bound to the surface of the sperm therefore have to cross the barriers of the zona pellucida and the membrane of the oocytes during natural

conception. A meta-analysis covering 11,585 cycles of assisted reproduction among 3,994 women with HIV+ partners showed that sperm-mediated HIV transmission never occurred following sperm washing (763). Although HIV DNA was detected in patients' sperm chromosomes (722), and the data from our laboratory suggests that HIV can enter and integrate into the genome of testicular germ cell *in vitro*, this event is rare, making successful vertical transmission a very low probability. HPV binds to sperm head in patients, using HSPGs as an attachment receptor, as with HIV-1 and HSV (191, 192). Based on *in vitro* experiments and reports in HPV+ patients, it has been postulated that HPV carried by spermatozoa can be transferred to fertilized oocytes and impair embryo development into blastocysts, and the invasiveness of trophoblast cells (191, 209, 539). HPV detection on spermatozoa was predictive of negative pregnancy outcome, whereas in infertile couples, HPV vaccination of the male partners with HPV in their semen significantly improved the pregnancy and live birth rate compared to the non-vaccinated group (212). Further studies on the consequences of sperm washing and removal of HPV-bound spermatozoa on assisted reproduction outcome in large cohorts of infertile couples with HPV+ men are warranted, to substantiate the negative impact of HPV+ spermatozoa on reproduction.
The vertical transmission of teratogenic ZIKV by spermatozoa is a possibility that merits investigation since infectious virus and viral proteins were detected in motile spermatozoa (326, 427). In a mouse model, experimental infection of ova with teratogenic CMV used to mimic sperm-mediated infection led to fetal anomalies upon transfer to surrogate mothers (44). HHV-6 specifically integrates into telomere regions of human chromosomes, establishing life-long latency. HHV-6 is endogenous in approximately 1% of the human population and vertical transmission of chromosomally integrated HHV-6 from either the father's spermatozoa or from the mother has been demonstrated (26, 130, 273, 479, 672, 725), leading to virus integration in every cell of the offspring (273, 725). For at least one subset of individuals with chromosomally integrated HHV-6, endogenization was estimated to have occurred 14 000- 35 000 years ago (769). Whether HHV-6 invasion of the male gametes continues to happen in present times, and the impact of such integration, is currently unknown.

Significantly, medically-assisted procedures such as intra-cytoplasmic sperm injection (ICSI) and in vitro fertilization (IVF), which overcome physiological barriers, can be at increased risk of virus transfer from infected sperm/testicular germ cells to the oocyte if infected gametes remain. The zona pellucida which surrounds the oocyte, and the oocyte membrane, although not impermeable, constitute natural barriers against viruses bound to the surface of spermatozoa that are bypassed during ICSI. The whole sperm/testicular germ cell, including its cell membrane, is injected into the oocyte cytoplasm, instead of the physiological requirement for zona pellucida crossing and cell membrane fusion between the male and female gametes. Also, the motility and fertilization ability of spermatozoa can be impaired by the infection (see paragraph on infertility), which represent another natural protection against viral contamination during fertilization that is broken by IVF and ICSI.

Finally, male gametes have the ability to take up foreign DNA and might therefore pass on viral gene fragments to the offspring. This property led to the development of many studies aiming to make transgenic animals using "transgenic spermatozoa" as vectors. However, the results have proven disappointing overall, essentially since most foreign DNA remains extra-chromosomal, leading to mosaicism in the offspring (89).

3. Viruses as invaders: persistence of emerging and contemporary viruses in the MGT

Zika virus

During the major 2015-2016 ZIKV outbreak in the Americas, high viral loads and prolonged shedding of ZIKV RNA (up to 1 year) and infectious particles in semen (up to 69 days) from infected men, despite viral clearance in the blood, supported the existence of ZIKV reservoirs within the MGT (43, 169, 452). Worryingly, seminal shedding, persistence and sexual transmission (the latter up to 41 days post symptoms) occurred even in asymptomatic patients (169).

The deleterious impact of the infection reported on sperm parameters, along with the association of ZIKV with ejaculated spermatozoa and exfoliated testicular germ cells, suggested infection of the testis and epididymis (307, 326, 427, 441). In human testis tissue infected *ex vivo*, ZIKV replicated in a wide range of testicular somatic cells: resident macrophages, peritubular cells and to a lesser extent Leydig cells and Sertoli cells, as well as immature and mature germ cells (441). Infection of the testis tissue did not trigger cytopathic effect or IFN up-regulation (needed to sustain an efficient antiviral defense), and induced only minimal pro-inflammatory cytokine stimulation, similar to the persistently-infected cerebrospinal fluid of Indian macaques (5). IFNs play a key role in inhibiting ZIKV replication and its production in humans is counteracted by the virus. However, the lack of IFN up-regulation following viral exposure could be a feature of the human testis that is not specific to ZIKV ((692) and unpublished data). Altogether, the survival of infected cells and weak innate immune response may represent favorable conditions for ZIKV persistence in the human testis (441). ZIKV infection persisted for up to 6 weeks in a human Sertoli cell line, leading to a relatively muted innate response (665). In immuno-competent mice, ZIKV preferentially infected testicular germ cells over somatic cells, and persisted in the testis for up to 60 days (581). Rodent meiotic and post-meiotic germ cells are known to have impaired IFN signalling (136, 602), increasing their susceptibility to ZIKV infection compared to other testicular cell types (581). ZIKV replication did not affect mouse germ cell survival or proliferation (581). In mice with deficient IFN signalling (e.g. IFNAR$^{-/-}$), a broader range of testicular cells was targeted by ZIKV as with human testis (441), and a high level of ZIKV was detected up to 42 days p.i. in both testis and epididymis (96, 247, 410, 696, 702). In IFNAR-/- mouse epididymis, the virus was associated with luminal sperm, macrophages and epithelial cells (696). In NHP, multiple anatomic sanctuaries of ZIKV were identified, including the central nervous system, lymph nodes and, at relatively low levels with inter-individual variations, testis, prostate and seminal vesicles (5, 287, 524, 657).

Vasectomy in mice and men significantly lowers ZIKV viremia in semen, which indicates that testis/epididymis are important viral sources (157, 452). However, vasectomy does not abrogate sexual transmission despite viral clearance in blood (30, 157). It is noteworthy that the longest duration of infectious ZIKV in semen (69 days) was observed in a vasectomized man, and that ZIKV RNA persisted in semen from vasectomized individuals up to 281 days post symptoms (30, 195, 307, 452). While divergent results were obtained regarding prostate and seminal vesicle infection in either immune-deficient mice or NHP (657), it is evident that MGT reservoirs other than testis and epididymis exist in ZIKV-infected men. How and which MGT organs other than testis can shelter ZIKV from immune clearance warrants investigation pertaining to the immune status of these organs and to the nature of the reservoir cell types.

Other arboviruses

Case reports of excretion in semen after systemic clearance of yellow fever virus (YFV) (40), dengue virus (DENV) (377) and Chikungunya virus (CHIKV) RNAs (38) for up to 19 days, 37 days and 30 days post-symptom onset respectively suggest that several arboviruses may persist in the MGT **(Table 7)**. Furthermore, WNV was recently suspected to be sexually transmitted 30 days post-symptoms onset (348), along with sexual transmission of DENV between 2 men (391). This concern is further substantiated by the persistence of arboviruses (e.g. Japanese encephalitis virus, JEV) in animal semen and MGT organs (see part VII). There is currently no

data on human MGT organs infection for these viruses. In mouse models, DENV did not productively infect testicular cells (247, 410, 581, 627). In contrast, YFV productively infected a human Sertoli cell line (634). The duration of viral excretion following peripheral clearance and the demonstration of infectious virus in semen are still to be explored in human cohorts to determine whether the MGT is a reservoir for these arboviruses.

Ebola and Marburg viruses

The ability of filoviruses to persist for extended periods in the MGT was reported in the late 1960s for the first human cases of EBOV and MARV infection (167, 434), but the issue only came to light properly during the major 2014-2016 West Africa outbreak of EBOV (28,000 cases and 17,000 survivors). EBOV RNA was found in the semen of survivors for as much as a remarkable 1,178 days (261), and proven sexual transmission from male survivors to female partners up to 470 days after disease offset (609). Alarmingly, persistent infection of the MGT by EBOV is asymptomatic. Sexual transmission cases from survivors distant from the epidemic contributed to its resurgence through the initiation of new transmission chains (609). Fortunately, as for ZIKV, filovirus persistence in MGT is not lifelong and steadily declines over time until the virus eventually disappears, in most cases within months (WHO currently recommends a nine-month abstinence in male EBOV survivors), but years for a subset of individuals (609). In a study on 267 Ebola survivors, a positive association between the presence of uveitis, an inflammation of the eye, and detection of viral RNA in semen samples was found. Since uveitis was associated with higher viral load during the acute stage of the disease, this may suggest that high viral load at the onset of the infection is associated with seeding of the MGT and in turn prolonged excretion in semen (646).

Higher seminal viremia during recovery, compared to blood viremia at peak illness, suggested persistent active replication of EBOV within the MGT. This was further demonstrated through the detection of positive sense RNA (i.e. non genomic, replicative form) in semen (41, 730). The low rate of change or absence of change in EBOV genome in longitudinal semen samples (41, 640, 730) suggests reduced immune pressure compatible with infection of immune-privileged sites (NB: similar low rates were found in the eye, another immune-privileged site of persistence) (730).

The nature of the reservoir(s) in the MGT which seed EBOV into semen is currently unknown. EBOV antigens were present in the testicular interstitium (including endothelial cells) and seminiferous tubules (suggestive of Sertoli and germ cell infection) from a fatal human case, with no histological lesions or inflammation (430). In acutely infected Rhesus and Cynomolgus macaques, EBOV was localized in the vascular structures, endothelial cells and mesenchymal cells within the interstitial tissue of the testis, epididymis, prostate and seminal vesicles, with no changes in organ morphology (541, 766). In a subset of animals with delayed time of death, EBOV infected the seminiferous tubules, with a staining suggestive of Sertoli cell infection (766). In one NHP survivor, EBOV was associated with macrophages in the lumen of the inflammatory epididymis (766). EBOV was not detected in the testis but animals were sexually immature (spermatogenesis had not started), which may have impacted EBOV tropism in the MGT. EBOV persisted in the testis of humanized mice that survived the infection (57), and infected the testicular interstitium of experimentally infected guinea pigs (113). In addition, EBOV infected clusters of epithelial cells as well as stromal macrophages and fibroblasts in the penis and foreskin of acutely infected guinea pigs (116). In semen, EBOV RNA and infectious particles were rescued from seminal plasma in several studies (609). To the best of our knowledge, there has been no attempt to identify EBOV infected cell types in semen. This information might help to shed light on the origin of persistent EBOV in semen.

