Review

Unraveling the Rectal Virome: Microbial Crosstalk, Immune Modulation, and Clinical Outcomes in People with and Vulnerable to HIV

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Review

Unraveling the Rectal Virome: Microbial Crosstalk, Immune Modulation, and Clinical Outcomes in People with and Vulnerable to HIV

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Abstract

The rectal mucosa houses a large number of viruses with important roles in shaping the local microbial communities and modulating immune responses which could influence host susceptibility to infection and other diseases. Unique composition of the gut microbiome, including the predominance of clinically significant eukaryotic viruses like herpesviruses, CMV, and human papillomavirus, has been described in both people living with HIV (PLWH) and men who have sex with men (MSM) vulnerable to HIV. Despite these insights, the rectal virome and the clinical implications of virome–bacteriome–immune interactions in the rectal mucosa remain poorly understood. In this review, we synthesize existing data on the composition of the rectal virome, its interactions with the bacteriome and the immune system, and implications on clinical outcomes in people living with or vulnerable to HIV. We also highlight the gaps and research needed to further explore and unravel these relationships.

Keywords: virome; bacteriome; microbiome; immunity; HIV; bacteriophages; eukaryotic viruses

1. Introduction

The gut virome is predominantly composed of bacteriophages, and to a lesser extent, eukaryotic viruses and plant viruses of dietary origin [1,2]. Besides shaping the local microbial communities [3] and contributing to the pathogenesis of disease [4,5], the gut virome has emerging therapeutic potential, including fecal virome transplant and phage therapy [3,6–8]. Furthermore, alterations in the gut viral communities may also serve as novel biomarkers for disease states, given their role in maintaining gut homeostasis [9–11]. The relationship between the virome, bacteriome, and the host immune system has led to the proposed "tri-kingdom network" involving interacting bacteria, phages, and human cells [12]. A disequilibrium in this network, called gut dysbiosis, has been observed across many chronic inflammatory disease states, including inflammatory bowel disease [13–15], cancers [16–18], and neurodegenerative diseases [19–24]. Despite efforts to specifically characterize the gut virome, large parts of the virome remain unclassified, which has been referred to as the "viral dark matter" [25–27]. Additionally, questions remain unanswered among the well-characterized parts, such as the degree to which phage-bacteriome-immune interactions are affected in the presence of chronic inflammation induced by HIV and other eukaryotic viruses, and if phage-induced gut dysbiosis could potentially contribute to the acquisition of sexually transmitted infections (STIs) in those who have receptive anal intercourse (RAI). Therefore, significant knowledge gaps persist in our understanding of the gut virome and its overall impact on human health.

Among men who have sex with men (MSM) and particularly among those living with HIV (people with HIV; PWH), prior studies have reported increased prevalence of clinically relevant viruses including herpes simplex virus (HSV), Epstein–Barr virus (EBV), cytomegalovirus (CMV), and human papillomavirus (HPV), as well as anelloviruses and adenoviruses [28–36]. The presence of these viruses in the gut can be linked to clinical outcomes (e.g., EBV-induced lymphoproliferation,

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HPV-induced anorectal cancer, and CMV retinitis) [37–39] as well as transmission during condomless RAI. Alterations in the gut bacteriome have also been demonstrated both in PWH as well as MSM vulnerable to HIV who are engaging in receptive anal intercourse exemplified by a high relative abundance of *Prevotella* [40–42]. Gut dysbiosis is thought to contribute to the chronic inflammation observed in PWH [43]. Among MSM both with and without HIV, the rectum is part of a potential rectal–penile interface which represents a microbial and viral transmission nexus where interpersonal virome and bacteriome exchange may occur during RAI. Therefore, the rectum represents both a gut mucosal and a sexual exposure site whose viral populations are not only influenced by diet and digestion and the resultant local immune responses, as in the rest of the gut virome, but potentially also by sex, semen exposure, lubricants, and partner penile microbiota exposure making it distinct from other mucosal surfaces in the gut.

