HHS Public Access

Author manuscript

Pharmacol Biochem Behav. Author manuscript; available in PMC 2024 August 01.

Published in final edited form as:

Pharmacol Biochem Behav. 2023 August ; 229: 173592. doi:10.1016/j.pbb.2023.173592.

THERAPEUTICALLY TARGETING THE CONSEQUENCES OF HIV-1-ASSOCIATED GASTROINTESTINAL DYSBIOSIS: IMPLICATIONS FOR NEUROCOGNITIVE AND AFFECTIVE ALTERATIONS

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Abstract

Approximately 50% of the individuals living with human immunodeficiency virus type 1 (HIV-1) are plagued by debilitating neurocognitive impairments (NCI) and/or affective alterations. Sizeable alterations in the composition of the gut microbiome, or dysbiosis, may underlie, at least in part, the NCI, apathy, and/or depression observed in this population. Herein, two interrelated aims will be critically addressed, including: 1) the evidence for, and functional implications of, gastrointestinal microbiome dysbiosis in HIV-1 seropositive individuals; and 2) the potential for therapeutically targeting the consequences of this dysbiosis for the treatment of HIV-1-associated NCI and affective alterations. First, gastrointestinal microbiome dysbiosis in HIV-1 seropositive individuals is characterized by decreased alpha (α) diversity, a decreased relative abundance of bacterial species belonging to the *Bacteroidetes* phylum, and geographic-specific alterations in *Bacillota* (formerly *Firmicutes*) spp. Fundamentally, changes in the relative abundance of *Bacteroidetes* and *Bacillota* spp. may underlie, at least in part, the deficits in γ-aminobutyric acid and serotonin neurotransmission, as well as prominent synaptodendritic dysfunction, observed in this population. Second, there is compelling evidence for the therapeutic utility of targeting synaptodendritic dysfunction as a method to enhance neurocognitive function and improve motivational dysregulation in HIV-1. Further research is needed to determine whether the therapeutics enhancing synaptic efficacy exert their effects by altering the gut microbiome. Taken together, understanding gastrointestinal microbiome dysbiosis resulting from chronic HIV-1

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

viral protein exposure may afford insight into the mechanisms underlying HIV-1-associated neurocognitive and/or affective alterations; mechanisms which can be subsequently targeted via novel therapeutics.

Keywords

Brain-Gut-Microbiota Axis; HIV-1-Associated Neurocognitive Disorders; Apathy; Depression; Synaptic Dysfunction; Neurotransmission

INTRODUCTION: BRAIN-GUT-MICROBIOTA AXIS

Trillions of microbes (predominantly bacteria; Qin et al., 2010, Yatsunenko et al., 2012), which outnumber human cells at a ratio of approximately 1.3:1 (Sender et al., 2016), are distributed in multiple organs throughout the human body. The gastrointestinal tract, in particular, harbors the largest microbial community (Sender et al., 2016); a bacterial community that is dominated by two phylogenetic categories, including *Bacteroidetes* and *Bacillota* (formerly *Firmicutes*; Hold et al., 2002; Eckburg et al., 2005; Qin et al., 2010). Nevertheless, the gut microbiome is highly diverse and individualized (Costello et al., 2009), whereby its composition is influenced by both intrinsic (e.g., Biological Sex: Mueller et al., 2006; Takagi et al., 2019; Genetics: Goodrich et al., 2014) and extrinsic (e.g., Dietary Habits: David et al., 2014; Sexual Behaviors: Noguera-Julian et al., 2016) factors. Fundamentally, the gut microbiome has a broad functional repertoire, ranging from metabolism and immunity to neurobehavioral functions (for review, Kamada et al., 2013; Sommer & Bäckhed, 2013; Sharon et al., 2016).

Resident gut microbiota dynamically communicate with the brain via multiple bidirectional pathways, which are collectively recognized as the brain-gut-microbiota axis, to influence neurobehavioral functions (for review, Cryan et al., 2019). The most direct and fastest route connecting the brain and gut is the vagus, or tenth cranial, nerve. Vagal afferent fibers, which outnumber efferent fibers at a ratio of approximately 8:2 (Agostoni et al., 1957), project from the gastrointestinal tract to the nucleus tractus solitarius via the nodose ganglion. In contrast, vagal efferent fibers exit the brain via the medulla oblongata, travel through the neck and thorax, and have branches that terminate in the stomach, small intestine, and large intestine (Berthoud et al., 1991). The functional importance of bidirectional signaling in the vagal nerve has been evidenced by both vagal nerve ablation and stimulation, whereby vagotomy induces neurocognitive impairments (NCI; Suarez et al. 2018) and affective alterations (Ghizoni et al., 2006); vagal nerve stimulation, in contrast, improves cognitive function (e.g., Clark et al., 1999; Driskill et al., 2022) and affective alterations (e.g., Rush et al., 2000). Subdiaphragmatic vagotomy of healthy mice who receive fecal microbiota transplantation from chronically stressed animals has revealed depressive-like behaviors and hippocampal neurogenesis to be dependent upon vagal afferent fibers for gut microbiome-mediated brain alterations to occur (Siopi et al., 2023). More fundamentally, the vagus nerve serves as a conduit for gut bacteria to influence both cognitive and affective function.

Sizeable alterations in the composition of the gut microbiome, or dysbiosis, may underlie, at least in part, NCI and/or affective alterations induced by infectious diseases (e.g., Human

Immunodeficiency Virus Type 1 (HIV-1); Lozupone et al., 2013; Pérez-Santiago et al., 2021). Gut microbiome dysbiosis is commonly evaluated by quantifying two components of species diversity, including 1) *alpha* (α) diversity; and 2) *beta* (β) diversity. α diversity, which estimates local (within-sample) diversity, can be measured using a variety of indices (e.g., Shannon Diversity Index (Based on the Shannon and Weaver Information Theory, Shannon, 1948); Simpson's Index: Simpson, 1949; Chao1: Chao, 1984) to reflect both the evenness and/or richness of a microbial sample. β diversity, initially formulated by Whittaker (1960, 1972), is a derived measure utilized to capture the similarity and dissimilarity between samples. Statistical methods, including Bray-Curtis (Bray & Curtis, 1957) and UniFrac (Lozupone et al., 2005), have been developed to quantify β diversity and establish the statistical significance of group differences (e.g., Permutational Multivariate ANOVA (PERMANOVA); Anderson, 2017). Furthermore, examination of the relative abundance of bacteria within a given phylum, genus, and/or species affords an opportunity to more directly interpret how group differences may mechanistically underlie NCI and/or affective alterations.

