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HIV infection of the penis

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Abstract

The penile foreskin, shaft, glans/corona, meatus and urethral introitus are all potential sites of HIV-1 acquisition in men. Circumcision decreases HIV infection in heterosexual men by 50–60%, indicating that the foreskin plays an important role, but that other sites are also involved. HIV target cells have been described throughout the male genital epithelium, but appear to be more accessible in the inner foreskin and urethral introitus, both of which are mucosal (wet) epithelia and infectable with HIV *in vitro*. Sexually transmitted co-infections can increase the risk of HIV infection at these and other sites by eroding the protective epithelial layer and by attracting and activating HIV target cells in the mucosal epithelium. The moist subpreputial cavity hosts a unique microbiome that may also play a role in HIV infection. Both innate and adaptive immune defense mechanisms are operative in the lower male genital region. The penile urethral mucosa contains accumulations of IgA^+ plasma cells and T lymphocytes, and may provide a responsive target for future mucosal vaccines to prevent HIV sexual transmission.

Keywords

Penis; HIV; foreskin; urethra; sexually transmitted infections; mucosal immunology

Introduction

Over 60 million people have been infected by the human immunodeficiency virus type 1 (HIV-1) during the past 30 years, most through sexual transmission. Men comprise approximately half of the HIV-infected population worldwide, and can acquire HIV from both female and male sex partners. Sexually transmitted HIV infections in exclusively heterosexual men are acquired through the penis, whereas acquisition of HIV in men that have sex with men (MSM) can occur through the rectal or penile epithelium. The risk of female-to-male transmission is estimated to be 0.04% per unprotected exposure [95% Confidence Interval (CI): 0.01 – 0.14] in high income countries and 0.38% per act (95% CI: 0.13 – 1.10) in low income countries. The risk of male-to-male transmission is considerably higher overall (1.7% per unprotected exposure, 95% CI: 0.3 – 8.9)[1].

Little is known about the mechanisms and prevention of HIV infection of the penis. In this article we will review published studies pertaining to penile HIV acquisition and identify gaps in knowledge that might be pursued in future research.

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Anatomy of the human penis

A schematic of the anatomy of the penis is shown in Figure 1. The erect adult human penis averages 14 cm in length (95% CI: 10.7 – 19.1 cm) and 12.3 cm in circumference[2]. Based on these dimensions, the surface area of the erect penis averages approximately 200 cm^2. The external surface of the nonerect penis is covered by a "dry" keratinized squamous epithelium that is relatively resistant to HIV infection unless the skin is broken, inflamed or infected (Fig 2). However, in noncircumcised men, which comprise approximately 70% of the male population worldwide[3], the glans/corona and meatus of the relaxed penis are covered by a fold of skin called the foreskin or prepuce (Fig 1). The subpreputial epithelia covering the inner foreskin surface and glans/corona are mucosal "wet" epithelia that may be more susceptible to HIV infection. Recent studies indicate that the protective keratin layer may be thinner at these sites, and HIV target cells more available. Furthermore, the inner foreskin mucosal epithelium is more susceptible than outer foreskin epithelium to HIV infection in vitro (described in more detail below). The moist subpreputial cavity in noncircumcised men is also a primary infection site for HSV, HPV and other infectious organisms that promote HIV infection[4–9], and also harbors a unique proinflammatory anaerobic microflora that could increase the susceptibility of bordering mucosal epithelia to HIV infection10. The moist mucosae of the penis have been associated with HIV acquisition11. Upon erection, the foreskin fold shrinks and the inner foreskin mucosal epithelium is retracted to form part of the external penile surface. As such it is directly exposed to physical trauma and genital secretions during intercourse. After intercourse, HIV virions and infected cells from infected sexual partners may be trapped under the foreskin affording an increased opportunity for infection.

In circumcised men, most if not all of the mucosal foreskin epithelium is removed leaving a dry keratinized epithelial surface which is more resistant to HIV infection. Circumcision has been demonstrated in large randomized clinical trials to reduce the risk of HIV acquisition in men by 50–60%[6, 12, 13].