Given the unique characteristics of the bacteriome and virome among MSM with and without HIV, it is important to further explore how the rectal virome influences the bacteriome and mucosal immune changes and the contribution to chronic inflammation and other clinical outcomes in people living with or vulnerable to HIV.

2. Composition, Diversity, and Functional Dynamics of the Gut Virome

The human gut contains the most abundant collection of viruses across the human body, consisting of both DNA and RNA viruses [4,26]. The gut virome is not present at birth; the neonatal gut begins to rapidly acquire its virome after membrane rupture and delivery, marking the first major exposure to the external environment [44–46]. This early period is very critical and may have implications for healthy gut development [47,48]. The initial composition of the infant virome is influenced not only by viruses present in the maternal gut and breast milk, but also by viruses from other maternal body sites, the mode of delivery, the individuals the infant comes into contact with, and the surrounding environment, depicting the role of environmental exposure in shaping the virome [48–53]. The early colonizers of the gut include phages of the newborn gut's bacterial communities, and the virome continues to change with age, reflecting shifts in the acquisition and relative abundance of host bacterial species over time. Host genetics and immunity, ageing, use of medications, and geographical location also play a role in shaping the virome, but environmental factors appear to dominate in their influence over the host's genetics [26,47,50,54].

The adult human gut virome is generally understood to consist of two major parts: the "Persistent Personal Virome" (PPV) and the "Transiently Detected Virome" (TDV) [1]. The PPV forms the core of an individual's viral community and is highly individualized as each person carries a unique set of phage populations that differ markedly from those of other individuals [1,55–57]. Aside from the individual specificity, the gut virome also has high temporal stability similar to the bacteriome, lasting for more than two years in some cases [1,55,56,58]. The *Microviridae* and crAss-like phages of the PPV are among the most stable colonizers of the human gut, infecting common gut microbiota such as *Bacteroides*, *Faecalibacterium*, *Eubacterium*, *Prevotella*, and *Parabacteroides*. By contrast, the TDV represents the more variable and short-lived component of the gut virome. Unlike the PPV, the TDV is not strongly individualized, suggesting that it may be acquired from shared environmental exposures, diet, interpersonal contact, or behavioral transmission. The TDV includes a higher proportion of *Siphoviridae* phages along with smaller viral families such as *Inoviridae*, *Genomoviridae*, *Papillomaviridae*, *Anelloviridae*, and *Virgaviridae*. TDV phages typically infect bacterial hosts that are less common or more transient in the gut, including *Streptococcus*, *Clostridium*, *Akkermansia*, *Acinetobacter*, *Listeria*, *Escherichia*, and *Bilophila* [1].

Phages are the most abundant members of the gut virome, making up more than 90% of the gut virome (the phageome) [59]. While phages do not infect human cells, they alter bacterial pathogens by transferring virulence factors that promote bacterial infectivity and colonization [12,60–62]. Phage-encoded proteins can also disable phagocytes involved in bacterial immune clearance [63]. Phage-driven virulence has been well documented in pathogens such as *Vibrio cholerae* [64–66] and *Escherichia coli* [67], amongst other organisms [68,69]. Because of the significance of these phage-

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bacteria interactions, the use of phage therapy for the treatment of diseases, including STIs, is a growing area of research, one that offers a promising approach for the treatment and development of vaccines against these STIs [70–72]. Researchers have used engineered phages to slow the growth and reduce the infectivity of *Chlamydia trachomatis* [73–75]. While similar findings are yet to be discovered for *Neisseria gonorrhoeae* [76,77], and *Treponema pallidum*, in this era of treatment failure due to antibiotic resistance [78–80], understanding these phage-bacteria interactions is particularly relevant given the increased prevalence of these STIs in the rectal mucosa of MSM [81,82].