HIV-1, which afflicts approximately 38.4 million individuals worldwide (WHO, 2022), is an infectious disease that induces profound NCI (Cysique et al., 2004; Heaton et al., 2011; for review, Zenebe et al., 2022) and affective alterations (e.g., Apathy: Kamat et al., 2012; Depression: Do et al., 2014); comorbidities which necessitate the development of novel adjunctive therapeutics. Using two interrelated aims, the present review will evaluate the potential for therapeutically targeting gastrointestinal dysbiosis for the treatment of HIV-1-associated neurocognitive disorders (HAND) and apathy/depression. First, we will discuss the evidence for gastrointestinal dysbiosis in HIV-1, with a specific focus on the functional implications of these changes in HIV-1-associated neurocognitive and affective alterations. Second, the present review will examine the opportunity to mitigate NCI and/or affective alterations associated with HIV-1 by therapeutically targeting the consequences (e.g., decrease butyrate production) of gut microbiome dysbiosis.

GASTROINTESTINAL MICROBIOME DYSBIOSIS IN HIV-1

Gastrointestinal microbiome dysbiosis is established during acute HIV-1 infection (i.e., Fiebig Stage I-V), whereby it is characterized by selective deficits in α diversity, clear alterations in β diversity, and significant changes in the taxonomic composition of gut bacteria (Sortino et al., 2020). During chronic HIV-1 infection, alterations in the gut microbiome persist, despite treatment with combination antiretroviral therapy (cART, i.e., the primary treatment regimen for HIV-1 seropositive individuals).

Thus, one of the primary goals of the present review is to utilize a multi-faceted approach, including examination of α diversity, β diversity, and taxonomic composition, to characterize gut microbiome dysbiosis in adults who are chronically infected with HIV-1. Establishing how chronic HIV-1 viral protein exposure alters the gut microbiome affords an opportunity to consider the functional implications of these changes with respect to HIV-1 associated neurocognitive and/or affective alterations. Herein, 38 case-control studies (see Figure 1) comparing the gut microbiome in HIV-1 seropositive adults with chronic infection and well-matched controls were identified and evaluated.

Alpha (α) Diversity

Amongst the 36 case-control studies evaluating α diversity, the Shannon index, a measure of community diversity whose formula weighs taxa evenness more heavily than richness (Strong, 2016), was most commonly implemented (i.e., 31 of 36 studies). The Simpson index was utilized much more sparingly (i.e., 12 of 36 studies) to evaluate gastrointestinal system community diversity. With regards to measures of community richness, the Chao1 index and number of observed species were examined in a similar number of studies (i.e., 17 of 37 and 18 of 37 studies, respectively). Unsurprisingly, given similarities in α diversity indices, intra-study variability (i.e., significant and/or non-significant group differences in α diversity) was generally low.

Empirical studies provide ample evidence for a statistically significant decrease in α diversity in chronically infected HIV-1 seropositive, relative to seronegative, individuals (e.g., Mutlu et al., 2014; Vujkovic-Cvijin et al., 2020). Indeed, in empirical studies, the profound downregulation of α diversity following chronic exposure to HIV-1 viral proteins is observed across multiple geographic regions (e.g., African: Parbie et al., 2021; Asian: Zhou et al., 2018; North American: Pinto-Cardoso et al., 2017) and in both the presence (e.g., Vujkovic-Cvijin et al., 2020) and absence (e.g., Nowak et al., 2015) of cART. Meta-analytic techniques, which synthesize and analyze independent empirical studies to yield effect estimates with greater statistical power (for review, Lipsey & Wilson, 2001), have also demonstrated the association between HIV-1 serostatus and decreased α diversity in the gastrointestinal microbiome (Tuddenham et al., 2020; Zhou et al., 2020). Stratification of meta-analytic analyses by gender and/or sexual orientation revealed that decreased α diversity is specific to female and non-MSM HIV-1 seropositive individuals; no significant alterations in α diversity were observed in HIV-1 seropositive MSM (Tuddenham et al., 2020; Zhou et al., 2020). Despite the strong empirical and meta-analytic evidence for the downregulation of α diversity in chronically infected HIV-1 seropositive individuals, it is notable that statistically significant increases have also been spuriously observed (e.g., Lozupone et al., 2013; Xie et al., 2021).

Gut microbiome diversity is significantly correlated with multiple lifestyle factors and clinical markers of peripheral health and disease (Manor et al., 2020); the functional impact of α diversity alterations on cognitive and/or affective function, however, remains understudied. Stepwise regression (Canipe et al., 2021) and mediation analyses (Cai et al., 2021) have demonstrated the association between α diversity (i.e., Shannon and Simpson indices, respectively) and neurocognitive function (e.g., working memory, attention). With specific regards to HIV-1 seropositive individuals, a comparison of individuals with and without NCI revealed no statistically significant differences in α diversity (Zhang et al., 2019; Dong et al., 2021); dichotomization of individuals, however, naturally decreases variability and statistical power (Rucker et al., 2015). Regressing continuous measures of neurocognitive performance on indices of α diversity in HIV-1 seropositive individuals ought to provide increased clarity regarding the functional implications for the profound downregulation of α diversity seen in this population.

Beta Diversity

Twenty-seven of the case-control studies comparing the gut microbiome in HIV-1 seropositive individuals with chronic infection evaluated β diversity. The UniFrac (weighted or unweighted; 17 of 27 studies) and Bray-Curtis (13 of 27 studies) indices were the most commonly utilized β diversity measures. Differential clustering of samples based on HIV-1 serostatus was evaluated using both exploratory (e.g., Principal Component Analysis, Principal Coordinate Analysis) and/or inferential (e.g., PERMANOVA) statistical approaches. Statistically significant (e.g., Mutlu et al., 2014; Bai et al., 2021) differences in the overall gastrointestinal microbiota community composition between HIV-1 seropositive and case-matched controls have been reported. Identification of specific changes in the taxonomic composition of bacteria in HIV-1 seropositive individuals may afford insight into the functional implications of β diversity changes.

Relative Abundance of Bacteria

Six hierarchical taxonomic categories, including phylum, class, order, family, genus, and species, are utilized to categorize organisms based on similarities in their phylogenetic lineage and characteristics (i.e., Gram's stain; Morphology). Within the gastrointestinal tract, the bacterial community is dominated by two phylogenetic categories, including *Bacteroidetes* and *Bacillota* (Hold et al., 2002; Eckburg et al., 2005; Qin et al., 2010); phylogenetic categories which will be the focus of the present review. However, it is notable that chronic HIV-1 viral protein exposure affects the gastrointestinal microbiome more broadly, as alterations in *Pseudomonadota* (formerly *Proteobacteria*; e.g., Dillon et al., 2014; Xie et al., 2021) have also been reported.