MARV was the first filovirus reported to be sexually transmitted. In 1967, a man with MARV antigens in semen cells contaminated his wife during sexual intercourse two months after recovering (434). Infectious MARV has been rescued from semen up to 84 days post-recovery (434, 509, 643). In contrast to EBOV, MARV induced testicular inflammation in infected individuals, as evidenced at autopsy and through reports of orchitis, testicular pain and swelling up to 52 days post-infection (609). In acutely-infected NHP, MARV was localized in the testis interstitium and endothelial cells, as well as in the epididymal smooth muscle cells and prostate stroma (117). In the testis of NHPs that survived MARV, inflammatory infiltrates were localized specifically in infected areas within the interstitium and seminiferous tubules, and were associated with BTB disruption and focal germ cell depletion (111). Overall sperm production was not affected. Similar to observations in mice infected with ZIKV (441, 696), MARV arising from testis blood vessels first infected interstitial Leydig cells and peritubular cells, and in a second phase persistently infected seminiferous tubules. Sertoli cells supported active viral replication and were the main viral reservoir within the testis, with only low numbers of germ cells and macrophages infected. Focal testicular immune infiltrates were composed of T and B lymphocytes, macrophages and neutrophils. T cells were essentially CD4+ (T helper -1,- 2, -17 and Tregs) with a few CD8+ cells. Interestingly, the presence of Tregs was specifically associated with persistence, along with a high TGFβ concentration and Cytotoxic T-lymphocyte-associated protein 4 (CTLA4) expression, suggesting localized immunosuppression, which may delay clearance of MARV in the testis (111). Infectious viral particles released by productively-infected Sertoli cells in the seminiferous tubule lumen could be a source of MARV in semen. MARV tropism for human Sertoli cells now needs to be established.

Human immunodeficiency virus

The persistence of HIV-1 RNA and DNA was reported in the semen of a subset of HIV-infected men receiving efficient antiretroviral therapy (ART), despite undetectable blood viral loads for several years (298). In experimentally-infected macaques with controlled blood viremia below 100 copies/ml during ART, SIV persisted in semen from a subset of animals after 4 months of treatment (440). HIV-1 and SIV infect a broad range of MGT organs and ducts (testis, efferent ducts, epididymis, vas deferens, prostate, seminal vesicles, urethra, foreskin and glans), as shown at autopsy from men deceased during AIDS (511, 557) or in the chronic asymptomatic stage (200, 322, 486), in experimentally infected NHPs during the acute (474, 693), chronic (299, 440, 625, 693) or AIDS stage (465), and using ex vivo-infected human MGT tissue (141, 201, 590, 694). Throughout the MGT, infected cells are composed of tissue-resident macrophages and/or CD4+T lymphocytes (298). In the testis, HIV/SIV was associated with isolated germ cells in a few studies (486, 511, 625, 693), with no spermatogenesis disruption. In SIV-infected macaques, the urethra was the most highly-infected MGT organ and the testis was the least infected, which could reflect a much higher number of immune target cells in the urethra than the testis (440). While the local sources of HIV in semen remain elusive (298), a recent study by our laboratory in the SIV-infected macaque model demonstrated that multiple MGT organs shed virus particles and infected cells in semen, as identified through phylogenetic analysis (299). Surprisingly, viral excretion from distinct organs was independent from inflammation and organ infection level, and varied among individuals (299).

Only a few studies attempted to decipher the organ reservoirs for HIV/SIV in the MGT of treated individuals. Our laboratory first revealed in SIV-infected macaques under ART for 4 months the persistence of SIV RNA+ macrophages in the urethra, whereas productively infected cells were no longer detectable in other MGT organs (440). In agreement, in HIV-infected individuals under suppressive ART for years, urethral macrophages localized in the stroma and epithelium harboured integrated replication-competent virus. Virus production

could be reactivated by bacterial lipopolysaccharide LPS, albeit at a low level.Virions were contained within intracellular compartments called VCC (Virus Containing Compartments) (200). VCCs were previously evidenced in blood-derived macrophages, allowing viruses to retain their infectivity for extended periods of time (582). Infected urethral macrophages had an intermediate M1-M2 polarized macrophage phenotype, which was enriched in HIV-infected men. The authors postulated that the high urethral concentrations of IFNγ could inhibit the killing ability of the cytotoxic T lymphocytes found associated with the infected macrophages (200). Although the urethra represents a reservoir for HIV, persistent HIV excretion in semen appears to involve different MGT: thus in 10 treated HIV-infected men with persistent HIV in the semen, no virus was detected in the pre-ejaculatory fluid produced in the urethra (547). Multiple MGT organs could act as reservoirs. Indeed, we showed in macaques that received 4 months of ART that SIV DNA levels in testis, epididymis, vas deferens, seminal vesicles and prostate were similar to those of untreated animals (440). Similarly, HIV DNA+ cells persisted in the testis from treated men (322), suggesting the persistence of latently-infected cells and the potential for reactivation. The organs excreting the virus in semen probably vary between individuals, as we demonstrated in macaques (299). Specific tissue micro-environments may play determining roles in the reactivation of latently-infected cells and in infection susceptibility of long-lived/drug resistant cells, such as the highly plastic tissue macrophages.

Human papillomaviruses

In men, most genital HPV infections are subclinical and clear within 1-2 years post-infection (236). HPV persistence in the penis and urethra has been investigated (85, 375), but results were complicated by the fact that the sexual partners of the male participants were also HPV positive, and therefore persistence could not be discriminated from new infection. In one study on elderly men who no longer had sexual intercourse, the same HPV subtype was estimated to persist in the skin of the glans penis for an average of 8 years in the absence of any new source of infection (359). Higher loads of HPV in penile samples conferred a greater probability of viral persistence of up to 12 months but not more, suggesting other factors as yet unidentified for long-term persistence in the MGT (398).

Herpes Simplex Virus type 2

An early study suggested that the MGT serves as a silent reservoir for HSV-2, based on the high incidence of actively replicating virus in the vas deferens and prostate from men of different age groups (up to 70+), in the absence of any history of genital herpes together with low frequency of detection in the urethra (93). HSV-2 infects genital epithelial cells during primary infection and spreads to the sensory neurons, where it establishes latency (363). HSV-2 reactivation is accompanied by an influx of both $CD4^+$ and $CD8^+$ T cells and is normally contained within days (608). High numbers of Tregs in HSV-2 reactivation areas was correlated with increased viral replication (466). It would therefore be interesting to investigate whether actively replicating HSV-2 in MGT organs is associated with elevated Treg numbers which impairs immune control, as postulated for MARV infection in the testis (111).

VI. Semen, a Trojan horse for the sexual transmission of viruses

Over 30 viruses were found in human semen, of which 15 are associated with sexual transmission **(Table 7)**. On top of well-known sexually transmitted viruses such as genital herpes viruses and blood-borne HIV, new additions include vector-borne ZIKV and blood-borne EBOV, which were shown to persist in semen for an extended period after blood clearance. Out of 16 case reports of various viruses in semen, 7 were reported as persistent **(Table 7).**

1. Prevalence and pattern of virus shedding in semen

The prevalence, level and duration of shedding in semen vary widely for different viruses and significantly impact the dynamics of an epidemic. During early infection associated with high viremia, there is frequent seminal shedding of HIV, HBV, HCV, ZIKV and EBOV, ranging from 29% to 100% **(Table 7).** Similar shedding frequencies are observed in the chronic stages of HIV, HBV and HCV despite the lower viremia **(Table 7)**. HIV load in semen is usually lower than in blood, but patients with an exceptionally high semen viral load were reported (533, 671, 741). Factors associated with HIV shedding prevalence in semen are blood viral load (104, 176, 267, 313, 329), STIs (329, 548), seminal CMV or EBV (226, 227, 229, 394, 482, 523, 628) and seminal cytokine levels (394, 395, 523, 548); the two latter reflecting elevated inflammation, which enhances HIV replication.

In most studies, HCV load in semen is positively correlated to viremia (71, 73, 700) and a higher prevalence of HCV shedding in semen from HIV-infected patients is controverted (71, 73). However, Turner et al. only observed a correlation between blood and semen HCV loads during the acute stage, suggesting that other factors such as concomitant shedding of human herpesviruses (HHVs) could affect HCV shedding (700).

Persistent seminal shedding designates the long-lasting excretion in semen of viruses that have been controlled or cleared in the periphery by antiviral treatments (e.g. HIV, HBV) or by the immune system (e.g. ZIKV, EBOV). It implies an undetectable viremia and strongly suggests that seminal viruses and infected cells originate from the MGT (see part V.C. on viral reservoirs and below). In HIV-infected patients, the virus level in semen is usually severely decreased in the first weeks following the start of antiretroviral treatment (313). However, HIV RNA persists in semen for months or years post-treatment initiation in about 13.4% (range 1.8% to 48%) of patients, despite undetectable viremia (223, 229, 298, 533). In contrast, there are no cases of HCV persistence in semen following treatment, and only two controverted cases of HBV persistence in semen in the absence of viral DNA in serum (177, 310, 351).

Viral RNA was detected in semen from ZIKV and EBOV-infected patients until day 370 and day 1178 respectively, after symptom offset **(Table 7)**. In about 50% of EBOV patients, the virus disappeared from the semen between 3 and 6 months post-infection (133, 640, 649) and in all studies, the EBOV titer in semen steadily decreased over time (41, 640, 649, 704). Nevertheless, 8% of a cohort of 137 EBOV patients still shed virus in semen two years after the disease (187), with older age associated with seminal shedding (187, 261, 649). For ZIKV, the mean clearance time in semen was 25 - 83 days, as opposed to 5 - 15 days in blood (43, 189, 307, 452, 536). Age, absence of ejaculation, conjunctivitis and joint pain were factors associated with prolonged virus shedding (452). Why older age would influence seminal shedding duration is unknown. Reduced immune functions, endocrine or anatomic (e.g. prostate hyperplasia) modifications might be involved.