Although underexplored, largely due to difficulty in obtaining tissue for research, the penile urethra is another potentially important HIV infection site in both noncircumcised and circumcised men. At the urethral orifice, which is approximately 0.6 – 1.2 cm in diameter, the meatus is covered by a keratinized stratified squamous reflexion of the skin (Fig 2). This transitions into the nonkeratinized stratified squamous epithelium of the fossa navicularis, which then transforms into the pseudostratified columnar epithelium that lines the penile urethra (Fig 2). The mucosal epithelium at this site is enriched with immune cells including HIV target cells[14]. The penile urethra is approximately 20 cm long and 1–2 cm in diameter, and contains numerous mucin-producing pseudoglands called the glands of Littre (Fig 2). In the majority of noncircumcised men, the urethral orifice is covered by the foreskin when the penis is in the relaxed state[15]. Therefore, the entire tip of the penis including the urethral opening is exposed to the moist subprepucial microenvironment, and may be colonized by unique microflora [10, 16]. HIV infection of the penile urethra could therefore be enhanced in noncircumcised men due to recruitment and activation of HIV target cells by microflora that colonize the moist epithelium. In circumcised men that lack a foreskin, the urethral orifice may be the principal site of HIV acquisition.

Susceptibility of different regions of the penis to HIV infection

Because circumcision cuts the risk of HIV acquisition in men by half, much research has focused on the foreskin as a major HIV infection site. The earliest studies to address this issue reported that the inner foreskin epithelium had a thinner protective keratin layer, more accessible HIV target cells, and was more susceptible to HIV infection (both R5 and X4

strains) *in vitro* than outer foreskin tissue17–19. Studies on foreskins from men with sexually transmitted infections (STIs) indicated that infections were associated with focal inflammation and increased numbers of HIV target cells19, 20. However other recent studies are beginning to question some of these findings. A study of keratin thickness in North American adult foreskins found no difference in keratin thickness between the inner and outer foreskin epithelia21, and another study of Chinese adult foreskins concluded that the inner foreskin was more keratinized than the outer foreskin epithelium22. Donoval et al[23] and Hirbod et al[24] did not find differences in densities and types of HIV target cells in foreskin tissue from African men with varying histories of sexually transmitted infections. Frischetti et al[25] reported that foreskin tissue was infectable with R5 but not X4 HIV, whereas Ganor et al[26] found that the mucosal epithelium of the inner foreskin was not readily infectable with free HIV virions, but was highly susceptible to infection by HIV-infected cells. Therefore conclusive evidence that the foreskin is the principal HIV infection site on the penis is eroding. In addition, the foreskin theory does not explain how circumcised men acquire HIV infections.

STIs increase the risk of HIV infection in men (Table 1). They may do so by disrupting the penile epithelium and by attracting and activating HIV target cells at the site of infection. Langerhans cells (LCs), which are the predominant HIV target cell in stratified squamous epithelia, appear to have a dual role in HIV acquisition depending on their activation state. Immature LCs protect against HIV-1 infection by internalizing and degrading HIV-1 viral particles[27], whereas after activation by exposure to microbial products and proinflammatory cytokines, LCs are efficient mediators of HIV transmission28, 29. For example, *N. gonorrhoeae* organisms enhance the susceptibility of LCs to HIV infection[30]. Other HIV target cells including $CD4^+$ T cells and macrophages may also be attracted to and activated by STI pathogens. *N. gonorrhoeae* enhances HIV infection of resting $CD4^+$ T cells through TLR 2 activation[31], and HIV-1 receptor-positive cells accumulate at HSV-2 lesions and persist for some time after the infection clears[32]. STIs can infect various sites along the penis, including the shaft, foreskin, glans/corona and urethra. Circumcision decreases HSV2 acquisition by 28 to 34%, HPV prevalence by 32 to 35% and the incidence of genital ulcer disease in men, which could contribute to the effect of circumcision on HIV acquisition[33].

Studies on HIV infection of the human penis at sites other than the foreskin have been limited by lack of availability of penile tissue. Immunohistochemistry studies of penile skin and urethral mucosal epithelium harvested at autopsy have shown that Langerhans cells are found throughout the stratified squamous epithelia (shaft, glans, meatus), whereas other types of HIV target cells, notably macrophages and $\alpha E\beta 7^+CD4^+$ T cells, are present in the columnar urethral mucosa[14, 18, 25]. Cells present at the urethral opening also express HIV coreceptors CCR5 and CXCR4[34]. Abundant cells expressing CCR5 are also present in the mucosa of the penile urethra (Fig 3). In the sole published study of HIV infection of various penile sites (fresh penile tissue acquired from sex change operations after long term estrogen treatment), explants of foreskin, glans, meatus and urethra were all susceptible to R5 HIV-1 infection in vitro[25]. Studies on HIV infection of the penile urethra and other nonforeskin sites of the human penis have been limited thus far to tissues from a small number of men from developed countries. Further studies are needed to delineate HIV target cells and infection mechanisms of penile tissues from men representing different racial and ethnic groups in HIV endemic areas, from men with different hygiene and sexual behaviors including gay men, and from men with penile/urethral inflammation and various STIs. SIV/SHIV penile infection studies could also contribute valuable insight.