Bacteroidetes—Bacteria belonging to the phylum *Bacteroidetes* are Gram-negative rod-shaped bacteria that represent an unexpected mix of physiological types (i.e., Anaerobic: Genus, *Bacteroides*; Aerobic: Genus, *Flavobacteria*). From a taxonomic classification perspective, the phylum *Bacteroidetes* is subdivided into six classes (Schoch et al., 2020), whereby the majority of the gastrointestinal *Bacteroidetes* spp. belong to one of four families (i.e., *Bacteroidaceae, Porphyromonadaceae, Prevotellaceae,* or *Rikenellaceae*; for review, Rajilić-Stojanović & de Vos, 2014). *Bacteroidetes* spp. become one of the most predominant taxa in the intestinal microbiome by the end of the first year of life (Palmer et al., 2007); a taxa that, in healthy adults, is one of the most stable microbiota components across time (Rajilić-Stojanović et al., 2013). The critical role of *Bacteroidetes* spp. is evidenced not only by their early colonization and long-term stability, but also by the absence of *Bacteroidetes* spp. in a terminally ill patient (i.e., resistant tuberculosis; Dubourg et al., 2013). Indeed, as symbionts, their primary function is the degradation of proteins or polysaccharides, which is fundamental for the optimal uptake of energy from the diet. In addition, *Bacteroidetes* spp. interact with the immune system to activate T-cell-mediated responses (Onderdonk et al., 1982) and provide protection from pathogens (Mazmaian et al., 2008).

Given the fundamental role of gastrointestinal *Bacteroidetes* spp., changes in their relative abundance may underlie the development of neurocognitive and/or affective disorders associated with HIV-1. At the phylum level, a pronounced decrease in the relative abundance of *Bacteroidetes* has been reported in chronically infected HIV-1 seropositive, relative to

seronegative, individuals (Ling et al., 2016; Sun et al., 2016; Zhou et al., 2018; Parbie et al., 2021; Xie et al., 2021). More specifically, the relative abundance of two genera, including *Bacteroides* (e.g., Dillon et al., 2014; Ling et al., 2016; Parbie et al., 2021) and *Prevotella* (e.g., Lozupone et al., 2013; Mutlu et al., 2014; Ancona et al., 2021), are significantly altered (i.e., decreased and increased, respectively) by chronic exposure to HIV-1 viral proteins. It is notable that even with cART, which mitigates CD4+ T-cells defects (Autran et al., 1997), *Bacteroides* spp. remain decreased in HIV-1 seropositive, relative to seronegative, individuals (Mutlu et al., 2014; Parbie et al., 2021). The potential functional implications of decreased *Bacteroides* and increased *Prevotella* with respect to neurocognitive impairments and/or apathy/depression in this population will be discussed in turn below.

Bacteroides.: Early in the course of HIV-1 infection, viral proteins productively infect CD4+ T-cells resulting in the progressive destruction of these cells (Dalgleish et al., 1984; Klatzmann et al., 1984); cell loss which may underlie, at least in part, the profound decrease in *Bacteroides* in chronically infected HIV-1 seropositive individuals. *Bacteroides* spp., including *Bacteroides fragilis*, *Bacteroides uniformis*, and *Bacteroides cellulosilyticus*, are capable of producing bacterial zwitterionic polysaccharides (ZPS; i.e., the presence of polysaccharide A (PSA) operons; Neff et al., 2016), whereby PSA, produced by *B. fragilis,* is the most well-studied. Indeed, the ZPS PSA has two fundamental characteristics, including: 1) repeating units with positively and negatively charged groups that are crucial to modulating immune responses (Tzianabos et al., 1993); and 2) reliance on CD4+ T-cell toll-like receptors for colonization (Round et al., 2011). Furthermore, the absence of PSA operons precludes the ability of *B. fragilis* isolates to colonize the gastrointestinal system (Round et al., 2011). The well-recognized reduction of CD4+ T-cells in chronic HIV-1 infection, therefore, supports a decrease in PSA resulting in the depletion of *Bacteroides* spp. in the gut microbiome of chronically infected HIV-1 seropositive individuals.

Decreased production of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) is likely one of the consequences of decreased *Bacteroides* spp. in chronically infected HIV-1 seropositive individuals (Figure 2A). GABA can be produced by intestinal bacteria via the glutamate decarboxylase (GAD) system, which utilizes pyridoxal-5'-phosphate glutamate decarboxylase (i.e., *gadA* or *gadB*) to remove the carboxyl group from l-glutamic acid resulting in the production of GABA and carbon dioxide (Fonda, 1985). A variety of *Bacteroides* spp. exhibit a high prevalence of *gadB* orthologs (Pokusaeva et al., 2017; Strandwitz et al., 2019), express genes encoding the GAD system (Otaru et al., 2021), and functionally produce GABA (Strandwitz et al., 2019; Otaru et al., 2021). Fundamentally, the ingestion of probiotic bacteria that produce GABA (e.g., *Lactobacillus rhamnosus*: Lin, 2013; *Bifidobacterium longum* subsp*. infantis*: Barrett et al., 2012) has beneficial behavioral (e.g., anxiolytic) and/or neurochemical (e.g., region-dependent alterations in $GABA_A$ and $GABA_B$ receptors) effects (Bravo et al., 2011; Bercik et al., 2011; Janik et al., 2016). The therapeutic effects of both *L. rhamnosus* (Bravo et al., 2011) and *B. longum* (Bercik et al., 2011) were blocked by vagotomy supporting the involvement of vagal pathways, which express a high density of $GABA_B$ receptors (Margeta-Mitrovic et al., 1999), in the transmission of GABA from the gastrointestinal system to the brain. Additional studies are needed to evaluate the cognitive and/or affective effects of GABA produced by *Bacteroides*

spp. on the central nervous system. Collectively, the data support a profound decrease in *Bacteroides* spp. in chronically infected HIV-1 seropositive individuals that is induced by the productive infection of CD4+ T-cells and leads to a dramatic reduction in GABA neurotransmission (Figure 2A).