HPV is responsible for genital infections that usually clear within 2 years. In line with this, the median duration of HPV detection in semen samples was 15.3 months (85). HHVs establish lifelong infection and are characterized by a high worldwide prevalence, ranging between 20% and 100% for all HHVs except KSHV. All HHVs were reported as being present in semen at least once **(Table 7)**. The reported prevalence of 37.3% for all HHVs in the semen of healthy patients (482) increased to 59%-92% in HIV-infected patients (225, 227, 394, 482). Considerable variations in semen prevalence exist between the herpes viruses, but also across studies, depending on geographic location, detection method and type of cohort - mostly HIV-infected and uninfected patients or fertility-clinic attendants (336). Overall, the semen prevalence of HHVs in HIV-negative men is under 15%, while HIV infection most dramatically increases CMV and EBV seminal shedding **(Table 7)** (203, 224, 628, 225–227, 229, 230, 394, 482, 523).

Longitudinal studies reported a mix of intermittent and continuous shedding patterns for HIV and HHV during the early and chronic stages of the disease **(Table 7)**. The link between virus shedding and other STIs, herpes/HIV co-shedding and seminal cytokine levels suggests that local factors related to transient infection/re-activation of virus sources could be involved in this intermittent process. However, during undetectable blood viremia in ART-treated patients, the HIV shedding pattern was intermittent, with intervals as little as one hour between positive and negative samples (181). Such short intervals suggest that intermittence may also reflect the natural variation of semen composition between ejaculates (422). Unlike HIV and HHVs, the shedding pattern during the persistent stage of EBOV and ZIKV is generally continuous (Table 7), with occasional intermittent detection most likely due to the assay sensitivity threshold (187). This suggests that the main factor driving the shedding pattern is poor efficiency of the local immune system to control ZIKV replication in the MGT. This is supported by the detection of pro-inflammatory cytokines together with infectious virus in seminal fluid long after viral clearance from serum (426, 519).

2. Where do virions and infected cells in semen originate from?

Systemic viruses that contaminate semen during the acute infection/high blood viremia stage most likely arise from the passive diffusion of viral particles and infected cells from the blood. In favor of this hypothesis are concomitant high blood and semen viremia in acute HIV infection, together with similarities in nucleic acid sequences of the blood and seminal HIV and SIV strains (298). In contrast, several studies reported an absence of association between semen and blood viral loads during the chronic stage of HIV infection (298). Phylogenetic studies comparing viral populations in blood and semen showed differences in over 50% of HIV-infected patients and SIV-infected macaques (298), suggesting a local origin within the MGT. This was recently demonstrated by Houzet et al. who showed, based on the phylogenetic comparison of viral strains in blood and semen fluids and cells with that in male genital organs from macaques chronically infected with SIV, that seminal virus and infected cells originated from various genital organs such as the seminal vesicles, vas deferens and epididymis (299). Regarding genital HPV, the excretion of virus in semen was associated with penis epithelium infection, probably reflecting the exfoliation of infected epithelial cells (407).
The absence of viremia during the persistent seminal shedding of HIV, ZIKV and EBOV strongly suggests a local origin at this stage per se. The presence of infected testicular germ cells and spermatozoa in the semen of ZIKV-infected patients points at the testis and/or epididymis as the sources of infected cells (326, 427, 441). Nevertheless, the persistence of ZIKV RNA and infectious viral particles in the semen of vasectomized patients indicate that distal MGT organs (e.g. prostate, seminal vesicles and urethra) constitute additional viral sources (30, 195, 307, 452).

3. Importance of semen contamination for virus dissemination

Fifteen out of the over 30 viruses detected in semen are sexually transmitted **(Table 7)**, including HIV, HSV-2, HPV and HBV, which are responsible for four major sexually transmitted diseases. Sexual transmission is also an important mode of transmission for HTLV-1 in endemic areas (526). Semen is a key vector of transmission for HIV-1, HSV-2 and HTLV-1, with more efficient men-to-women transmission than women-to-men (526, 744). While the sexual transmission of HCV has long been considered negligible, seminal HCV is now thought to play a significant role in HCV spreading in MSM (700). For viruses like EBOV and ZIKV, sexual transmission is a minor mode in endemic countries compared to other modes (i.e. other body fluids, fomites and mosquitoes). However, recent work reported transmission via semen

as the source of multiple flare-ups during the last EBOV outbreak (62, 144), and mathematical models integrating the sexual transmission mode demonstrate a significant impact on epidemic dynamics (2, 406, 714). Similarly, computational models show that sexual transmission of ZIKV might be underestimated (14) and could impact on the size of the epidemic and length of the outbreak (204). Recently, the analysis of risk factors in 336 household contacts of ZIKV patients showed an increased risk for sexual partners in an endemic context (587). For both EBOV and ZIKV, long-lasting virus in semen represented the main issue regarding sexual transmission. Vertical transmission of viruses such as ZIKV through semen, as demonstrated in mice (156), is another important issue to consider.

Accumulating case reports demonstrate that a number of (re)emerging viruses can infect semen (e.g. NiV, YFV, DENV, CHIK), some for extended durations (e.g. 278 days for ANDV, 117 days for RVFV, 103 days for LFV) (Table 7). This raises great concerns since some of these viruses are lethal and detected in the semen of survivors (e.g. NiV, LFV). Sexual transmission was recently suspected for WNV 30 days after symptom onset, and sexual transmission of DENV between two men reported **(Table 7)**. Whether sexual transmission of the emerging viruses that contaminate human semen can occur, warrants study.

4. Semen is more than a passive vector for viruses

Viruses can be present in semen as cell-free virions, in infected cells (e.g. leukocytes infected with HIV and spermatozoa infected with HBV) and/or attached to cell surfaces (e.g. HPV and HIV bound to spermatozoa). Both cell-free and cell-associated virus transmission occurs through the anogenital mono- or pluri- stratified mucosa of the recipient (20, 245), involving a number of distinct mechanisms for crossing the mucosal epithelial barrier **(Figure 11)**. Over the last 2 decades, the accumulated *in vitro* data has shown that seminal plasma exerts a complex mix of inhibitory and enhancing effects on viral infection, depending on the target cells and pathogens. It is important to note that some of these seminal effects may be transient since seminal fluid is a dynamic fluid, which composition changes over time post-ejaculation due to many enzymatic reactions.

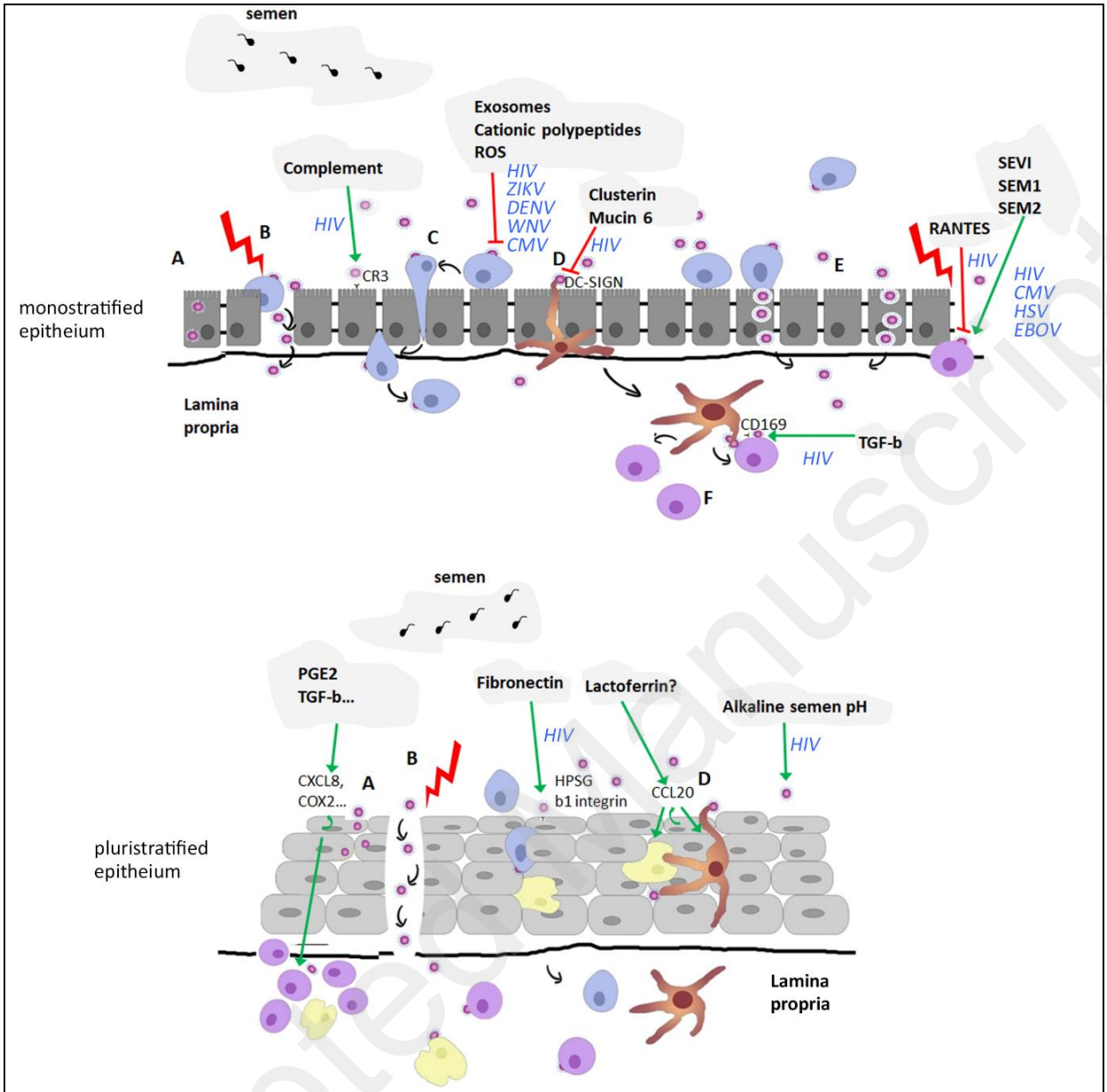


Figure 11: Mechanisms for sexual transmission of viruses through the recipient mucosal epithelia (A-E) and modulation by seminal plasma components. Viruses present in genital secretions (semen, cervico-vaginal fluid) as virions and within infected cells can be transmitted through the monostratified (e.g. endo-cervix, colon, penile urethra) or pluristratified (e.g. vagina, ecto-cervix, foreskin, glans) mucosa of the recipient through a range of mechanisms. **(A)** For sexually transmitted viruses with a tropism for epithelial cells such as HSV or HPV, the epithelium that covers mucosal tissues is productively infected, providing a direct entry way. Viruses which do not infect epithelial cells, such as HIV or HTLV, may reach their sub-epithelial target cells through either: **(B)** Breaches in the mucosa resulting from micro-abrasions of the epithelial barrier triggered by sexual intercourse or by other STIs favoring mucosa inflammation or abrasions; **(C)** Transmigration of infected cells between the epithelial barrier; **(D)** Capture of viral particles by DCs sampling pathogens on the apical side of the epithelium barrier, which then migrate back into the sub epithelium tissue; **(E)** Transcytosis of viral particles across the epithelial cells leading to their release on the basal side. For detailed reviews of these mechanisms, see (21, 626). Multiple semen components (showed in grey clouds of semen in the schema) are thought to enhance (green arrows) or inhibit (red bars) viral transmission (see text section VI. 4. for more details on their mechanisms of action).