Phage-driven horizontal gene transfer can facilitate the movement of antibiotic resistance genes (ARGs), although ARG carriage within human phageomes appears limited [83–85]. Antibiotic exposure has also been shown to perturb the bacteriome, drive rapid shifts in phage communities, and promote the transfer of virulence factors [4,83–87]. PWH, particularly those with advanced disease (CD4 <200 cells/μL), frequently experience recurrent bacterial infections and sexually transmitted infections, and therefore often receive repeated courses of antibiotics or long-term prophylaxis to prevent opportunistic infections [88,89]. Among MSM, higher rates of bacterial STIs similarly contribute to higher antibiotic use [90–92]. In this group, the increasing uptake of doxycycline post-exposure prophylaxis (Doxy-PEP) for STI prevention represents an additional and ongoing source of antibiotic exposure [93–96]. Despite this, it remains unclear whether chronic antibiotic exposure meaningfully alters the rectal virome in PWH and/or MSM, or whether such changes have downstream effects on mucosal inflammation, local immunity, or systemic immune activation.

Phages also function as active immunomodulators, with direct and indirect effects on human host immunity. They adhere to mucus and form a protective mucosal layer, providing a non–host-derived form of immunity that protects host cells from bacterial-induced damage [97,98]. Alternatively, phages can disrupt the intestinal barrier by altering the bacteriome and increasing intestinal permeability, thereby permitting the translocation of bacterial endotoxins through this compromised barrier [99]. Upon crossing the gut epithelium into the circulation, they interact with both innate and adaptive immunity by influencing immune signaling, including cytokine release, bacterial recognition, and T and B cell regulation [100–104]. Researchers have demonstrated that phage-induced gut dysbiosis and leaky gut contribute to many chronic inflammatory diseases, such as inflammatory bowel disease, Alzheimer's disease, diabetes, and others [99]. This is relevant to PWH, where bacterial translocation is thought to be a major driver of chronic inflammation, and chronic immune activation and mucosal barrier dysfunction are central to disease progression [105–107]. It is possible that the impaired gut mucosal barrier that occurs in HIV infection favors phage DNA translocation [108], producing an environment that amplifies phage-bacteriome and phage-immune interactions. Future research should explore the contribution of phage-induced immune activation to persistent inflammation seen in HIV infection. Perhaps, establishing this link would deepen our understanding of HIV-associated immune activation and may reveal phage-directed novel therapeutic targets.

3. The Gut Virome in PWH and MSM Vulnerable to HIV Acquisition

3.1. Overview of the Gut Microbiome in PWH and MSM Vulnerable to HIV Acquisition

Prior research has shown that the rectum of MSM who engage in RAI have increased production of pro-inflammatory cytokines and relative abundance of *Prevotella* taxa compared to men who do not engage in RAI [40–42,109]. Multiple studies have shown that bacteriome changes are largely demonstrated by variation in *Prevotella* taxa abundance [109–111]. With respect to the virome, the abundance of *Prevotella* in the human gut has been linked to higher viral diversity, greater proportions of temperate phages, and lower total viral genome loads in fecal samples [1], reflecting the close-knit and dynamic relationship between the bacteriome and virome. The bacteriome changes in MSM have been linked to sexual practices including condomless RAI, increasing number of sexual partners, use of hyperosmolar lubricants, and other behaviors and environmental factors [111–113].

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We hypothesize that these same exposures and factors likely influence the rectal virome, both directly through the introduction of viruses from partner exposures and indirectly through bacteriome shifts, which in turn drive changes in phage populations.

The presence of gut dysbiosis in MSM has also been linked to chronic inflammation and increased acquisition of HIV in MSM [40,41,109,114–116] and perhaps other clinically significant eukaryotic viruses in these groups. During receptive anal intercourse, it is likely that there is transfer of partner-derived bacteria, bacteriophages, and sexually transmitted eukaryotic viruses into the rectum. The micro-abrasions which occur during RAI may permit deeper entry of viruses, potentiating immune activation. While this direct transfer of viruses between the penis and rectum has not been studied, research has demonstrated sharing of genital taxa and bacteriome changes following sexual intercourse among heterosexual couples [117–121]. Extending this evidence, we hypothesize the concept of a "penile–rectal interface," a bidirectional transmission node where bacterial taxa, phages, and eukaryotic viruses may be exchanged during insertive and receptive anal intercourse. Understanding of this interface could reshape our knowledge of the distinct rectal ecosystem that can be observed in MSM and PWH.