Immunologic Protection of the Penis

Keratinized squamous epithelia are defended by innate and acquired immune defense mechanisms. We have carried out immunological studies on human adult foreskin removed for cosmetic reasons We recently profiled mucin gene expression in the foreskin[35]. RNA for 8 mucin genes, including the gel-forming mucin 5AC, was detected by RT-PCR in human foreskin tissue. However, we were only able to confirm expression of two mucins, Muc 1 and Muc 4, at the protein level. Muc 1 and 4 are membrane-associated mucins found at many sites throughout the male genital tract.

The predominant immune cell population in the healthy foreskin is the macrophage, found primarily in the lamina propria (Fig 3). A variable number of Langerhans cells are also found within the foreskin and penile epithelium (Fig 3). These Langerhans cells are positive for CD1a, langerin and HLA-DR. A few $CD4^+$ lymphocytes are found in the lamina propria; by contrast, a larger number of $CD8^+$ lymphocytes can be detected in both the lamina propria and epithelium. A majority of these lymphocytes expressed the memory marker CD45RO. Foreskin tissue was examined by immunohistology for expression of Toll-like receptors (TLR) 1–9[36]. One sample was distinctly positive for TLR-5. $TLR5^+$ keratinocytes were detected in the basal and suprabasal regions of the epithelium, and numerous $TLR5^+$ cells that morphologically resembled lymphocytes were also found in the lamina propria. The foreskin was also studied for the presence of the type 1 interferons (IFN) alpha and beta. IFN-α was not detected, but many keratinocytes at the base of the epithelium and a few cells in the lamina propria expressed IFN-β (Fig 4). Cells expressing lactoferrin and lysozyme were detected in the lamina propria of the foreskin (data not shown).

Little is known about the composition of foreskin secretions. It is likely that they contain mucins, as the human foreskin expresses a number of mucin genes[35]. It is also likely that foreskin secretions, like other mucosal secretions, contain soluble mediators of immune defense that play an important role in preventing infections at this site. The foreskin is highly vascularized and serous transudation could supply antibodies to foreskin secretions. In preliminary studies, we have detected immunoglobulins, proinflammatory cytokines and antimicrobial proteins in human foreskin secretions, providing evidence that this region is protected by mediators of innate and acquired immunity.

The penile urethra is an immunologically dynamic mucosal epithelium. We and others have begun to characterize mediators of innate immunity in urethral tissues and secretions. Several membrane–associated mucins (MUC 1, 3, 4, 13, 15, 17, and 20) were confirmed to be expressed by the urethral epithelium, and one gel-forming mucin, MUC5AC, was detected in urethral glands[35]. Further characterization of the structure and function of urethral mucins will be important for a complete understanding of immune defense at this site.

A large number of cells in the penile urethra express diverse TLRs[36]. The mucosal epithelium of the penile urethra was one of few genital tissues that expressed TLR9, a receptor that detects viral nucleic acids and plays an important role in antiviral immune defense. Immune cells in the urethral mucosal epithelium expressed a variety of TLRs. The expression of the human defensin HD-5 has been studied in the penile urethra. HD-5 was secreted as a propeptide, and its expression was upregulated by *C. trachomatis* and *N. gonorrhoeae* infections. HD-5 was activated when levels of HNP 1–3 were elevated, suggesting that neutrophils contribute key proteases to convert proHD-5 to its bioactive form in the urethra during infection[37, 38]. Lysozyme was often detected in the glands of Littre and in intraepithelial cells resembling macrophages (Fig 4). Lactoferrin was consistently expressed by columnar epithelial cells of the urethra. The production of

lactoferrin was most prevalent in crypt-like infoldings that were present along the length of the urethral epithelium. Secretory leukocyte protease inhibitor (SLPI), a component of innate immunity that plays a role in reducing inflammation as well as inhibiting infection by bacteria, viruses and fungi, was abundantly expressed by both columnar epithelial cells and urethral glands in the penile mucosa (Fig 4).