Prevotella.: The gastrointestinal barrier is breached by chronic HIV-1 viral protein exposure, evidenced by increased neutrophil infiltration, independent of cART (Somsouk et al., 2015), and increased circulating lipopolysaccharides (LPS; Brenchley et al., 2006; Pedro et al., 2018). Further, HIV-1 gut microbiome dysbiosis itself may compromise the integrity of the epithelial barrier, as the bacteria *Akkermansia muciniphila,* which serves as the "gatekeeper of the gut" (for review, Ouyang et al., 2020; Reunanen et al., 2015; Plovier et al., 2017), and *Faecalibacterium* spp. are decreased in HIV-1 seropositive individuals (e.g., Mutlu et al., 2014; Rocafort et al., 2019; Xie et al., 2021). Nonetheless, the impaired gut barrier induced by chronic HIV-1 infection affords a mechanism for the intestines to become permeable to harmful microbes, including *Prevotella* spp.

One of the key structural features of Gram-negative bacterium, including *Prevotella* spp., is the presence of an outer membrane that consists of phospholipids and LPS (Figure 2B; for review, Bos et al., 2007). Indeed, a positive relationship between the abundance of *Prevotella* spp. in the gut microbiome and LPS concentration has been observed (Leite et al., 2017); a relationship that supports a higher concentration of LPS in chronically infected HIV-1 seropositive individuals. The higher concentration of LPS can be transmitted from the gastrointestinal system to the brain either directly (Zhang et al., 2020) or indirectly (e.g., toll-like receptor 4 (TLR4; Hosoi et al., 2005)) via the vagus nerve. Further, the integrity of the blood-brain barrier (BBB) is disrupted by the constitutive expression of HIV-1 viral proteins (e.g., Petito & Cash, 1992; Chaganti et al., 2019) affording another mechanism for circulating LPS to enter the brain. Upon entering the brain, LPS binds to TLR4 receptors expressed on microglia (Bsibsi et al., 2002); the activation and/or dysfunction of microglia results in neurite and/or synaptic damage (e.g., Moraes et al., 2014; Liu et al., 2018), which may subsequently underlie cognitive and/or affective alterations. Taken together, the increased abundance of *Prevotella* spp. in chronically infected HIV-1 seropositive individuals likely results in a higher concentration of LPS; a concentration that induces a cascade of molecular signaling events that ultimately results in neuronal injury and/or synaptodendritic alterations.

Bacillota (Formerly Firmicutes)—When originally described by Gibbons and Murray (1978), the *Bacillota* phylum encompassed all Gram-positive bacteria. Under the current classification system, however, bacteria belonging to the *Bacillota* phylum are generally characterized by a low guanine-cytosine content in their DNA and exhibit either a round (i.e., cocci) or rod-like (i.e., bacillus) form; Gram-positive staining is no longer a unifying feature of *Bacillota* spp. The phylum *Bacillota* is subdivided into nine classes (Schoch et al., 2020), whereby the majority of the gastrointestinal *Bacilloa* spp. belong to one of four classes (i.e., *Bacilli*, *Clostridia, Erysipelotrichia,* and *Negativicutes*; Rajilić-Stojanović & de Vos, 2014). From a developmental perspective, *Bacillota* spp., much like bacteria belonging to the *Bacteroidetes* phylum, becomes preponderant in the gastrointestinal microbiome

by the end of the first year of life (Palmer et al., 2007). In healthy adults, the stability of *Bacillota* spp. is dependent upon taxonomic order and/or genera; members of the *Faecalibacterium* genera, which is of particular relevance, exhibit high stability across time (Rajilić-Stojanović et al., 2013). The pivotal role of *Bacillota* spp. in the gastrointestinal system is evidenced by their early colonization, high prevalence, and function, whereby they are involved in the production of vitamins and short-chain fatty acids, including butyrate.

At the phylum level, the direction of changes in the relative abundance of *Bacillota* is dependent upon HIV-1 status and geographical region, whereby pronounced decreases are observed in HIV-1 seropositive, relative to seronegative, individuals sampled in African (Parbie et al., 2021) and North American (Dillon et al., 2014; González-Hernández et al., 2019) countries. In sharp contrast, statistically significant increases in the relative abundance of *Bacillota* are observed in chronically infected HIV-1 seropositive individuals in Asian countries (Ling et al., 2016; Sun et al., 2016). At the genera level, the relative abundance of *Faecalibacterium* is altered by chronic exposure to HIV-1 viral proteins, whereby constitutive expression of HIV-1 viral proteins induces both increases (Ling et al., 2016; Sun et al., 2016) and decreases (Mutlu et al., 2014; Nowak et al., 2015; Dubourg et al., 2016; Zhou et al., 2018; Ancona et al., 2021; Parbie et al., 2021; Xie et al., 2021) relative to seronegative controls. Notably, the relative abundance of other *Bacillota* genera is also altered by HIV-1 serostatus (e.g., *Coprococcus:* Decreased in a North American sample (Dillon et al., 2014); *Lactobacillus*: Increased in an Asian sample (Zhou et al., 2018)). The present review, however, will focus on the functional implications of changes in *Faecalibacterium* spp., as they represent approximately 5% of the total bacteria in the gastrointestinal system (Arumugam et al., 2011).

Faecalibacterium.: Bacteria belonging to the *Faecalibacterium* genera serve as one of the main producers of butyrate, a four-carbon short-chain fatty acid, in the gastrointestinal system (Duncan et al., 2002). Butyrate acts as a strong histone deacetylase (HDAC) inhibitor (Candido et al., 1978), whereby it favors histone acetylation (Riggs et al., 1977), and binds to G protein-coupled receptors (GPCRs; e.g., Free Fatty Acid Receptor 2 and 3, hydrocarboxylic acid receptor 2 (formerly GPR109a), for review, Priyadarshini et al., 2018). From a functional perspective, butyrate, at least at low concentrations, is critically involved in maintaining the integrity of both the gastrointestinal epithelial barrier (e.g., Mariadason et al., 1997; Peng et al., 2007) and BBB (Braniste et al., 2014); paradoxically, high concentrations of butyrate may disrupt the gastrointestinal epithelial barrier (Peng et al., 2007). Alterations in the prevalence of *Faecalibacterium* in chronically infected HIV-1 seropositive individuals, therefore, may be involved in the development of both gut epithelial (for review, Epple & Zeitz, 2012) and BBB (for review, Strazza et al., 2011) dysfunction in this population.