Studies have also shown that HIV infection has been associated with changes in the gut microbiota [35,110,122], and these changes are significantly different in MSM compared to non-MSM [110]. Chronic HIV infection has been shown to decrease gut levels of *Akkermansia*, *Anaerovibrio*, *Bifidobacterium*, and *Clostridium* [35]. HIV infection also results in the depletion of gut CD4+ T cells and Th17 cells [123,124], which are relevant in defense against bacterial invasion and maintaining the intestinal barrier [125,126]. These immune changes have been shown to be amplified by the presence of *Escherichia coli* [127]. Furthermore, HIV is associated with chronic inflammation in the gut primarily due to the loss CD4+ T regulatory cells (Tregs), which function to maintain homeostasis and modulate the activity of other immune cells [128–130]. The loss of these Tregs has been suggested to contribute to HIV-induced gut dysbiosis. The gut dysbiosis, increased intestinal permeability, and persistent inflammation that occur in HIV infection drive oncogenesis [131] and could permit the translocation of microbial products into the systemic circulation, further worsening clinical outcomes in these groups. It is unlikely that the effects of HIV are limited to the bacteriome and immune activation, as we do not know the effect of HIV on the phage community in the gut and how these HIV-driven virome changes contribute to chronic inflammation and influence the clinical progression of the disease.

Researchers have demonstrated across various studies that changes in the gut virome occur with HIV infection [35]. A study reported that severely immunosuppressed people have an increase in adenoviruses in the gut, which might worsen gut mucosal damage [30,35]. Another study found reduced phage diversity in untreated HIV infection that improved after starting antiretroviral therapy (ART) [132]. A recent study also associated dramatic increases in anelloviruses with worsening immune deficiency, returning towards normal levels as the immune system improves [30]. Given that PWH likely have a unique rectal virome, it is possible that shifts within rectal virome composition and diversity could offer a useful surrogate marker for disease progression.

Similarly, because bacterial dysbiosis is linked to advanced HIV infection [35,36], it is plausible that changes in the rectal virome also reflect disease severity, given the close relationship between the bacteriome and the virome. Individuals with advanced HIV disease (CD4 <200) have significantly lower gut bacterial diversity (Shannon index) and reduced phage richness (*Inoviridae* bacteriophages) than people with higher CD4 [30]. *Anelloviridae* [133–135], *Papillomaviridae* [136–139] and *Adenoviridae* [35,140] are also far more abundant in those with advanced HIV. Low CD4 counts and the presence of *Anelloviridae* before ART has also been linked to poorer immune recovery [30]. Persistent use of ART (24 months) has also led to a significant drop in the levels of *Anelloviridae*. Therefore, these virome patterns may complement traditional immunologic markers such as Viral Load (VL) and CD4 T-cell and provide added insight into immune recovery.

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3.2. Eukaryotic Viruses of the Gut of PLWH and MSM at Risk of HIV Acquisition

Certain eukaryotic viruses have been detected more commonly in the gut of PWH and MSM. These viruses, reviewed below, may be associated with gut dysbiosis, immune activation, and worsen clinical outcomes. Despite significant advances in microbiome research in the gut of PWH and MSM, scientists are only beginning to understand the interactions between these co-morbid eukaryotic viruses (CMV, EBV, HSV, and HPV) with the bacteriome and the rectal mucosal immune system. These discoveries have created a potentially revolutionary niche for advancing our understanding of dysbiotic and inflammatory changes in the gut of PWH and MSM, and for developing targeted, novel therapeutics aimed at improving health outcomes in these groups.