We recently measured concentrations of SLPI and lactoferrin in urethral lavages of men with and without acute *N. gonorrhoeae* infections. SLPI was detected in both groups, and was not elevated in secretions from the GC group (Fig 5). Lactoferrin was also detected in both groups and was significantly elevated in urethral secretions from the GC group (Fig 5). These data provide evidence that antimicrobial proteins play an important role in limiting urethral infections.

The penile urethral epithelium contains a full contingent of cellular mediators of adaptive immunity. In the urethra proper, $CD1a^+$ dendritic cells are absent and macrophages are the major antigen presenting cells. Macrophages were detected mostly in the epithelium with few located in the lamina propria (Fig 3). Abundant T-lymphocytes are present in the urethral mucosa. $CD8^+$ lymphocytes are the predominant sub-population occurring in both the epithelium and lamina propria. By contrast $CD4^+$ lymphocytes are primarily restricted to the lamina propria (Fig 3). Large concentrations of CD45RO (memory) T lymphocytes were present in both the epithelium and lamina propria of the urethra. Many of these T lymphocytes also expressed CD103, the αEβ7 integrin that mediates adhesion of mucosal lymphocytes to epithelial cells. Urethral T lymphocytes present in the epithelium and lamina propria also expressed TIA-1, a cytotoxic granule associated protein found in lymphocytes with cytotoxic functions (Fig 3). These data indicate that the human penile urethra has classical mucosal T cell and antigen-presenting cell populations potentially capable of mounting local immune defense.

Whereas a number of animal studies have begun to characterize cellular immune responses to infections in the penile urethra[39–41], few studies have been conducted on urethral samples from men with sexually transmitted infections. T lymphocytes isolated from first catch urine samples were more numerous in men with gonorrhea and chlamydia infections than from men with nongonococcal urethritis[42]. In a recent study from our group, urethral lavages from men with *N. gonorrhoeae* infections contained significantly higher concentrations of proinflammatory cytokines and antiviral factors than comparable samples from men without infections (Fig 5). It should be possible to use these collection techniques to more fully describe cellular immune responses occurring at this site.

Immunoglobulin (Ig)-producing plasma cells and polymeric Ig receptor expression have also been described in the penile urethra[43]. Numerous IgA and IgM producing plasma cells were present in the lamina propria (Fig 4). Furthermore most of these plasma cells were positive for the presence of the J chain indicating secretion of polymeric IgA or IgM. Fewer IgG^+ plasma cells compared to IgA^+ plasma cells were detected in the urethra. Polymeric IgA and IgM are transported across epithelia by means of the polymeric Ig receptor (pIgR) which is mediated via the secretory component (SC). The epithelium of the urethra highly expressed the pIgR as evidenced by the intense positive staining for SC (Fig 4). Also the glands of Littre and their contents were often positive for the presence of IgA, J chain and SC. Furthermore, the mucus layer covering the surface of the urethral epithelium was also strongly positive for IgA and SC. This suggests that the mucosal secretion produced by the glands of Littre contains abundant secretory IgA and coats the epithelial surface to form an immunological barrier against invading pathogens. The stratified squamous epithelium lining the meatus and fossa navicularis did not express pIgR. Whereas few plasma cells of

any phenotype were present in the meatus, numerous IgA^+ and J $chain^+$ plasma cells were observed in the mucosa of the fossa navicularis.

Surprisingly little data are available concerning immunoglobulin levels and isotypes in human penile urethral secretions. Based on the immunohistologic evidence of abundant IgA^+ plasma cells and polymeric Ig receptor in urethral tissues, it is likely that secretory IgA predominates in urethral secretions.

Conclusions

HIV infection and immune defense of the human penis is an understudied area of research. Much of the focus has been on foreskin tissue, but research studies should be expanded to include other tissues including the penile urethra which appears to be an important site of both HIV infection and immune defense (Table 2).