4.1. Inhibitory effects of interactions between semen components and viral particles or their target cells

Semen exosomes
Also called prostasomes, exosomes are membranous nanovesicles produced within MGT organs, the content (proteins, mRNAs and miRNAs) of which is involved notably in sperm maturation and fertilization. Seminal plasma and isolated semen exosomes blocked the binding of ZIKV, DENV, WNV (487) and CMV (393) to their target cells and inhibited HIV transcription and cell-to-cell spread (166).

Cationic polypeptides
In high concentrations in semen, several cationic peptides demonstrated antiviral activity *in vitro*. Similar to seminal plasma, a natural fragment of semenogelin I transiently inhibited HIV infection of the target cells (429). Seminal vesicle-derived gp17 glycoprotein specifically competed with HIV for binding to its cell entry receptor CD4 (33), while a cysteine proteinase inhibitor, cystatin C, was postulated to counteract viral proteases necessary for viral protein processing (164, 709).

Reactive Oxygen Species (ROS)
ROS, mostly produced by neutrophils and macrophages in semen, modified lipid rafts in the membranes of enveloped viruses including HIV, in turn inhibiting fusion with the cell and viral entry (290, 361).

Clusterin and Mucin 6
The glycan motifs of Clusterin and Mucin 6 bind to DC-SIGN, a PRR of the C-type lectin family expressed by genital mucosa immature DCs, which recognizes many viruses (HIV, HSV, HCV, DENV, ZIKV, EBOV, CMV) (276, 367). These glycoproteins competed with HIV for binding to DC, in turn inhibiting trans-infection of CD4+ T cells, similar to whole seminal plasma (597, 659).

RANTES/CCL5
Elevated concentrations of the chemokine RANTES, a ligand of the HIV receptor CCR5, were found in semen from HIV+ men and diminished HIV infection of semen-exposed CD4+ T cells by decreasing their CCR5 expression (84).

4.2. Enhancing effects of semen components/properties on virus transmission

Amyloid-forming fibrils
Over 10 years ago, Munch et al. identified seminal amyloid-forming peptides that boost HIV infectivity *in vitro*, similar to whole seminal plasma (488). These peptides comprise fragments of the prostatic acid phosphatase (with a dominant peptide called SEVI for Semen-derived Enhancer of Viral Infection) (488) and seminal-vesicle-derived semenogelins (SEM1 and SEM2, resulting from cleavage by the prostate specific antigen) (577, 578). The positive charges of the peptides interact with the negatively charged surfaces of cells and virions to form an electrostatic bridge that promotes viral attachment and fusion (29, 578). Seminal plasma, SEVI, and semenogelin amyloids enhanced *in vitro* infection of isolated cells by HIV-1 (355, 488), HIV-2 (355) SIV (775), HSV (690), CMV (673) and EBOV (42) but not that of ZIKV, WNV and DENV, which were inhibited by seminal plasma (487). SEVI also increased the internalization of EBOV particles by macropinocytosis, the canonical EBOV entry pathway, and stabilized EBOV viability and infectivity (42). However, seminal plasma or SEVI

enhancement of HIV infection in ano-genital explants was inconsistent (15, 315, 368) and *in vivo* experiments using humanized mice (120, 148) or NHP models (489) failed to demonstrate any enhancing effect of semen on HIV/SIV transmission. This discrepancy could result from the complex interactions between seminal and mucosal factors counteracting amyloid fiber enhancement. It is also possible that the higher viral doses used *in vivo/ex vivo* compared to *in vitro* may bypass the semen-enhancing effect, which is restricted to low viral doses (488).

Cytokines

The role of seminal cytokines in viral transmission is ambiguous. Semen has very high concentrations of TGFβ (mostly under a latent form activated by vaginal pH and enzymes) and prostaglandin PGE2, which both inhibit leukocyte activation and induce naïve CD4+ T cell differentiation into Tregs (580). Semen immunosuppressive properties, believed to allow maternal tolerance against paternal-derived antigens, might facilitate virus spreading. In addition, TGFβ increased CD169 expression on mature DC, which facilitated HIV capture by DC and may enhance its transmission to permissive cells (599).

Conversely, semen deposition onto the female genital mucosa triggers a strong post-coital inflammatory response with massive influx of neutrophils, and to a lesser extent lymphocytes and macrophages, which may eliminate pathogens (580). PGE2 stimulated neutrophil chemotactic CXCL8 in cervix tissue (142), while SP, PGE2 and TGFβ up-regulated COX2 in female genital cells (315, 328, 623), which may further amplify the inflammation by catalyzing prostaglandin synthesis. Compared to blood, semen contained elevated concentrations of pro-inflammatory cytokines (e.g. MCP-1, IL-8, CXCL1, MIP1-β, IL-6, IL1α, granulocyte-macrophage colony-stimulating factor (GM-CSF)) and adaptive cytokines (IL-7 and IL-15) (522, 707). In cervix and endometrial tissue cultures and in vaginal, cervical and endometrial isolated cells, seminal plasma upregulated a range of genes and proteins linked to cytokine signaling, inflammation, antigen presentation, leukocyte migration and cellular immune responses, a modulation in part mediated by TGFβ (99, 315, 622). Unfortunately, semen cytokine-mediated inflammation and immune activation attract HIV immune target cells and stimulate replication of the virus in female genital tissue (50, 315).

Semen upregulated CCL20 chemokine in cells derived from endocervical and vaginal epithelium, possibly through the action of seminal lactoferrin (403), which in turn recruited CCR6+ Langerhans cells *in vitro* (50). In NHPs, CCL20 concentrations were positively correlated to recruitment beneath the vaginal epithelium of CCR6+ plasmacytoid DCs and macrophages, which in turn attracted T helper 17, a preferential target cell type for HIV/SIV (662).

Fibronectin

Fibronectin, an abundant extracellular matrix glycoprotein that stimulates sperm capacitation and semen coagulation, coats HIV virions (69). Fibronectin recognition of B1 integrin and HSPGs expressed by epithelial cells might help HIV attachment to the female genital epithelium (419, 576). Multimeric fibronectin enhanced the HIV infection of T lymphocytes through increased cell attachment, and protected virions from degradation (254, 678).

Complement molecules

The opsonization of virions coated by complement molecule present in semen by epithelial cells, DC and macrophages bearing the CR3 complement receptor, was postulated as an enhancing mechanism for HIV transmission (66).

Semen pH

The alkaline pH and high buffering capacity of seminal fluid protected HIV particles from the acidic environment of the vaginal mucosa, in turn stimulating infection (68).

VII. What lessons can we learn from animals?

Of the 87 new human pathogens catalogued since 1980, approximately 80 percent are zoonotic (498). Considering the potentially high impact of sexual transmission of viruses in upcoming human pandemics, and the urgency to fill gaps in this domain revealed by the recent ZIKV and EBOV epidemics, it is essential that we learn from diverse research fields. This includes research into economically-significant farm animals (e.g. bulls, pigs, sheep and horses). Since artificial insemination is used extensively worldwide in these animals, viruses that infect and persist in the MGT represent a threat for the disease spreading and breeding, and have been sought intensively. The main findings on viruses in the MGT of farm animal are summarized below and in **Table 8**, in order to learn from the mechanisms of seminal viral shedding and persistence evidenced, and prompt research into viruses that might infect the human MGT.

Although ZIKV was the first arbovirus to be reported in human semen in 2015 (493), 5 arboviruses were already known to infect the semen of pigs [African swine fever virus (ASFV), classical swine fever virus (CSFV), JEV] and bulls [Schmallenberg virus (SBV) and bluetongue virus (BTV)]. This list now includes seminal excretion of Peaton virus (PEAV) in bulls, BTV and Rift Valley fever virus (RVFV) in sheep, and CHIKV, RVFV and DENV in humans, suggesting that MGT infection by arboviruses is more common than expected **(Table 8)**. Importantly, some of these animal arboviruses are zoonotic (JEV, RVFV) and impact embryonic development (BTV, CSFV) **(Table 8)**. The attention paid to ZIKV in terms of sexual transmission and congenital effects, therefore, should be extended to other arboviruses that affect humans. Although the detection of a given zoonotic virus in the animal MGT does not imply that this virus will infect the same organs/cells in humans, it can reasonably be argued that it deserves investigation. As an example, RVFV, a zoonotic arbovirus that infects the sheep testis (514), was found in the semen of an immunosuppressed, infected patient 4 months post-symptoms (277). Two other zoonotic viruses, JEV and HEV, infect the MGT of animals and are forecasted as future pathogens for North American populations (476).

In contrast to humans, the persistence in the MGT of acute viruses has long been recognized in farm animals, with over 8 viruses from different families reported in semen, and in at least one male genital organ, in pigs, bulls, sheep and horses **(Table 8)**. A large panel of MGT organs and cells, including germ cells, were associated with virus persistence in animal semen **(Table 8)**. The origin of the viruses persistently shed in semen appears complex. For example, the accumulation of data on porcine reproductive and respiratory syndrome virus (PRRSV)-infected animals suggests that seminal viruses arise from testicular germ cells during the acute phase of the infection, and from infected macrophages that infiltrate MGT organs during the persistent phase (554). Lifelong MGT infection and seminal shedding was demonstrated for two acute animal viruses, equine arteritis virus (EAV) in horses (37) and bovine viral diarrhea virus (BVDV) in bulls (75). Consequently, the infected male horses and bulls are major viral reservoirs, spreading the disease among cattle herds. The processes generating these lifelong infected animals differ between EAV and BVDV. EAV persistence is specific to the MGT, testosterone-dependent and concerns 10-70% of stallions infected during adulthood; the vas deferens ampullae was identified as the main virus reservoir (443). Long-term persistent infection has been correlated to the susceptibility to EAV infection of a subpopulation of ampullae-specific CD3+ T lymphocytes expressing an isoform of the CXCL16 gene with EAV receptor activity (37). The mechanisms responsible for immune evasion during the persistent infection of this MGT duct are still under investigation. In contrast to EAV, lifelong BVDV infection is not restricted to MGT and results from infection during fetal life, before the

development of the immune system. The neonate calves become immunotolerant to BVDV, recognized as self, and remain viremic, shedding virus in semen lifelong (75, 542).