3.2.1. Cytomegalovirus (CMV)

The presence of CMV infection has been associated with a reduction in the ratio of *Firmicutes* to *Bacteroidetes* in the gut during early infection [141]. This ratio is commonly used as a marker of gut dysbiosis, and an abnormal pattern is often seen in people who have inflammatory bowel disease [13–15], a pattern that may be observed as relevant in PWH, as both diseases are marked by chronic inflammatory states. CMV co-infection has also been suggested to worsen the progression of HIV infection and to potentiate inflammation even when on suppressive ART [142–145]. CMV can infect the intestinal epithelial cells and disrupt their tight junctions, reducing the barrier integrity and increasing permeability, doing so by triggering the production of pro-inflammatory IL-6 [29]. Several other studies have also demonstrated that CMV triggers inflammatory cytokines like TNF-α, IL-1β, IFN-γ, and IL-6 in several immune and tissue cell types, even in healthy states [141]. This suggests that CMV co-infection may be an important cofactor in driving the gut dysbiosis and chronic inflammation observed in PWHV or MSM.

3.2.2. Epstein–Barr Virus (EBV)

EBV infection has also been associated with gut microbiome shifts and immune activation. [146–148]. EBV infection tends to decrease the levels of *Firmicutes* and *Lactobacilli* [146] and to trigger colonic expression of IL-17A, FOXP3, and IFN-γ, all of which are markers of inflammation and autoimmunity [147]. Likewise, the tumorigenic effect of EBV is enhanced by the presence of HIV co-infection [149], and PWH are at increased risk of EBV-induced cancers [150]. EBV's role in causing cancer has also been shown to be due to its ability to infect many immune cells (B cells, T cells, NK cells) and epithelial cells, pushing them to grow uncontrollably [148].

The lifecycle of EBV also involves a latent phase during which its DNA resides in the host cells and consistently triggers cytokine production, producing viral versions of human cytokines (IL-10) to suppress immune activity [148]. While the immune system is unable to completely clear out the infection [151], the immunosuppression that occurs in HIV infection further worsens the clinical outcomes [37,152].

3.2.3. Herpes Simplex Virus (HSV)

The relevance of HSV-associated gut microbiome dysbiosis is particularly important for PWH and MSM, as these groups tend to have a higher prevalence of HSV infection and more frequent episodes of viral reactivation [153–156]. HSV infection has been shown to cause alterations in the Firmicutes phylum and certain Clostridium species that produce short-chain fatty acids (SCFAs) [157]. These SCFAs have been found to be essential in maintaining the integrity of the gut barrier and also reducing inflammation [157–159]. Treatment with Acyclovir and Intravenous immunoglobulin (IVIG) can further disrupt the bacteriome, leading to significant changes in *Bacteroidetes*, *Firmicutes*, *Akkermansia muciniphila*, *Verrucomicrobia,* and other bacterial species [157]. Some of these bacteria have been shown to play a protective role against diseases in human patients [160–164]. HSV-induced gut dysbiosis weakens the blood-brain barrier, activates microglia, and increases inflammation, allowing the HSV-1 reach the brain to establish latent infection and reactivate [165,166].

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HSV-1 also infects neurons and releases monocyte chemoattractant protein-1 (MCP-1/CCL2) which attract macrophages that produce reactive nitrogen species, damaging enteric neurons, causing abnormal gut motility [167,168]. It also causes the expression of viral antigens which attract activated CD8+ T cells to the gut [168] and CD4+ Tcells to the genital area [169]. Studies have shown that the mechanism by which HSV increases the acquisition of HIV infection is by recruiting these activated CD4+ Tcells, which are target cells for HIV and through HSV-induced damage in the mucosal barrier that permits the entry of HIV particles [169–172]. More research is therefore needed to determine how HSV affects the virome, and whether the virome-driven changes contribute to the pathogenic effects of HSV infection. There is also a need to identify potential new treatment modalities, given that existing treatments (acyclovir and IVIG) alter the microbiome and may influence long-term clinical outcomes.