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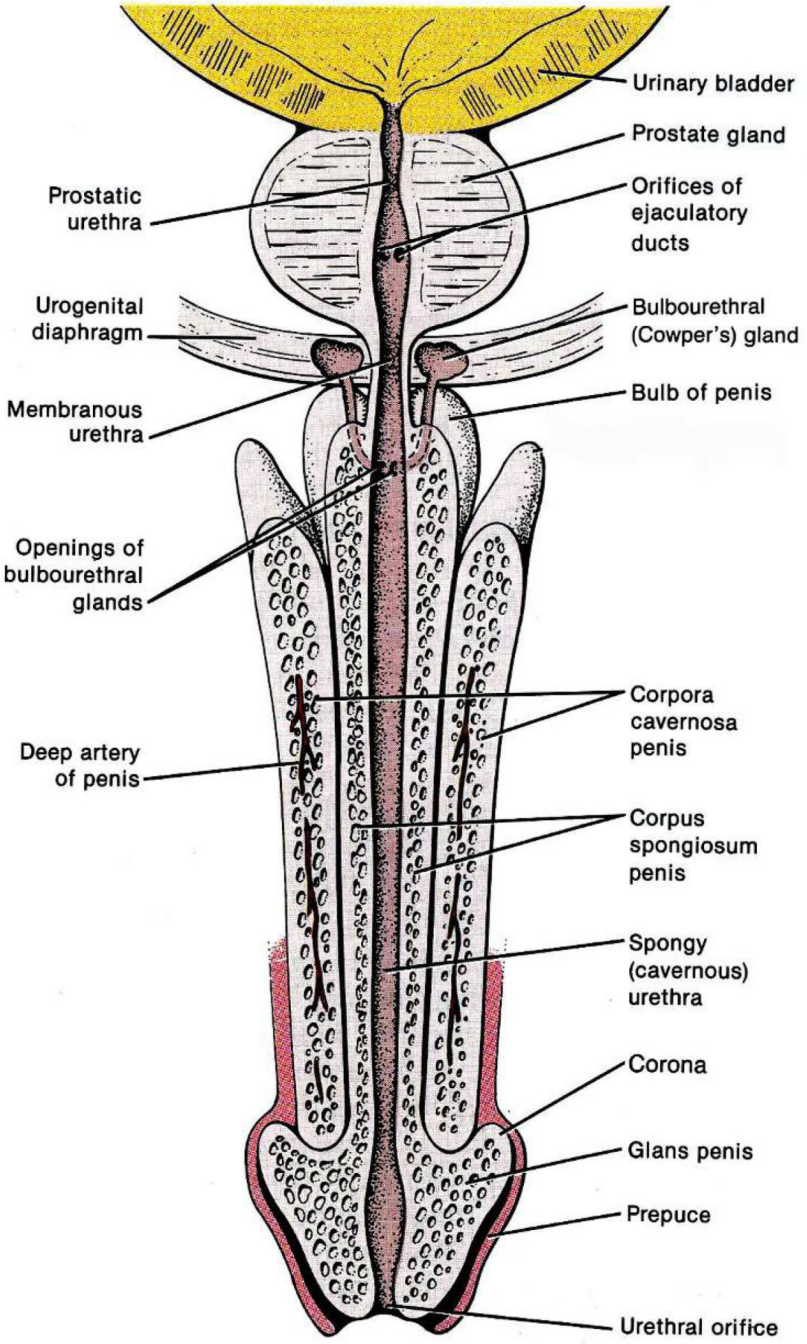


Figure 1.
Schematic of the anatomy of the human penis modified from G. J. Tortora and N. P. Anagnostakos[44].