More directly, profound alterations in butyrate production induced by changes in the relative abundance of *Faecalibacterium* may preclude the production and/or release of the excitatory neurotransmitter serotonin (5-HT; Figure 2C). Enterochromaffin cells or neurons within the gastrointestinal system synthesize the vast majority (i.e., >90%) of the total body 5-HT, whereby 5-HT release is modulated, in part, by the interactions between butyrate and the OR51E1 GPCR (Priori et al., 2015). Fundamentally, butyrate induces 5-HT release in a

dose-dependent manner (Reigstad et al., 2015). Indeed, low concentrations (i.e., 0.5 and 1 mM) of butyrate increase the transcription of tryptophan hydroxylase 1 (TPH1; i.e., the rate-limiting enzyme in 5-HT production), whereas transcription is suppressed when butyrate is absent (i.e., 0 mM) or present in high concentrations (i.e., 8mM and 16 mM; Reigstad et al., 2015). The dose-dependency of butyrate's effects on 5-HT production/release support a convergent mechanism (i.e., Reductions in 5-HT) by which an increase or decrease in *Faecalibacterium* would induce functional alterations in the brain.

5-HT can be transported from the gastrointestinal system to the brain via vagal afferent fibers, which express functionally active 5-HT_3 receptors (Hillsley et al., 1998; Lacolley et al., 2006) and are in close proximity to neurohormones, including 5-HT, released from enterochromaffin cells (Powley et al., 2011). An examination of the mechanism by which luminal or oral selective serotonin reuptake inhibitors (SSRIs) exert their therapeutic effects revealed increased vagal spike firing and antidepressive behavior. Beneficial behavioral effects of oral SSRIs were abolished following vagotomy (McVey Neufeld et al., 2019) supporting the vagus nerve as a communication pathway by which SSRIs exert their effects. In addition, a surge in 5-HT firing rates in the dorsal raphe nucleus, the brainstem nuclei for 5-HT, occurs after chronic stimulation of the vagus nerve (Dorr & Debonnel, 2006). Collectively, alterations in the relative abundance of *Faecalibacterium* induced by chronic HIV-1 viral protein exposure likely lead to profound changes in butyrate production which preclude the production and/or release of 5-HT.

Experimental Design Considerations for Microbiome Studies

Despite the compelling evidence for gastrointestinal microbiome dysbiosis in chronically infected HIV-1 seropositive individuals, it would be remiss to neglect the substantial inter-study heterogeneity (Figure 1) that has been observed. In light of the considerable inter-study heterogeneity, a brief discussion of experimental design considerations (e.g., statistical power), biological and environmental factors (e.g., age, biological sex, sexual behavior, geographic location), and the potential impact of cART underlying these discrepancies is warranted.

Statistical Power—Statistical power is defined by Cohen (1988) as "the probability [assuming the null hypothesis (H_0) is false] that it will lead to the rejection of the null hypothesis". Estimates of statistical power are influenced by three factors, including: 1) level of significance (i.e., α level); 2) effect size; and 3) sample size; increasing any of these factors yields increased statistical power. Fundamentally, the relationship between statistical power, α level, effect size, and sample size is such that one parameter can be determined as a function of the other three. For example, in an *a priori* power analysis, researchers can ascertain the necessary sample size based on the level of significance, effect size, and statistical power. Based on the recommendations of Cohen (1965), statistical power is conventionally established at 0.80 or greater for a medium effect size and α level of 0.05.

Inconsistencies in the defining characteristics of gastrointestinal microbiome dysbiosis in chronically infected HIV-1 seropositive individuals are likely due, in part, to low statistical power. To illustrate the risk for low statistical power in the 38 case-control studies

identified in the present review, the number (i.e., sample size) of chronically infected HIV-1 seropositive individuals evaluated in each study was examined based on statistical significance in the Shannon Index (Figure 3). Indeed, studies finding statistically significant effects of HIV-1 serostatus on α diversity, measured using the Shannon Index, had a significantly greater number of HIV-1 seropositive individuals relative to studies failing to find a statistically significant effect (Main Effect of Statistical Significance: $F(1,33)=6.3$, $p \leq 0.017$; Three outliers, defined as being greater than 2.5 standard deviations above the mean, were removed from the analysis). More broadly, an examination of the total sample size in 28 microbiome studies that evaluated α diversity using the Chao1 index reported similar observations, whereby the distribution of sample sizes was highly skewed towards zero (Median Sample Size: 39, Mode: 8 Subjects; Kers & Saccenti, 2022).

In light of these observations, it seems prudent to establish reporting practices that can enhance the biological insight gleaned from microbiome studies. First, presenting effect sizes, which highlight the practical significance of results, will aid in the interpretation of a manuscript. Indeed, effect sizes, commonly described using Cohen's *d*, provide a standard metric that represents the magnitude (i.e., Small: $d = 0.2$; Medium: $d = 0.5$; Large: $d \geq 0.8$) of the differences between groups. Second, effect sizes are fundamental for conducting a meta-analysis, as they are utilized as a standardized metric to represent and compare findings across studies (Lipsey & Wilson, 2001). To date, meta-analyses conducted on gut microbiota α diversity in chronically infected HIV-1 seropositive individuals have been limited by their reliance upon raw 16S rRNA gene sequence reads (Tuddenham et al., 2020; Zhou et al., 2020). Finally, published effect sizes can be utilized to estimate the sample size needed for future studies via *a priori* statistical power analyses.

It is acknowledged that the advanced statistical approaches implemented in the analysis of microbiome data create challenges for the calculation of both statistical power and effect size. In light of these challenges, novel approaches, including utilization of the Dirichlet-Multinomial distribution (La Rosa et al., 2012) and simulated distance matrices (Kelly et al., 2015) have been developed to estimate statistical power and sample size; a more comprehensive resource to facilitate sample size calculations for microbiome studies has also been provided by Ferdous et al. (2022). Nevertheless, continued efforts are needed to optimize methods for calculating statistical power and effect size in microbiome studies. Further, the challenges of calculating statistical power and effect size do not diminish, but rather bolster, their fundamental value as a key aspect of reporting results.

Biological and Environmental Factors—Biological and environmental factors, including age, biological sex (for review, Valeri & Endres, 2021), geography, and sexual behavior influence the diversity and composition of the gastrointestinal microbiome. The gut microbiome undergoes significant age-related development, characterized by a period of rapid change in early development (i.e., 1–3 years of age), increased stability during adulthood, and gradual modifications during aging (Yatsunenko et al., 2012; Odamaki et al., 2016). The maturation of the gastrointestinal microbiome, however, is sexually dimorphic, whereby during adulthood, biological sex is significantly associated with key components of microbial diversity (e.g., Mahnic & Rupnik, 2018) and composition (e.g., Mueller et al., 2006; Takagi et al., 2019). Similarly, both sexual behavior (i.e., MSM vs. non-MSM)

and geography also influence both diversity (Sexual Behavior: Noguera-Julian et al., 2016; Zhou et al., 2020; Geography: Yatsunenko et al., 2012) and composition (Sexual Behavior: Noguera-Julian et al., 2016; Geography: He et al., 2018) of the gut microbiome. Elucidating the unique role of chronic HIV-1 viral proteins on gastrointestinal microbiome dysbiosis, therefore, requires careful consideration of both biological and environmental factors.