3.2.4. Human Papillomavirus (HPV)

The impact of HPV on the gut bacteriome has not been comprehensively explored despite the high burden of anal HPV infection in PWH and MSM [173–177]. The majority of the research has been focused on the cervicovaginal environment [178–182] where HPV infection results in lower levels of *lactobacillus*, and increased levels of bacteria such as *Gardnerella*, *Prevotella*, *Sneathia*, *Megasphaera*, *Streptococcus*, and *Fusobacterium* [180,182]. The resulting cervicovaginal bacteriome dysbiosis weakens the mucosal barrier, increases inflammation and creates an environment that supports the persistence of HPV and integration of HPV into host DNA [180,183,184]. Studies have shown that women with HPV induced cervical cancer have higher gut bacteriome α-diversity and differences in the overall composition of gut microbes (β-diversity) [16], and an abundance of *Proteobacteria* [90]. Studies have also shown that the cervical bacteriome and the gut bacteriome may influence how patients respond to cervical cancer treatment and what outcomes they experience [17,185]. Similarly, HPV-related locally advanced SCCA is associated with higher levels of *Peptoniphilus*, *Fusobacteria*, *Porphyromonas*, and *Prevotella,* concluding that the development of the cancer is associated with anorectal bacteriome changes [18]Similarly, HPV-related locally advanced squamous cell carcinoma (SCCA) is associated with higher levels of *Peptoniphilus*, *Fusobacteria*, *Porphyromonas*, and *Prevotella,* concluding that the development of the cancer is associated with anorectal bacteriome changes [18].

HPV infects keratinocytes in the epidermis of the skin and the epithelium of the gut and stimulates the production of cytokines (TH1 and TH2) and cytotoxic responses in CD4+ T and CD8+ T cells [186–188]. By activating TLRs (TLR9) on keratinocytes, it induces the release of pro-inflammatory cytokines [189,190]. Persistent HPV infection can lead to the transformation of epithelial cells and to the development of warts and cancers [38]. The significant contributions of HPV to morbidity and mortality in PWH and MSM call for prioritized research to better understand the HPV-induced gut bacteriome and virome changes that occur in the gut of these groups and the consequent effects on clinical outcomes. This understanding could guide the development of interventions aimed at reducing the negative impact of HPV on PWH and MSM.

3.2.5. GB Virus C (GBV-C)

GB virus C (GBV-C) is a sexually transmitted lymphotropic eukaryotic virus prevalent among PWH [191–193] and remains a largely unexplored area of virome research in HIV. While its presence in gut-associated lymphoid tissue (GALT) or fecal samples has not been established, research has shown that it primarily replicates in T and B lymphocytes [194]. The transmission of this virus during RAI needs to be explored, given that other lymphotropic viruses like HIV can be transmitted through this route [195,196]. Multiple studies have shown that the virus is associated with improved clinical outcomes in PWH [197–201]. GBV-C decreases the entry of HIV [202,203] and inhibits its replication within T cells [204–207]. In addition, it enhances the immune system's response to infection by upregulating interferon expression [208], modulating cytokine signaling [209,210] and regulating $CD4^+$ T-cell apoptosis [211]. However, the mechanism in which this virus modulates the progression

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of HIV is still poorly understood [212]. Despite these important roles, GBV-C has been rarely considered within the scope of the gut or rectal virome research in PWH and MSM. Understanding if sexual behaviors associated with MSM influence its transmission dynamics, how GBV-C coinfection interacts with local microbial and phage communities, and integrating GBV-C status into virome and bacteriome analyses could inform broader efforts to understanding the rectal virome in PWH and MSM.