Conclusions and future directions

Viral infections of the MGT raise a broad range of issues at the interface between the fields of reproductive biology/endocrinology/urology (e.g. infertility, endocrine disturbances, genital cancers) and infectious diseases/virology (e.g. horizontal and vertical transmission of viruses, viral reservoirs and persistence). Studies on viral infections in the MGT have significantly increased over the last 2 decades in these distinct fields. However, much remains to be done to improve our understanding of the interplay between viruses and the MGT, and bring mechanistic insights to help targeted therapeutics interventions. We highlight below research questions and needs pertaining to these different issues, and conclude with proposition of approaches.

- ***Viral infections and infertility: what are the mechanisms at play?***

Beside the well-known deleterious consequences of MuV on testis functions, an accumulation of observational data incriminate viral infections, especially chronic (e.g. hepatitis viruses, HPV), in altered semen/sperm parameters and diminished fertilization abilities. The mechanisms behind those alterations are largely unknown. To discriminate between indirect systemic (e.g. generalized inflammation, oxidative stress, endocrine disturbances at the hypothalamic-pituitary level) and direct negative effects of viral infections on MGT reproductive functions, there is now a need to deepen these data "at the bench". The focus should not only be on ejaculated spermatozoa (the end product) but also on testis, epididymis and accessory glands functions to establish whether the incriminated viruses modify the cellular homeostasis and male tissue micro-environment. Moreover, in the view of the paucity of data, further investigations on the hypothalomo-pituitary gonadal axis functions in men suffering from MGT infections are warranted Importantly also, it is now established that environmental factors can affect epigenetic marks, and that non-genetic alterations can be passed on by the male gametes to the offspring (727). Whether testis and epididymis infections and/or an inflammatory environment can impact the gamete epigenome and in turn its ability to produce viable offspring has never been explored.

- ***Viruses and cancers of male genital organs: is there anything left to uncover?***

Whether viral infections play a part in the etiology or in the progression of prostate and testis cancers is unproven, despite numerous studies investigating the implication of well-known oncogenic viruses. There are most likely multiple environmental contributors to MGT cancers, which interact with each other and with host genetics and immune system in a temporal manner. Measuring the exposome of the individuals, defined as the totality of environmental exposures from conception onward including chemicals and infectious agents, should advance our understanding of environmental contributors. As shown in **Figure 6**, MGT organs, including the prostate and the testis, are the target of multiple viruses. Viral metagenomics recently revealed the existence of a human virome (i.e. viral community in tissues) that, as suspected for the microbiome, might influence health and disease (569). Viral metagenomics, as a wide unbiased approach, has great potential for uncovering novel viruses as well as yet unsuspected known viruses or specific viral combinations in diseased versus healthy MGT samples.

- ***Viral integration in the human germ line and endogenization: can it happen again?***

Genome sequencing and paleovirology have revealed the fascinating interactions between viruses and the gametes, demonstrating repetitive infections of the germ line during evolution

by both retroviruses and non-retroviral viruses, and highlighting the possibility of new viral integrations by a whole range of contemporary viruses. Whether HIV and non-retroviral viruses that associate with germ cells and spermatozoa could be "en route" for integration in the germ line and future endogenization in humans is indeed an exciting question. Deciphering how human male germ cells are equipped to face viral colonization should provide some interesting answers.

- ***Vertical transmission of viruses through semen: an important issue for medically assisted reproduction***

In the context of increasing use of medically assisted reproduction, it is crucial to determine whether the different semen compartments (i.e. seminal fluid, spermatozoa and/or other semen cells) or the testicular germ cells (in the case of ICSI) are targeted by emerging viruses in order to prevent transmission to the partner and embryo. Indeed, viruses contaminated seminal fractions may induce congenital defects and/or viral chronicity (156, 218, 350). Long lasting ZIKV infection in infants after *in utero* acquisition (74) and reports of fetal testis infection by ZIKV (45) justifies careful monitoring of early life infection cases.

- ***Sexual transmission of viruses through semen: how can we anticipate future epidemics?***

The transmission of viral diseases through semen is more than ever a major global health concern. Indeed, after ZIKV and EBOV, several emerging viruses forecasted to generate future outbreaks in human population (476, 492) represent suspects for sexual transmission (table 7). As highlighted in this review, sexual transmission through semen represents a very powerful mode of dissemination for viruses and is extremely complicated to control, as exemplified by the HIV-1 pandemic and its over 35 million deaths, and by the resurgence of EBOV epidemics foci following sexual transmission. Whether the acquisition of sexual transmission mode by emerging viruses reflects virus evolution associated with novel tissue tropism or changes in host ecology is unknown (25). Inter and intra-individual analysis of genomic sequences of sexually transmittable emerging viruses would be helpful to determine if unique signatures are involved in MGT tropism. Monitoring and controlling pathogens in non-human species including NHP and livestock is essential for anticipating human epidemics since most emerging viruses are zoonotic. This is underlined in the concept launch in 2004 of "one world- one health", whereby animal and human health are considered inter-dependent (www.oneworldonehealth.org). Assessing MGT tropism of animal viruses in their host as well as in human tissues, for instance using *ex vivo* approaches, should greatly improve anticipating and in turn preventing sexual transmission. As highlighted in this review, a number of zoonotic viruses persist in animal semen (including HEV and JEV), suggesting potential for sexual transmission in future outbreaks (476, 718). Importantly however, molecular detection of viral sequences in semen is insufficient to determine capacity for sexual transmission. Sensitive culture techniques along with molecular detection of replication-competent virus in semen are warranted to assess the transmission potential of these viruses.

- ***Mechanisms of viral persistence in semen: the new quest***

Researches in HIV-infected patients over the last 30 years, along with the recent reports of viral persistence in cured EBOV and ZIKV patients, have demonstrated that systemic viruses in semen do not exclusively arise from passive blood diffusion and have uncovered the existence of local MGT sources. Yet, we know very little about these sources and the specificities of their tissue micro-environment. Because of its status as an immune-privileged organ and as a

pharmacological sanctuary, the testis is widely considered to be responsible for viral persistence in semen. However, recent data in HIV-infected patients and in ZIKV-infected men with undetectable viremia have demonstrated that other MGT organs can also be sites of persistent infection (30, 200, 440). Interestingly, we recently demonstrated that multiple MGT organs seed both virus and infected cells in the semen from SIV-infected monkeys, and that these sources vary among individuals (299). These findings, which need to be confirmed in larger studies, echo the inter-individual variations of virus excretion pattern and persistence in semen (**Table 7**). Many questions awaits to be answered: - What are the cellular and molecular actors that support viral persistence? - What are the host/viral determinants leading to the continuous/intermittent excretion from specific MGT organs into the seminal lumen of virions and infected cells? - Is this persistence the result of active replication or long-term maintenance of a stock of virus with little *de novo* viral production? - How are viruses eventually cleared from the MGT?

- ***Target cells and routes of infection of MGT organs by systemic viruses: still a lot to learn***

Our understanding of the routes of infection of both external and internal MGT organs and of viruses'cell targets in the MGT is surprisingly limited, even for viruses, such as HBV, for which sexual transmission represents a prime mode of dissemination. Recent data suggest that alternative routes to hematogenous spread exist that involve virus exchange between MGT organs (299, 696). Moreover, many viruses reported in the MGT are neuro-tropic (371, 405), and viral trafficking between the MGT and the central nervous system through nerves has been described (219–221, 668, 767) for several human viruses (371). Neuronal pathways might allow viruses to traffic between immune-privilege niches like the brain and testis and escape from immune surveillance potentially leading to virus persistence and cross-reservoir seeding. Since several emerging viruses have become neuro-tropic (e.g. ZIKV, WNV, DENV) or able to cause neurological diseases (EBOV) (490), it would be of great interest to establish whether these viruses can disseminate to the MGT through nerves.

Summary of research needs and proposition of approaches

Answering the questions raised in this review implies three pre-requisites, namely: i) decipher for each virus of interest the nature of infected cells in the different male genital organs. Even for viruses with an established tropism for the MGT, we know surprisingly very little about their targeted organs and cells. This is an obstacle for understanding their action mechanisms in the range of pathological processes described above; ii) determine the immunological specificities of the different male genital organs in humans. While the basis for immune-privilege is well established in rodent testis, it has been poorly investigated in humans. In addition, recent findings revealed that the testis is not the only viral reservoir in the MGT. Thus attention need to be paid as to how MGT organs other than testis can also shelter viruses from adaptive immune system; iii) establish the species and cells innate immunity differences in MGT organs, along with the mobilization of innate effectors and repressors upon exposure to different viral pathogens. As pointed in this review, evidence is building up of unique features for testicular germ cells as well as for human testis versus rodents.

To achieve this, there is a need for a combination of animal models and *ex vivo* models of human MGT tissues. The choice of animal model is however complicated by both the host specificity of the virus under investigation, and the necessity for morphological and immunological features of MGT organs close to humans. As highlighted in this review, caution is needed when extrapolating from rodent models. NHP constitute a model of choice for many

human viruses (e.g. HIV) and their MGT is very similar to humans. Nevertheless, NHP raise cost and ethical issues. Pigs, which share many testis features with humans and natural virus tropism for MGT, might represent an interesting alternative.
We have provided in this review several examples of the usefulness of *ex vivo* approaches for the study of human MGT organs' infections. The development of 3D bio-printing, organoids and microfluidic systems hold great promise for long-term maintenance and improved reconstruction of human tissues. In addition to the preservation of primary cells characteristics in long-term culture, organoids obtained through the reorganization of different isolated cell types offer the extra bonus of possible genome editing, which could provide useful insights into host/virus interactions (18). However, while brain and digestive tract organoids are becoming more and more robust and standardized, there are currently no satisfactory examples of male genital organoids, especially testis. Indeed, the very complex testis structure (e.g. cell-to-cell contacts, specific spatial association of germ cells along the tubules…) is a major obstacle to faithful reconstruction. Microfluidic cultures of testis tissue may represent a better alternative: indeed, microfluidic culture of mouse testis explants succeeded in maintaining functional tissue for over 6 months and allowed full spermatogenesis (365).
Finally, the onset of viral metagenomics (virome) as well as the incrementation of human organs and cells' atlas should provide key elements to improve our understanding of the interplay between viruses and the MGT and inter-individuals variability.