Unfortunately, however, biological and environmental factors are not consistently accounted for and/or reported in studies of HIV-1-associated gut microbiome dysbiosis; an experimental design failure that has the potential to confound results. For example, multiple studies include both male and female subjects, but do not appear to account for the factor of biological sex in statistical analyses (e.g., Dillon et al., 2014; Zhou et al., 2018). Further, the need to construe sexual behavior from the reported route of transmission precludes the consideration of this factor in HIV-1 seronegative individuals (e.g., Villanueva-Millán et al., 2017; Bai et al., 2021). Potentially of the greatest concern, however, is the failure to report subject characteristics of either biological and/or environmental factors that may confound the study.

Multiple approaches are readily available to mitigate these potential confounds; approaches which, when implemented, may enhance our understanding of gastrointestinal microbiome dysbiosis induced by chronic HIV-1 viral protein exposure. First, inclusion criteria for the study can be defined to only include a specific subgroup, thereby isolating the main effect of HIV-1 serostatus in these individuals (e.g., Inclusion of all Male, MSM individuals: Nowak et al., 2017). Second, the stratification of individuals (e.g., Gelpi et al., 2020; Vujkovic-Cvijin et al., 2020) and/or inclusion of interaction terms in statistical analyses (i.e., HIV-1 Serostatus × Biological Sex × Sexual Behavior) affords another practical approach to directly evaluate the influence of biological and environmental factors. The inclusion of interaction terms, however, will necessitate an increased sample size, as the sample size required to detect interactions is significantly greater than main effects (e.g., Leon & Heo, 2009). Finally, at a minimum, the implementation of stringent reporting practices, including any potential confounding subject characteristics, may improve the interpretability of findings. In addition, the evaluation of the gastrointestinal microbiome in preclinical biological systems may afford a more controlled venue with which to elucidate the specific role of chronic HIV-1 viral protein exposure on dysbiosis.

Combination Antiretroviral Therapy—cART, the primary treatment regimen for HIV-1 seropositive individuals utilizes a combination of drugs to suppress HIV-1 viral replication. HIV-1 seropositive individuals are typically prescribed a cART regimen that includes two to four drugs belonging to one of four drug classes: Integrase Strand Inhibitors (INSTI), Nucleoside Reverse Transcriptase Inhibitors (NRTI), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI), or Protease Inhibitors (PI). The widespread implementation of cART has undoubtedly enhanced the quality of life for individuals living with HIV-1, evidenced by a dramatic increase in life expectancy (Romley et al., 2014; Teeraananchai et al., 2017) and decreased prevalence of the most severe forms of NCIs (for review, Saylor et al., 2016). Nevertheless, cART may be adversely affecting the gastrointestinal microbiome composition of HIV-1 seropositive individuals (for review, Pinto-Cardoso et al., 2018).

Drugs classified as either NRTIs or NNRTIs suppress the microbial diversity and composition of the gut microbiome in HIV-1 seropositive individuals (Imahashi et al., 2021; Ray et al., 2021; Hanttu et al., 2023), whereby treatment with zidovudine (NRTI) and/or efavirenz (NNRTI) have the most dramatic adverse effects (Shilaih et al., 2018; Ray et al., 2021). Broadly, HIV-1 seropositive individuals treated with conventional NRTI- or NNRTI-based cART exhibit a pronounced decrease in α diversity and richness across time (Imahashi et al., 2021; Ray et al., 2021) and relative to HIV-1 seronegative controls (Hanttu et al., 2023). More specifically, the NRTI zidovudine and NNRTI efavirenz show pronounced antibacterial activity. Indeed, both zidovudine and efavirenz strongly inhibit the growth of *Bacteroides* spp. and *Prevotella* spp. (Shilaih et al., 2018; Ray et al., 2021).

Other classes of drugs included in contemporary cART regimens (e.g., INSTIs, PIs) have fewer adverse effects on the gastrointestinal microbiome (Ray et al., 2021); albeit additional studies are warranted. Indeed, modifying the cART regimen by replacing the NNRTI efavirenz with the INSTI raltegravir enhances α diversity in the gastrointestinal microbiome of HIV-1 seropositive individuals (Hanttu et al., 2023). Furthermore, there are indications that treatment with a combination of NRTIs and INSTs has fewer adverse effects on gastrointestinal microbiome diversity relative to treatment with a NRTI and PI combination (Villanueva-Millán et al., 2017).

THERAPEUTICALLY TARGETING THE CONSEQUENCES OF GUT MICROBIOME DYSBIOSIS FOR NEUROCOGNITIVE AND/OR AFFECTIVE ALTERATIONS IN HIV-1

γ-Aminobutyric Acid (GABA)

A pronounced reduction in the inhibitory neurotransmitter GABA is likely one of the consequences of decreased *Bacteroides* spp. in chronically infected HIV-1 seropositive individuals. Indeed, a profound downregulation of GABAergic markers, including glutamate decarboxylase messenger RNA (mRNA; *GAD1*, *GAD2*), has been observed in the brains of postmortem HIV-1 seropositive individuals independent of HAND status and/or cART (Buzhdygan et al., 2016). Preclinical biological systems that express the HIV-1 transactivator of transcription (Tat) viral protein have been instrumental in defining how GABAergic neurotransmission is altered (e.g., Musante et al., 2010; Marks et al., 2016; Xu et al., 2016; Barbour et al., 2020; Xu et al., 2022). Specifically, HIV-1 Tat transgenic (Tg) mice exhibit decreased GABA exocytosis (Musante et al., 2010), dose- and sex-dependent alterations in spontaneous and miniature $GABA_A$ receptor-mediated inhibitory postsynaptic currents (sIPSC and mIPSC, respectively; Xu & Fitting, 2016; Xu et al., 2016; Xu et al., 2022), and region-specific reductions in the percentage of hippocampal somatostatin neurons (Marks et al., 2016). Related to GABAergic activity, dysregulation of glutamate metabolism is present in HIV-1 seropositive individuals. In vitro studies utilizing microglia and/or macrophages have shown that HIV-1 infection increases extracellular concentrations of glutamate in microglia and glutamine in macrophages and is correlated with elevated levels of neurotoxicity (Huang et al., 2011; Datta et al., 2016). One possible explanation may be elevated glutamine and glutaminase C levels which have been found in individuals with