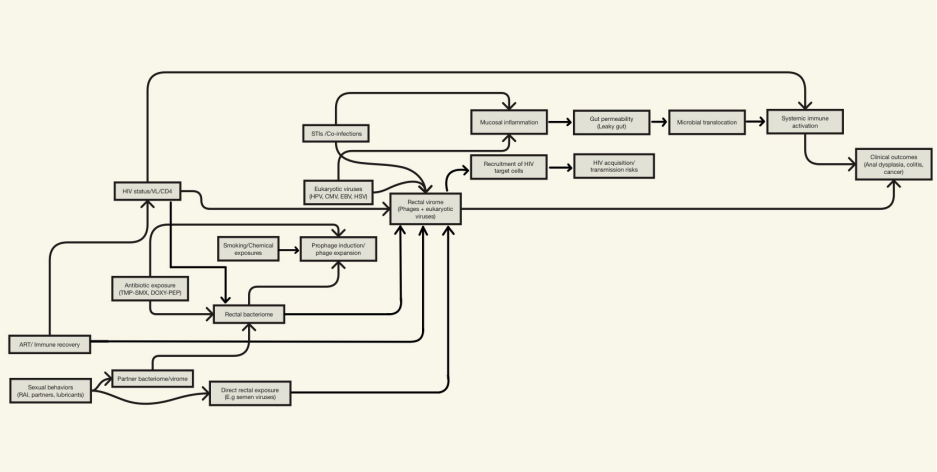

Figure 1. This figure summarizes the various determinants and hypothesized interactions of the Rectal Virome in PWH and MSM.

4. Current Gaps and Future Research Directions

There is no doubt that HIV infection is associated with alterations in the gut virome, yet, how HIV-related immune dysfunction, microbial dysbiosis, and shifts in the virome are linked still remain poorly understood. Despite extensive research on the gut and its microbiome in MSM vulnerable to HIV and PWH, major gaps remain in our understanding of the rectal virome and how it contributes to mucosal health, immune activation, and clinical outcomes in both groups. This knowledge gap is primarily driven by the lack of a baseline characterization of the rectal virome in PWH and MSM, and the difficulty in establishing causality in the presence of multiple confounding factors like ongoing HIV viral replication, immune deficiency, ART, sexual practices, and antibiotic exposure. There are also very scarce longitudinal data that further complicate our understanding of whether these virome changes are drivers or instead arise as a consequence of chronic inflammation and bacteriome changes. Also, much remains to be learned concerning phage–host relationships within the context of HIV infection and among MSM and their potential as either protective modulators of the mucosal barrier or as contributing factors to inflammation and immune activation.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

HIV	Human Immunodeficiency Virus
STIs	Sexually Transmitted Infections
RAI	Receptive Anal Intercourse
MSM	Men who have Sex with Men
PWH	People With HIV
HSV	Herpes simplex virus
EBV	Epstein-Barr virus
CMV	Cytomegalovirus
HPV	Human Papillomavirus
DNA	Deoxyribonucleic acid

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RNA	Ribonucleic acid
PPV	Persistent Personal Virome
TDV	Transiently Detected Virome
crAss	Cross-Assembly
ARG	Antibiotic Resistance Genes
CD4	Cluster of Differentiation 4
Doxy-PEP	Doxycycline Post-Exposure Prophylaxis
Th17	T-helper 17
Tregs	T regulatory cells
ART	Anti-Retroviral Therapy
VL	Viral Load
IL	Interleukin
IFN	Interferon
FOXP3	Forkhead Box P3
NK	Natural Killer
SCFAs	Short-chain fatty acids
CD8	Cluster of Differentiation 8
IVIG	Intravenous Immunoglobulin
MCP	Monocyte Chemoattractant Protein-1
CCL2	C-C Motif Chemokine Ligand 2
SCCA	Squamous cell carcinoma
TH1	T-helper 1
TH2	T-helper 2
TLR	Toll-like receptors
GBV-C	GB Virus C
GALT	Gut-associated lymphoid tissue

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