To conclude, the many gaps in knowledge of the organs/cells and molecular processes involved in the infection and persistence of viruses in the MGT urgently need to be addressed if we want to develop tools to prevent sexual transmission, reproductive disorders, chronic inflammation and cancer development/ progression.

Callout box for clinicians

- Over 30 contemporary and emerging viruses are released in semen. Both genital (e.g. HSV, HPV) and systemic viruses (e.g. HIV, HBV, ZIKV, EBOV) can infect not only the testis, but multiple male genital organs, which can represent viral reservoirs. Viral infections in the MGT are frequently silent and seminal shedding can be prolonged or intermittent, making it difficult to detect.
- Viral infections can affect male reproductive function through endocrine disturbances, inflammation, oxidative stress, high fever, or through direct testis, epididymis and accessory glands dysfunctions caused by viral replication.
- Clinicians should be aware that a number of acute emerging viruses, including arthropod-borne and life threatening viruses, can persist in semen despite systemic clearance (e.g. YFV, Nipah virus) and lead to sexual transmission for extended durations (e.g. ZIKV, EBOV, WNV).
- Screening for viruses in semen and seminal fractions is key to establish potential for transmission to partner and embryo (through determination of infectiousness), and pattern of excretion (through longitudinal samples analysis)
- Clinicians should perform this investigation in symptomatic patients, or asymptomatic patients wishing to conceive, according to the epidemiological risk/ geographical area and must give appropriate counselling to the patients in order to avoid infection complications for the patient, his partner or the future embryo/infant.

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Tables

Table 1: Overview of viruses detected in human MGT organs and/or semen

Virus	Family	Genus	Genome	Main clinical syndromes
Human papillomavirus (HPV)	Papillomaviridae	Alpha-, beta-, gamma-papillomavirus	dsDNA	Warts, precancerous lesions associated to genital, anal and oropharingeal cancers
Herpes simplex virus-1 (HSV-1)	Herpesviridae	Simplexvirus	dsDNA	Herpes labialis, genital herpes
Herpes simplex virus-2 (HSV-2)	Herpesviridae	Simplexvirus	dsDNA	Genital herpes
Varicella zooster virus (VZV)	Herpesviridae	Varicellovirus	dsDNA	Chikenpox
Epstein-Barr virus (EBV)	Herpesviridae	Lymphocryptovirus	dsDNA	Infectious mononucleosis, Burkitt lymphoma, Nasopharingeal carcinoma and posttransplant lymphoproliferative Disease
Cytomegalovirus (CMV)	Herpesviridae	Cytomegalovirus	dsDNA	Congenital CMV, can be life-threatening for immunocompromised patients
Human herpes virus -6 (HHV-6)	Herpesviridae	Roseolovirus	dsDNA	Common childhood disease exanthema subitum

Human herpes virus -7 (HHV-7)	Herpesviridae	Roseolovirus	dsDNA	Common childhood disease exanthema subitum
Kaposi sarcoma associated herpesvirus (KSHV)	Herpesviridae	Rhadinovirus	dsDNA	Kaposi sarcoma, primary effusion lymphoma, Castleman's disease.
Molluscum contagiosum virus (MCV)	Poxviridae	Molluscipoxvirus	dsDNA	Self-limiting papules in genitals and other parts of the body
Adenovirus (AdV)	Adenoviridae	Mastadenovirus	dsDNA	Conjunctivitis, respiratory or gastroenteric syndromes, meningoencephalitis, urinary tract infections
Parvovirus B19	Parvoviridae	Erythrovirus	ssDNA	Fifth disease or erythema infectiosum, hydrops fetalis
Adeno-associated virus (AAV)	Parvoviridae	Dependovirus	ssDNA	Not known to cause disease. Used in virus-vectored gene-therapy trials
JC polyomavirus (JCPyV)	Polyomaviridae	Betapolyomavirus	dsDNA	Almost exclusively in immunosuppressed individuals: progressive multifocal leukoencephalopathy

BK polyomavirus (BKPyV)	Polyomaviridae	Betapolyomavirus	dsDNA	Almost exclusively in immunosuppressed individuals: BK virus associated nephropathy, hemorrhagic cystitis.
Simian virus 40 (SV40)	Polyomaviridae	Betapolyomavirus	dsDNA	Controversy over SV40 involvement in human tumorigenesis
Merkel cell polyomavirus (MCPyV)	Polyomaviridae	Alphapolyomavirus	dsDNA	Suspected to cause Merkel Cell Carcinoma (skin cancer)
Torque teno virus (TTV)	Anelloviridae	Alphatorquevirus	ssDNA	Unknown
Hepatitis B virus (HBV)	Hepadnaviridae	orthohepadnavirus	dsDNA (RT)	Hepatitis, cirrhosis and hepatocellular carcinoma.
Hepatitis D virus (HDV)		deltavirus	ssDNA	Hepatitis, cirrhosis and hepatocellular carcinoma upon superinfection and coinfection with HBV
Human immunodeficiency virus (HIV)	Retroviridae	lentivirus	ssRNA (RT)	AIDS
Human T-lymphotropic virus (HTLV)	Retroviridae	deltaretrovirus	ssRNA (RT)	Adult T cell leukemia/lymphoma and HTLV-associated myelopathy/tropical spastic paraparesis

Hepatitis C virus (HCV)	Flaviviridae	Hepacivirus	ssRNA (+)	Hepatitis, cirrhosis and hepatocellular carcinoma.
Zika virus (ZIKV)	Flaviviridae	Flavivirus	ssRNA (+)	Zika fever, congenital Zika leading to microcephaly and other central nervous system disorders.
West-Nile virus (WNV)	Flaviviridae	Flavivirus	ssRNA (+)	Encephalitis, meningoencephalitis
Japanese encephalitis virus (JEV)	Flaviviridae	Flavivirus	ssRNA (+)	Encephalitis, meningoencephalitis
Dengue virus (DENV)	Flaviviridae	Flavivirus	ssRNA (+)	Dengue fever, severe dengue hemorrhagic fever
Chikungunya virus (CHIKV)	Togaviridae	Alphavirus	ssRNA (+)	CHIKV disease, arthralgia, myalgia.
Coxsackie virus (CoxV B5, A6)	Picornaviridae	Enterovirus	ssRNA (+)	Hand-foot-mouth disease (HFMD), cardiomyopathy, gastrointestinal diseases, central nervous system manifestations.
Hepatitis E virus (HEV)	Hepeviridae	Orthohepevirus A	ssRNA (+)	Hepatitis
Severe acute respiratory syndrome (SARS)	Coronaviridae	Betacoronavirus	ssRNA (+)	Severe acute respiratory syndrome

Mumps virus (MuV)	Paramyxoviridae	Rubulavirus	ssRNA (-)	Swelling of the parotid glands, salivary glands and other epithelial tissues
Nipah virus (NiV)	Paramyxoviridae	Henipavirus	ssRNA (-)	Acute respiratory illness, fatal encephalitis
Ebola virus (EBOV)	Filoviridae	Ebolavirus	ssRNA (-)	Hemorrhagic fever
Marburg virus (MARV)	Filoviridae	Marburgvirus	ssRNA (-)	Hemorrhagic fever
Andes hantavirus (ANDV)	Hantaviridae	Orthohantavirus	ssRNA (-)	Hantavirus cardiopulmonary syndrome, hantavirus pulmonary syndrome
Lassa fever virus (LFV)	Arenaviridae	Mammarenavirus	ssRNA (-) ambisense, segmented	Hemorrhagic fever
Rift Valley fever virus (RVFV)	Bunyaviridae	Phlebovirus	ssRNA (-) ambisense, segmented	A small percentage of infected individuals develops ocular diseases, encephalitis or hemorrhagic fever.

Table 2 : Viruses that infect human penis

Virus	Penile acquisition	Penile entryway	Detection in penile tissues	Risk factor for penile infection	Effect of circumcision	Non-sexual transmission	Prevalence in human population	Effect on external genitalia
HPV	Skin-skin contact with lesions, vaginal, oral and anal sex (90)	Infection of basal cells in stratified epithelium (447, 655)	Shaft, glans, foreskin and urethra (in vivo) (23, 158, 168, 630)	Urethritis, damaged epithelium (630)	Reduced acquisition, increased clearance (8, 686, 782)	Contact with lesions, vertical (598)	Europe: males 12,4 -30,9 % (280) USA: males 45.2% ; females 39.9%	Genital warts- Penile cancer for high risk HPV types (79, 147)

							High-risk genital HPV males 25.1%, females 20.4% (450)	
HSV-1/2	Skin-skin contact with lesions, vaginal, oral and anal sex (91)	Basal epithelial cells, capture by dendritic cells, cell-to-cell (1, 196)	Foreskin (607), glans and shaft (584), urethra (664)	HIV infection (>2.5 fold increase), genital ulcers and penile epithelial trauma (455, 647)	Moderate reduction (28-30%) or no effect (647, 687)	Oral contact, contact with lesions, vertical (734)	3.7 billion/471 million (734)	Genital herpes, penile shaft, urethritis, prostatis, genital pain (604)
HBV	Vaginal, oral, and anal (insertive over receptive) sex (314, 357)	Unknown mechanism	not reported	Other STIs (82, 502)	Reduced risk of infection (82, 720), or no effect (MSM) (530)	Parenteral, vertical (314)	257 million (732)	
HIV-1/2	Vaginal, oral and anal (receptive > insertive) sex (593)	Foreskin (inner>>outer), glans, coronal sulcus, fossa navicularis and urethra (19)	Glans, foreskin, urethra (200, 298, 776)	Other STIs (701, 735), penile microbiome and anaerobic dysbiosis (396, 605), penile inflammation (19, 556)	Circumcision reduces acquisition by 56-61 % (174)	Parenteral, vertical (735)	36,9 million (735); 51% are female (701)	
HTLV-1	Vaginal, anal sex (526)	CD4+ T cells, virions capture by dendritic cells (311)	not reported	Syphilis (235, 491), HSV-2 (246), potentially other STIs (526)	Unknown	Parenteral, vertical (311)	5-10 million (222)	Erectile dysfunction (520, 521)
HTLV-2	Vaginal, anal sex (585)	CD4+ T cells, virions capture by dendritic cells (311, 585)	not reported	Potentially other STIs (235)	Unknown	Parenteral (612), vertical (58)	Not estimated in the global population	Erectile dysfunction (552)

MCV	Skin-skin contact with lesions, vaginal, oral and anal sex (131)	Lower and outer layers of the epidermis (131, 568)	Glans, shaft, foreskin (568)	HIV, immunosuppression (92, 266)	Not reported	Fomites, contact with lesions (131)	Worldwide: 2- 8% HIV-infected: 5-18% (309)	Skin-colored papules (131)
HDV	Vaginal, anal sex (17)	unknown mechanism	not reported	HBV infection (733)	Unknown	Parenteral, vertical (733)	15-20 million (733)	