HIV-1-associated dementia (Huang et al., 2011). The Tat-induced decrease in GABAergic neurotransmission occurs, at least in part, via an μ-opioid receptor mechanism (Xu & Fitting, 2016) while the HIV-1 viral protein R (Vpr) is in part responsible for the dysregulation of glutamate metabolism and potentially contributes to the neuropathogenesis of HAND (Datta et al., 2016) via NMDA receptor mechanisms (Huang et al., 2011). To date, however, there is limited evidence for the direct relationship between GABAergic neurotransmission and HAND, as GABAergic mRNAs (i.e., *GAD1*, *GAD2*, *GJD2*) are associated with only one neurocognitive domain (i.e., verbal fluency) in HIV-1 seropositive individuals. Further, despite reaching statistical significance, GABAergic mRNAs explained merely 3.8% to 5.6% of the variance in verbal fluency in HIV-1 seropositive individuals (Buzhdygan et al., 2016). Likewise, the glutamine-glutamate cycle is indicated to be dysregulated in the presence of HIV-1 infection but has failed to reach significance in current magnetic resonance spectroscopy (MRI) studies investigating HIV-1 seropositive individuals experiencing cognitive deficits (Ernst et al., 2010).

Based on a critical review of the literature, there remains a fundamental need for additional studies elucidating the importance and/or utility of targeting GABAergic neurotransmission deficits associated with HIV-1. First, a more comprehensive evaluation of the relationship between GABAergic alterations and HIV-1-associated neurocognitive and/or affective alterations would provide clarity on whether these neurochemical changes induce functional alterations. Second, the HIV-1 genome contains nine genes and fifteen viral proteins necessitating an investigation of how GABAergic neurotransmission is altered in the presence of a more complete genome (rather than the single protein Tat). Finally, if GABAergic alterations are involved in the development of HIV-1-associated neurocognitive and/or affective alterations, evaluating novel therapeutics may be fruitful.

Even under these conditions, directly targeting the deficit in GABAergic neurotransmission observed in HIV-1 seropositive individuals may be futile for the mitigation of HIV-1-associated neurocognitive and/or affective alterations. For example, GABAergic neurotransmission can be enhanced via therapeutic treatment with benzodiazepines, which are positive allosteric modulators of $GABA_A$ receptor subtypes α_1 and α_2. Although benzodiazepines are beneficial for some affective alterations (e.g., anxiety, panic disorders), they have multiple adverse side effects (e.g., drowsiness, dizziness, blurry vision) and are associated with neurocognitive impairments in HIV-1 seropositive individuals (Saloner et al., 2019). Probiotic supplementation, however, may serve as an indirect way to enhance GABAergic neurotransmission via the gastrointestinal microbiome. Indeed, in HIV-1 seropositive individuals, treatment with an oral probiotic supplement that included the GABA-producing bacteria *Bifidobacterium longum* enhanced neurocognitive function (Ceccarelli et al., 2017a; Ceccarelli et al., 2017b); whether these beneficial effects were due to an enhancement in GABAergic neurotransmission, however, remains unknown. Taken together, the evidence for the importance and/or utility of therapeutically targeting deficits in GABAergic neurotransmission for HAND and/or apathy/depression associated with HIV-1 remains inconclusive and demands further study.

Synaptic Dysfunction and Estrogen Receptor β

The abundance of *Prevotella* spp., which is significantly increased in chronically infected HIV-1 seropositive individuals, is strongly associated with LPS concentration, whereby higher LPS concentrations induce microglial activation leading to neuronal and/or synaptic damage. Indeed, chronic HIV-1 viral protein exposure induces profound HIV-1-associated neuronal injury (Moore et al., 2006) and dendritic spine dysmorphology/loss (Moore et al., 2006; Gelman & Nguyen, 2010; Desplats et al., 2013; Weiss et al., 2021). Synaptodendritic alterations are also common amongst preclinical biological systems utilized to model HAND (e.g., Tat Tg Mice: Fitting et al., 2010, Fitting et al., 2013; gp120 Tg Mice: Kang et al., 2010, Speidell et al.,2020; HIV-1 Tg rat: Roscoe et al., 2014, McLaurin et al., 2019, Festa et al.,2020; chimeric HIV rat: Li et al., 2021, McLaurin et al., 2022a), whereby the generalizability (i.e., across brain regions and ages) of these deficits has been illustrated. Fundamentally, synaptic dysfunction has been implicated as a potential neural mechanism underlying HIV-1-associated neurocognitive and/or affective alterations, as it is highly correlated (i.e., r=0.648–0.827, r^2=0.42–0.68) with global neuropsychological impairments in HIV-1 seropositive individuals (Moore et al., 2006) and motivational alterations in the HIV-1 Tg rat (McLaurin et al., 2022b). Therapeutically targeting the prominent neuronal injury and dendritic spine dysmorphology/loss, therefore, may mitigate HAND and/or apathy/depression associated with HIV-1.

The ovarian steroid hormone 17β-estradiol has the potential to serve as either a neuroprotective and/or neurorestorative treatment via its actions on neurons and dendritic spines, respectively. First, 17β-estradiol attenuates neuronal apoptosis induced by neurotoxic compounds, including HIV-1 (e.g., Corasaniti et al., 2005; Kendall et al., 2005; Adams et al., 2010), via an estrogen receptor β (ERβ) sensitive mechanism (Adams et al., 2010). Neuronal apoptosis, however, does not correlate with neurocognitive impairments (Adle-Biassette et al., 1999) and is rarely observed in HIV-1 seropositive individuals receiving cART. Second, 17β-estradiol promotes the growth of new dendritic spines, evidenced by increases in dendritic spine density (e.g., Khan et al. 2013; Hao et al. 2006; Tuscher et al. 2016; Wang et al., 2018); an effect resulting from the activation of the ERβ pathway (Wang et al., 2018). Further, treatment with 17β-estradiol induces a morphological shift towards more mature dendritic spines (Li et al., 2004; Hao et al., 2006). 17β-estradiol, or structurally similar compounds (i.e., phytoestrogens), may restore synaptodendritic integrity and/or function in HIV-1.