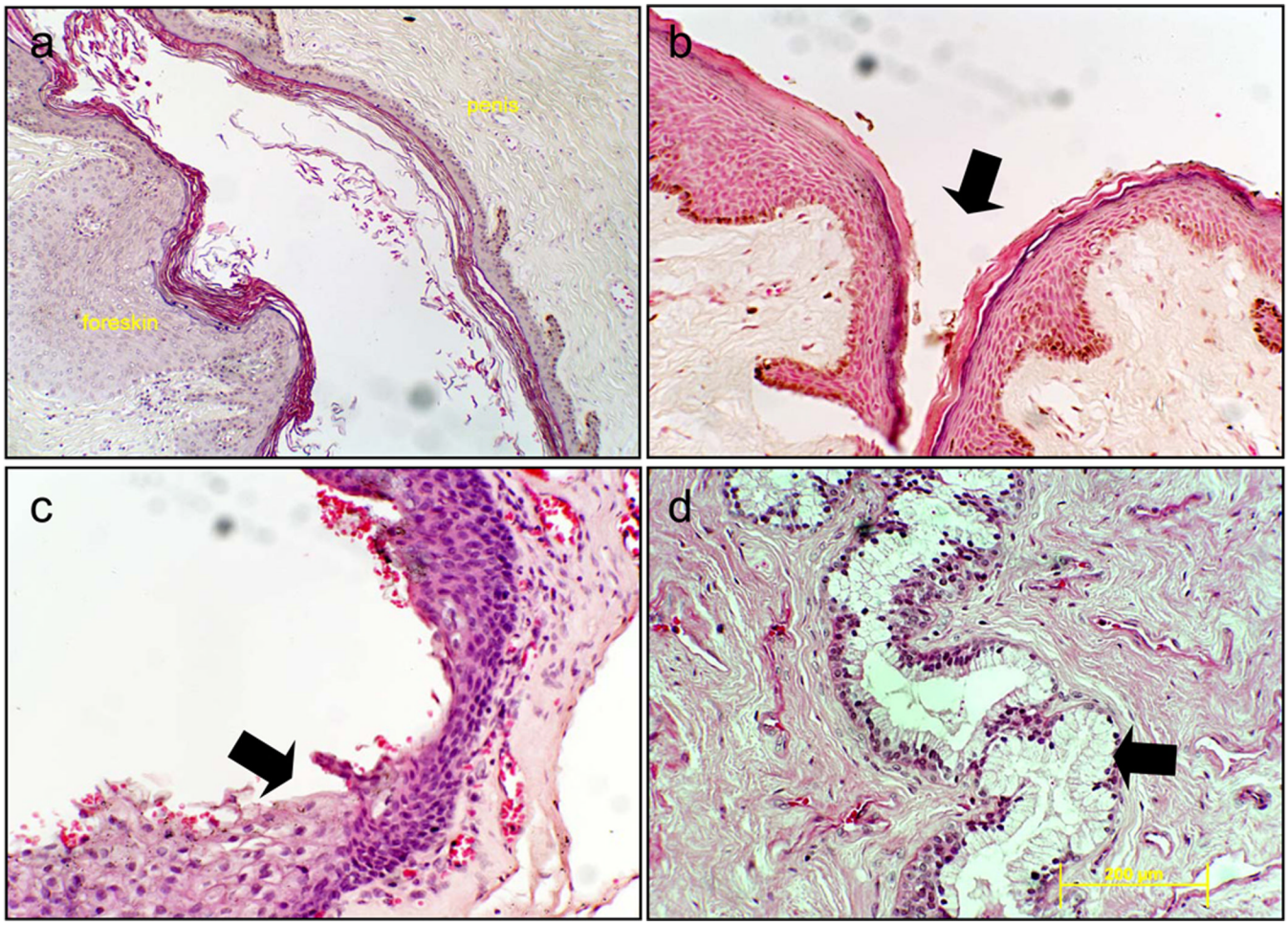


Figure 2.
Histology of the human penis.

- **a.** Section through the penile skin and inner aspect of the foreskin. Both are composed of a keratinized stratified squamous epithelium.
- **b.** The meatus (arrow) is covered by a reflexion of the skin.
- **c.** The non-keratinized stratified squamous epithelium of the fossa navicularis abruptly transitions (arrow) into the pseudostratified columnar epithelium of the penile urethra.
- **d.** Penile urethra with a gland of Littre (arrow).