Acronyms of viruses are spelled out in table 1. STIs: sexually transmitted infections

Table 3 : Cell tropism of viruses detected in testicular tissues from humans and animal models

Virus	Human		Animal models		References
	in vivo	in vitro	NHPs	Rodents	
HPV	Int, SC				(435)
HSV-1				Int, SC, GC	(423)
HSV-2	Specific tropism not defined			GC	(143, 256)
EBV	Specific tropism not defined				(106)
CMV		LC, GC, F			(500)
HHV-6	Endogenous				(480)
AdV		Specific tropism not defined		Specific tropism not defined	(127)
Parvovirus B19	Specific tropism not defined				(149, 170, 251)
AAVs	Specific tropism not defined			LC, PT, SC, GC (Sptg)	(171, 454, 726)
HBV	F, End				(378, 438)
HIV-1 (2)	Mϕ, T cells, GC	Mϕ, T cells	SIV: Mϕ, T cells, GC		(742)
HERVs	Endogenous				(125)
MuV	Specific tropism not defined	LC		LC, SC, GC, Mϕ	(59, 244, 748)
ZIKV	GC*	LC, SC, GC, Mϕ, PT	Specific tropism not defined	LC, SC, GC, Mϕ, PT	(441, 657)
WNV	Within ST, SC	SC			(28, 634, 645)
JEV				Specific tropism not defined	(682)
EBOV	End, within ST		End, GC	Int	(113, 430, 541, 766)
MARV			SC, GC, Mϕ, F, End		(111, 117)
CoxV B5	Specific tropism not defined				(122)
Poliovirus		Specific tropism not defined	Specific tropism not defined (in vitro)		(670)
HEV			GC (Sptg)	Within ST	(303, 652)
SARS	LC, Ep				(770)
LCMV				Int, GC (Sptg)	(179)

Acronyms of viruses detected in human male genital tract are spelled out in table 1. HERV: human endogenous retrovirus ; LCMV : lymphocytic choriomeningitis virus; SIV :simian immunodeficiency virus
End: endothelial cells; Ep: epithelial cells; F: fibroblasts; GC: Germ cells; Int: interstitial cells; LC :Leydig cells; Mϕ :macrophages; PT: peritubular cells; SC: Sertoli cells; Sptg: spermatogonia; ST : seminiferous tubules:; Exp: experimental ; NHPs: non human-primates
* Immature germ cells found in human semen

Table 4 : Viruses detected in epididymis and accessory glands from infected patients or, when specified, in animal models

Virus	Epidydimis	Vas deferens	Seminal vesicles	Prostate
HPV	Viral DNA (669)	Viral DNA (573, 669)	Viral DNA in seminal plasma of vasectomized men (573)	Viral DNA (101, 448, 449, 573, 642, 729, 749, 764)
HSV-2	Viral isolation in guinea pig (661)	Viral isolation in guinea pig (661)	Viral isolation from biopsies (143)	Viral DNA (95, 749)
EBV				Viral DNA (101, 259, 729)
CMV		Detection in epithelium (356)	Detection in epithelium (13, 356)	Viral DNA (101, 600, 749, 761)
KSHV				Viral DNA (285, 473)
JCPyV				Viral DNA (101, 642, 764)
BKPyV				Viral DNA (101, 764)
MCPyV				Viral DNA (642)
SV40				Viral DNA (101)
HIV	Viral RNA and antigens in leukocytes (511, 557)	NHP models: viral RNA and antigens in leukocytes (299, 440)	Viral RNA and antigens in leukocytes (141)	Viral RNA and antigens in leukocytes (114, 511, 557, 644)
WNV				Viral antigens detected in biopsies (28)

CoxV A6	Viral RNA in epididymal fluids (719)			
ZIKV	Mouse models: in mature sperm, epithelial cells and stroma (96, 110, 151, 157, 247, 257, 345, 445, 702, 703)	Mouse model (345)	Mouse model: in epithelial cells and stroma (110, 157, 445); NHP model (287, 524)	Mouse model: in epithelial cells and stroma (96, 110); NHP model (287, 524)
EBOV	NHP model: in stromal cells, endothelial cells, macrophages (541, 766)		NHP model: in stromal and endothelial cells (541)	NHP model: in stromal and endothelial cells (541)
MARV	NHP model (117)			NHP model (117)
HEV	NHP model (303)			

Unless differently specified, virus detection occurred in infected patient tissues.

Acronyms of viruses detected in human male genital tract are spelled out in table 1. NHP: non-human primate.

Table 5: Protein expression of pattern recognition receptors (PRRs) in the MGT of human and animal models

PRR		PRR ligand and virus sensed	Testis		Epididymis		Prostate		Urethra	Foreskin
			Rodent	Human	Rodent	Human	Rodent	Human	Human	Human
TLRs	**TLR2**	Surface viral gp MuV CMV HSV	Sertoli cells (572, 747)	Sertoli cells Peritubular cells, and a subset of interstitial cells (376, 442)	Strongly expressed by epithelial cells except clear cells (528)	ND	Epithelial cells (215, 414)	mRNA but (-) for protein expression (510)	Lymphocytes (558)	Keratinocytes (777)
	TLR3	Cytosolic dsRNA KSHV	Sertoli cells (656, 747) Leydig cells (620) Macrophages (56) Spermatogonia and spermatocytes (302, 724)	Sertoli (376, 442)	Epithelial cells except clear cells (528, 781)	Epithelial cells (cauda> caput cells) (77)	ND	Epithelial cells in a subset of prostate samples (559)	Lymphocytes (558)	Keratinocytes (777)

	TLR4	Surface viral gp HIV-1 gp120	Sertoli cells (572, 747) Leydig cells (620) Macrophages (low level) (56)	ND	Strongly expressed by epithelial cells except clear cells (528)	ND	Epithelial cells and stromal cells (215, 414, 565)	Epithelial and stromal cells (214)	Lymphocytes (558)	Keratinocytes (777)
	TLR7	Cytosolic ssRNA SeV VSV	ND	ND	Strongly expressed by epithelial cells except clear cells (528)	mRNA poorly expressed (77)	ND	Intraepithelial macrophages (559)	Intraepithelial macrophages (558)	ND
	TLR8	Cytosolic ssRNA	ND	ND	Strongly expressed by epithelial cells except clear cells (528)	mRNA poorly expressed (77)	ND	Epithelial cells in a subset of prostate samples and intraepithelial macrophages (559)	(-)	ND
	TLR9	Cytosolic DNA HSV-1/2 KSHV	ND	ND	Strongly expressed by epithelial cells except clear cells (528)	mRNA poorly expressed (77)	ND	Intraepithelial macrophages (559) Epithelial and stromal cells in BHP (312, 705)	Epithelial cells and intraepithelial macrophages (558)	Keratinocytes (777)

RLRs	**RIG-1**	Cytosolic dsRNA MuV ZIKV SeV	Leydig cells (779)	ND	Epithelial cells (781)	Epithelial cells (cauda> caput cells) (77)	ND	ND	ND	ND
	MDA-5	Cytosolic dsRNA DENV WNV	Leydig cells (779) Spermatids (779)	ND	ND	Epithelial cells (cauda> caput cells) (77)	ND	ND	ND	ND
	LGP2	Cytosolic dsRNA			ND	ND	ND	ND	ND	ND
NLRs	**NLRP3**	Cytosolic ssRNA	ND	ND	ND	ND	Rat prostatic cells (98)	ND	ND	ND
	NOD2	Cytosolic dsRNA	ND	ND	ND	ND	Mouse Epithelial cells (330)	ND	ND	ND
ALRs	**cGAS**	Cytosolic DNA HIV KSHV		ND	Epithelial cells, following HSV-60 stimulation (781)	ND	ND	ND	ND	ND
	ZBP1/ DAI	Cytosolic DNA		ND	DAI: epithelial cells (781)	mRNA ZBP1 in epithelial cells	ND	ND	ND	ND

		CMV				(cauda> caput) (77)				
	p204/ IFI16	Cytosolic DNA KSHV	p204 in Leydig cells (780)	ND	p204 in epithelial cells following HSV-60 stimulation (781)	mRNA IFI16 in epithelial cells (cauda> caput) (77)	ND	IFI16 in epithelial cells (750)	ND	ND
CLRs	**CD206**		ND	ND	ND	ND	ND	Macrophages	ND	ND

ND: not determined, (-) not expressed

PRR: pattern recognition receptor; TLRs: Toll like receptors; RLRs: RIG-I-like receptors; NLRs: NOD-like receptors; ALRs: absent in melanoma 2 (AIM2) -like receptors; CLRs: C-type lectin receptors; RIG-I: Retinoic-acid inducible gene I; MDA-5: Melanoma Differentiation-Associated protein 5; LGP2: laboratory of genetics and physiology-2: NLRP3: NOD-like receptor family, pyrin domain containing 3 ; NOD2: nucleotide-binding oligomerization domain 2; cGAS: cGMP-AMP synthase ; ZBP1: Z-DNA-binding protein 1; DAI: DNA-dependent activator of IFN-regulatory factors; IFI16: interferon gamma inducible protein 16.

Table 6: Non retroviral viruses with potential for germ line integration

Viral family	Endogenous sequences in	Postulated role	Potential for integration in human
Filoviridae (RNA virus)	Bat, marsupials (49)	- Overexpression of a viral glycoprotein may prevent EBOV disease (424)	- EBOV and MARV in testis of patients and NHPs (111, 117, 430, 541, 766)
Bornaviridae (RNA virus)	Human and other vertebrates (49, 297) Marsupials	- Protect against exogenous related virus (Borna Disease Virus) in ground squirrel through an endogenous viral protein expression and incorporation in exo-virus (197, 295) - Integration in piwi-interacting RNA (small non coding RNA expressed in germ cells and early embryo) to silence transposons (reviewed in (295)). - Silencing of related exogenous viral RNAs (295)	
Parvoviridae - AAV (DNA virus)	Parvovirus-related DNA sequence in human genome (single integration more than 98 M years) (397)		- Establish site-specific integration into human chromosome and latency (369, 601) - Detection in testis tissue (454)
Hepadnaviridae - HBV (DNA virus)	Zebra finch	*Benefits:* - In utero acquisition of HBV in human enhances newborn immune cell ability to respond to unrelated pathogen exposure through a "trained immunity" process (296, 515) *Deleterious consequence:* - Chronicity	- HBV Integrates into host genome - Integrates into sperm from patients (269, 304) - Spermatozoa with integrated HBV can fertilize oocytes in vitro (304) but viral gene expression from sperm-introduced HBV may interfere with embryonic development and cause abortion (12, 366)

Herpesviridae – HHV-6 (DNA virus)	Human (1% of the population) (480) Endogenization date back 14000-35000 years for some individuals (769) Ongoing integration in germline? (480)	- Full set of intact viral genes with potential to reactivate in patients: impact on health? (769)	- HHV-6 integrates into telomeres of chromosomes (26) - Vertical transmission of chromosomally integrated HHV-6 from father's spermatozoa and from mother (26, 130, 273, 479, 672, 725)

Acronyms of viruses detected in human male genital tract are spelled out in table 1.

Table 7: Prevalence and characteristics of virus shedding in human semen

	Prevalence of virus shedding in semen [b]					
	Early stage of infection	**Chronic stage of infection**	**Persistent semen infection despite undetectable viremia**			
			Max. duration reported/ % of persistent shedders	**Median time until RNA clearance**	**Shedding pattern (% continuous)**	**Sexual transmission reported**
HSV-1, -2	NA	0%-10% [c,e] (225, 227, 229, 394, 482, 523)			50% (482)	+
VZV	NA	NA			NA	
EBV	NA	4%-56% [c,e] (225, 227, 229, 394, 482, 523)			66% (482)	+
CMV	NA	4%-70% [c,e] (203, 225, 227, 229, 230, 394, 482, 523, 628)			81% (482)	+
HHV-6	NA	1%-7% [c,e] (225, 227, 229, 394, 482, 523)			46% (482)	+
HHV-7	NA	6%-15% [c,e] (225, 227, 229, 394, 482, 523)			57% (482)	
KSHV	NA	NA			50% (482)	+

HIV-1	61%-100% [b] (104, 227, 228, 482)	81%-100% [b] (313, 523, 628)	d1789 (13.4%) (123, 223, 229, 298, 533)	9 days (313)	Chronic: 56%-61% (115, 265); ART: 50%-75% (80, 272, 629)	+
HBV	NA	68% [c,d] (180)	d120 (2 cases) (177, 310)	NA	NA	+
HCV	29%-39% (71, 700)	32%-46% [c,d] (71, 73, 386, 532, 700)			0%-28% (73, 532)	+
EBOV	73%-100% [a, b] (133, 583, 591, 640, 704)		d1178 (0.4%) (261)	4 months (640)	100% (41, 640, 704)	+
ZIKV	50%-68% [a, b] (43, 307, 381, 452)		d370 (10%) (43)	25-83 days (43, 307, 452, 536)	100% (30, 129, 195, 207, 381, 493, 506)	+
HPV	11.4%[c,f] (409)		d730 (15%) (85)	15 months (85)	NA	+
AAV	0%-5%[c] (210)					+
SV40	33%-45%[c] (431, 432)					
JCPyV	0-21%[c] (112, 432, 472)					

BKPyV	0-95%[c] (112, 431, 432, 472)					
GBV-C/HGV	15%[c] (617)					
TTV	59%[c] (439)					
MARV (case report)	+ (433)					+
HTLV-1 (case report)	+ (318)					+
WNV (case report)						+ (348)
YFV (case report)	NA		d21 (40)	NA		
DENV (case report)	NA		d37 (377)	NA		+ (391)
CHIKV (case report)	NA		d30 (38)	NA		
LFV (case report)	NA		d103 (566)	NA		
RVFV (case report)	NA		d117 (277)	NA		
ANDV (case report)	NA		d278 (372)	NA		
NiV (case report)	NA		d26 (31)	NA		

MuV (case report)	NA		d40 (319)	NA		
SFV (case report)	+ (61)					

[a] Data for early infection prevalence for ZIKV and EBOV correspond to samples collected up to 30 and 60 days after symptoms onset respectively, which includes the beginning of persistence stage relative to viremia;
[b] Prevalence in infected individuals;
[c] Prevalence in general population;
[d] 80% of HCV infected individuals, infants and adults, will have long-term chronic infection. For HBV, 90% infants, 25%-50% of children aged 1-5 years, and only 5% of adults will have chronic infection;
[e] values retrieved from 9 studies (CMV) and 6 studies (HSV-1, HSV-2, EBV, HHV-6 and HHV-7) performed on HIV-infected and/or healthy men. A significant difference was observed between healthy and HIV- infected patients for EBV and CMV with average 9% and 11% in healthy and 42% and 57% in HIV- infected patients for EBV and CMV respectively. For additional data from different populations, see the meta-analysis by Kaspersen et al.(336)
[f] Prevalence of HPV in fertility clinic attendees is higher (20.4%) than that mentioned in general population

NA: not available.
Acronyms of main viruses detected in human semen are spelled out in Table 1. GBV-C/HGV: GB virus type C/Hepatitis G virus ; YFV: yellow fever virus ; SFV: Semliki forest virus.

Table 8: Viruses that infect farm animals MGT

Host	Viral family	Virus	MGT organs and cells infected	Seminal excretion (S) and persistence (S+)	Venereal Transmission (V)/ Reproduction failure (R)/ Teratogen (T)/ Abortion (A) /Embryo death (E)
Swine	Anelloviridae	TTV	T (574)	S+ (347, 574)	
	Asfarviridae	ASFV*		S (680)	
	Circoviridae	PCV2 [a]	T, E, SV,P, BG (250, 416, 574)	S (380, 416)	R
	Flaviviridae	CSFV*	T+ (germ cells), E+, VD+ (107)	S+ (108)	E
	Flaviviridae	JEV*†[a]	T (268)	S (400)	
	Flaviviridae	BVDV	T+[b], P+[b] (Mϕ), SV+[b] (Mϕ) (679)	S+[b] (679)	
	Flaviviridae	APPV		S (614)	
	Parvoviridae	PPV	E (248)	S (354)	V?; R
	Parvoviridae	PPV4		S (126, 216)	
	Herpesviridae	PRV	T, E, foreskin (274, 467)	S (453)	
	Paramyxoviridae	PoRV	T+, E+ (575, 650)	S+ (575)	R

	Arteriviridae	PRRSV	T (germ cells, macrophages), E, VD, SV, PR (Mϕ) (109, 632)	S+ (109)	V; R
	Coronaviridae	PEDV	(ND)	S (199)	V?
	Picornaviridae	PEV		S (544)	
	Picornaviridae	PTV		S (544)	
	Picornaviridae	FMDV		S (451)	
	Picornaviridae	SVDV [a]		S (451)	
	Hepeviridae	HEV† [a]		S (388)	
Bull	Flaviviridae	BVDV	T+ (Sertoli, germ cells, epithelial cells), P+, E+, SV+, U+ (epithelial cells, fibrocytes) (63, 238, 358, 504, 716)	S+[c] (63, 358)	R; E; T; A
	Flaviviridae	BDV		S (72, 208)	
	Peribunyaviridae	PEAV*	T (46)		
	Peribunyaviridae	SBV*		S+ (289, 549)	
	Herpesviridae	BHV-1	Penis, forskin, U (518)	S (237)	
	Retroviridae	BLV		S (162, 237)	
	Retroviridae	BIV		S (495)	
	Poxviridae	LSDV	T+, E+ (24)	S+ (316)	
	Picornaviridae	FMDV		S (119)	

	Reoviridae	BTV*		S (706)	R; E; T; A
Sheep	Reoviridae	BTV*	T+, E, P, BG (endothelial cells) (560)	S+ (383)	E; A; T
	Phenuiviridae	RVFV*† [a]	T (endothelial cells, fibroblasts, smooth muscles, Mϕ) (514)		
	Retroviridae	MVV	T, E, SV, P, BG, AG (543, 595)	S (595)	
	Retroviridae	CAEV	T, E, VD, SV, P, BG (10, 699)	S (10)	
	Retrovirida	SRLV genotype E	T+ (255)		
Horse	Herpesviridae	EHV	T+ (endothelial cells, macrophages), E, P+ (epithelial cells) (294, 677)	S (10, 279, 677, 721)	A ; E
	Arteriviridae	EAV	T, E+, VD+, AG+[d], P+, BG+, SV+	S+[d] (87, 293, 684)	V ; R

* = arbovirus; † = zoonotic virus; + = virus persistence in organs and cells.

[a] viruses with potential to infect the human male genital tract (MGT): RVFV, JEV and HEV infect humans and are present in animals' MGT (discussed in the text). SVDV, detected in pig semen, is strongly related to human coxsackieviruses, some of which infect human testis and epididymis (122, 719). PCV-2 is detected in pigs' MGT organs and semen and PCV DNA is present in 5% of stool samples from US adults (389), probably due to pork consumption, and in vaccines and stools from vaccinated infants (173), possibly because of use of pork-derivative material in vaccine elaboration.

[b] BVDV persistence in semen and MGT organs until slaughter at 26 months was reported in congenitally infected pig (679).

[c] BVDV persistence in semen can last from 33 months in bulls with prolonged testicular infection to lifelong in bulls with persistent infection acquired through *in utero* infection (237).

[d] EAV persistence in the semen and ampullary gland of infected stallion can last from several weeks to lifelong (37).

Organ abbreviations: AG, ampullary gland; BG, bulbourethral gland; E, epididymis; P, prostate; SV, seminal vesicles; T, testis; U, urethra; VD, vas deferens.

Acronyms of main viruses detected in human male genital tract are spelled out in table 1. Others virus abbreviations: ASFV, African swine fever virus; BDV, Border disease virus; BHV-1, Bovine herpesvirus-1; BIV, Bovine immunodeficiency virus; BLV, Bovine leukemia virus; BTV, Bluetongue virus; BVDV, Bovine viral diarrhea virus; CAEV, Caprine arthritis encephalitis virus; CSFV, Classical swine fever virus; EAV, Equine arteritis virus; EHV, Equine herpesvirus; FMDV, Foot-and-mouth disease virus; LSDV, Lumpy skin disease virus; MVV, Maedi-visna virus; PCV2, Porcine circovirus type 2; PEAV, Peaton virus; PEDV, Porcine epidemic diarrhea virus; PEV, Porcine enterovirus; PoRV, Porcine rubulavirus; PPV, Porcine parvovirus; PRRSV, Porcine reproductive and respiratory syndrome virus; PRV, Pseudorabies virus; PTV, Porcine teschovirus; SBV, Schmallenberg virus; SRLV, Small ruminant lentivirus; SVDV, Swine vesicular disease virus.