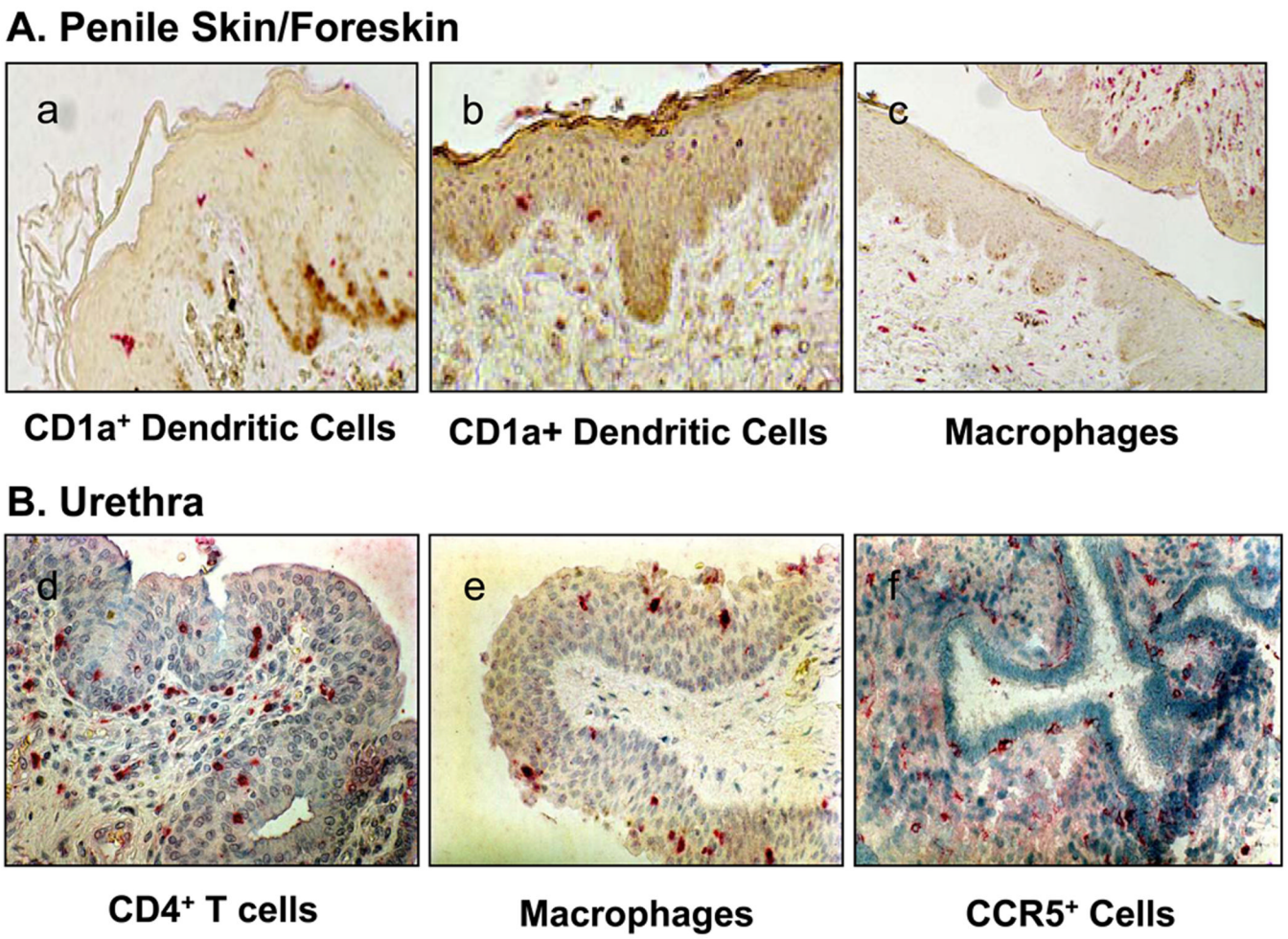


Figure 3.
HIV target cells in the human penis.

1. Penile skin/foreskin
   - **a)** $CD1a^+$ dendritic cells in epithelium of penis.
   - **b)** $CD1a^+$ dendritic cells in epithelium of foreskin.
   - **c)** Macrophages present in foreskin.
2. Urethra
   - **e)** $CD4^+$ T cells in the penile urethra present in the epithelium and lamina propria.
   - **f)** Macrophages were located primarily in the epithelium of the urethra.
   - **g)** $CCR5^+$ cells were abundant and detected in the epithelium and lamina propria.

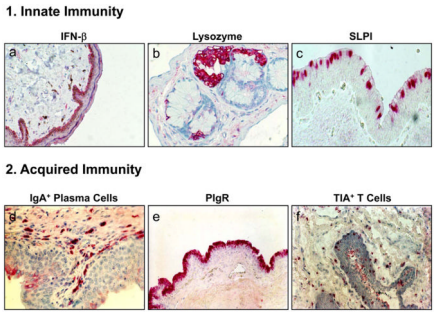
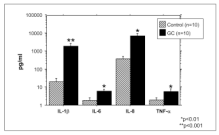


Figure 4.
Immune defense of the human penile epithelium.

1. Innate immunity.
   - **a)** IFN-β expressed by the epithelium of the penis.
   - **b)** Lysozyme detected in the urethral glands of Littre.
   - **c)** SLPI expressed by epithelial cells of urethral mucosa.
2. Acquired immunity.
   - **d)** IgA^+ plasma cells were abundant in the lamina propria of the urethra.
   - **e)** The Poly IgR was expressed by the epithelium of the urethral muscosa.
   - **f)** TIA^+ T cells present in the epithelium and lamina propria of the urethra.



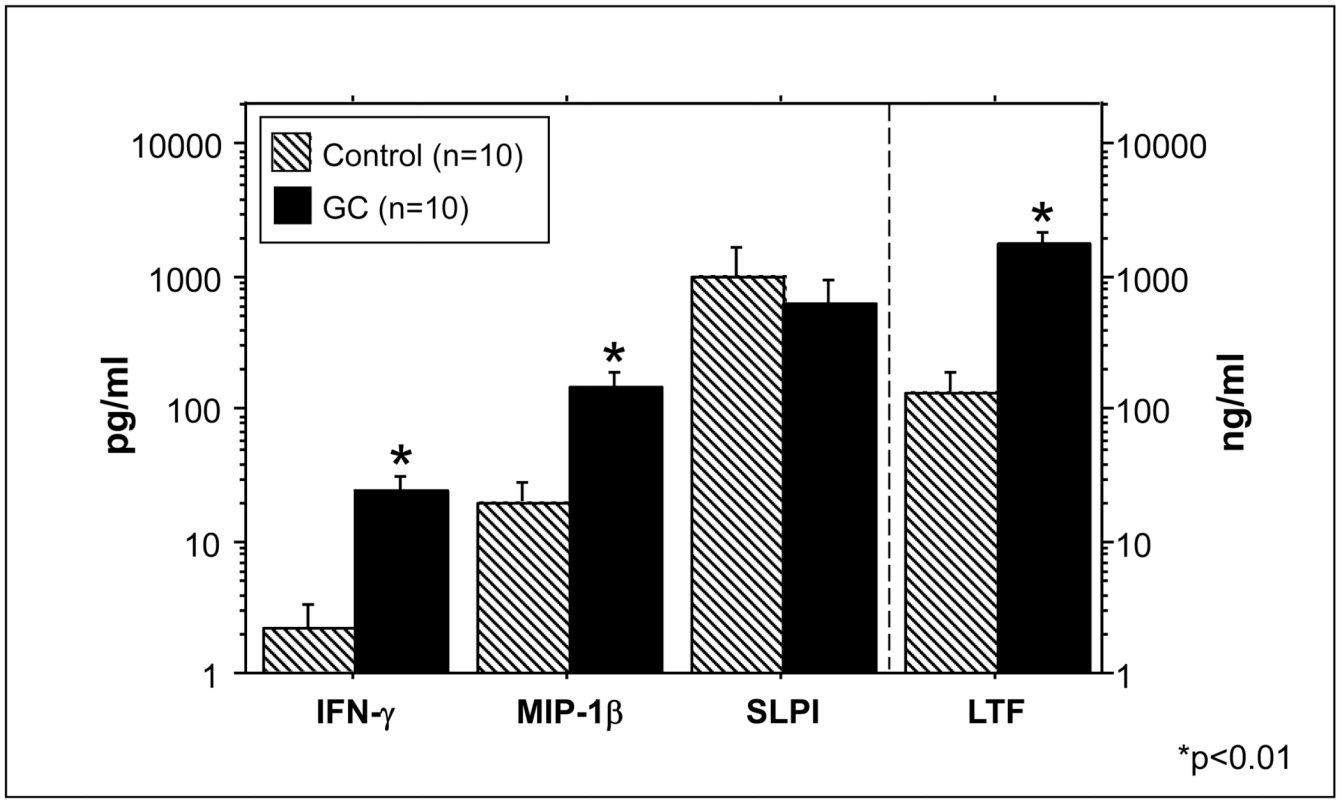


Figure 5.
The effect of *N. gonorrhoeae* infection on:

- **a.** proinflammatory cytokines in urethral secretions
- **b.** levels of antiviral factors in urethral secretions.

Table 1

Effects of STIs on Penile HIV Acquisition

STI	Ratio (95% Confidence Interval) HIV Acquisition (Men)[a]	Penile Infection Sites	Effect of Circumcision on STI
HPV	1.8 (1.1–2.9)[b],[7]	Glans, coronal sulcus, inner foreskin, external foreskin, shaft, urethra[5–7]	Reduced HPV prevalence[45]; Decreased detection of HPV in several penile sites[46]; Increased clearance of penile HPV[47, 48]
HSV-2	2.7 (1.9–3.9)[c],[49]	Penile skin, urethra[4, 8, 9]	Reduced HSV-2 incidence[45]

[a] The data shown are from publications using different statistical methods. All ratios are adjusted.

[b] Hazard ratio

[c] Summary relative risk of 19 studies

Table 2

Major Gaps in Knowledge

Microbiome of male genital tract
Effects of androgens on male genital tract mucosal immunology and HIV infection mechanisms
Standardized human inner foreskin and penile urethral sampling protocols
In vitro and animal models of urethral HIV infection and immune defense