Phytoestrogens are naturally-occurring plant-derived compounds that are structurally similar to the ovarian steroid hormone 17β-estradiol (Glazier and Bowman, 2001) and exhibit a selective affinity for ERβ (e.g., Kuiper et al. 1998; Mueller et al. 2004). Daidzein (DAI), which is of particular interest, is a soy-derived phytoestrogen that is converted into the active metabolite Equol by gut microbiota (Setchell et al., 1984). Equol (7-hydroxy-3-(4-hydroxyphenyl)-chroman), whose chemical structure contains a chiral center at C-3 of the furan ring, can exist in either the R- or S- conformation, whereby S-Equol (SE) is the only enantiomer produced by humans (Setchell et al., 2005). Critically, SE penetrates the central nervous system via the blood-brain barrier (Johnson et al., 2019), supporting its potential utility to ameliorate HIV-1-associated synaptic dysfunction.

Indeed, the phytoestrogen DAI affords an efficacious therapeutic for synaptodendritic alterations resulting from HIV-1 viral protein exposure. Initial *in vitro* assessments demonstrated the potential utility of DAI as either a neuroprotective (i.e., via pre-treatment prior to HIV-1 Tat exposure) or neurorestorative (i.e., via induction of synaptodendritic damage by HIV-1 Tat exposure prior to treatment) therapeutic for HIV-1 associated neuronal and/or synaptic damage (Bertrand et al., 2014). Despite the promise of DAI, its clinical relevance was potentially limited by two fundamental caveats, including: 1) gastrointestinal microbiome dysbiosis, as reviewed above, is profound in chronically infected HIV-1 seropositive individuals; and 2) only 25–30% of the Western population convert DAI to SE (Rowland et al., 2000; Setchell & Cole, 2006). Subsequent *in vitro* studies embraced these challenges by evaluating the utility of the active metabolite SE rather than the parent compound DAI, whereby pretreatment with SE precludes interactive HIV-1 Tat and cocaine synapse loss in cortical neurons via an ERβ dependent mechanism (Bertrand et al., 2015).

In vivo studies were initiated in the HIV-1 Tg rat to evaluate whether SE can ameliorate and/or protect against HIV-1 associated neurocognitive and/or affective alterations. Treatment with SE between six to eight months of age dose-dependently mitigated deficits in a subset of HIV-1 Tg rats (i.e., 40%) in a sustained attention operant task, whereby 0.2 mg SE served as the most efficacious dose (Moran et al., 2019); a dose which was subsequently utilized to examine the generality of these effects. Indeed, the efficacious therapeutic effects of SE generalize to both HIV-1-associated neurocognitive impairments (i.e., Preattentive Processes, Sustained Attention, Selective Attention, Flexibility, and Inhibition; McLaurin et al., 2020a; McLaurin et al., 2020b) and affective alterations (i.e., motivational dysregulation; McLaurin et al., 2021), as well as across biological sex (McLaurin et al., 2020b). Further, early (i.e., Postnatal Day 28: McLaurin et al., 2020b vs. 2–3 Months of Age: McLaurin et al., 2020a vs. 6–8 Months of Age: Moran et al., 2019) initiation of SE treatment enhances its therapeutic efficacy (i.e., precluded the development of neurocognitive impairments in all HIV-1 Tg animals assessed). Fundamentally, SE treatment leads to a population shift in dendritic spine morphological parameters consistent with a more mature dendritic spine phenotype, supporting an underlying neural mechanism by which SE exerts its therapeutic effects (McLaurin et al., 2021); it remains unknown as to whether these enhancements result from mitigation of gastrointestinal microbiome dysbiosis. Collectively, the *in vivo* efficacy of SE for at least a subset of HIV-1 Tg animals supports its utility as either a neuroprotective and/or neurorestorative therapeutic for HIV-1 associated neurocognitive and affective alterations; a therapeutic that exerts its therapeutic effects via long-term enhancements to dendritic spines.

The clinical and translational relevance of SE cannot be understated. First, the utilization of SE, rather than its precursor DAI, fully embraces any potential heterogeneity and/or dysbiosis in the gastrointestinal microbiome. Second, the 0.2 mg dose of SE tested in the *in vivo* studies yields a daily amount of 0.25 to 1.0 mg/kg SE (i.e., approximately 2.5 to 10 mg in a 60 kg human), whereby the isoflavone intake of most Japanese is 30–50 mg per day (Akaza, 2012). Third, there is no evidence of any adverse peripheral effects of SE in either preclinical (Neese et al., 2014; Moran et al., 2019) or clinical (Tousen et al., 2011; Oyama et al., 2012) studies. Finally, SE is being critically evaluated in ongoing clinical trials

for neurocognitive impairments associated with Alzheimer's disease and HAND (Ausio Pharmaceuticals; NCT03101085).

Despite the evidence supporting the utility and clinical relevance of SE, it is notable that there is some, albeit not comprehensive, evidence for other therapeutics (e.g., NMDA Receptor Antagonists, Escitalopram) targeting synaptic dysfunction. NMDAR antagonists, including memantine and ifenprodil, ameliorate synaptic loss and learning deficits induced by the HIV-1 viral protein Tat supporting its potential utility as a neurorestorative therapeutic (Shin et al., 2012; Raybuck et al., 2017). To date, however, NMDAR antagonists are unable to preclude synapse loss (Shin et al., 2012) and have only been evaluated in the presence of one HIV-1 viral protein (i.e., Tat); considerations which diminish their immediate clinical relevance. With regards to the therapeutic potential of escitalopram, HIV-1 Tg animals chronically treated with escitalopram exhibited decreased apathetic and anxiolytic behaviors in conjunction with enhanced neuronal and dendritic spine morphology (Denton et al., 2021); the generality of these effects, however, has not yet been systematically evaluated. Nevertheless, cumulatively, the evidence strongly supports targeting synaptodendritic alterations as an efficacious therapeutic for HIV-1-associated neurocognitive and affective alterations.

Serotonin (5-HT)

HIV-1-induced alterations in the relative abundance of bacteria belonging to the *Faecalibacterium* genera may alter the production of butyrate, a four-carbon short-chain fatty acid; an effect which may ultimately preclude the production and/or release of the excitatory neurotransmitter 5-HT. Pronounced decreases in 5-HT, or its precursor tryptophan, have been reported in HIV-1 seropositive individuals since the beginning of the epidemic (Jean-Marie et al., 1998); deficits which have persisted in this population, despite treatment with cART (e.g., Keegan et al., 2016; Qi et al., 2018). The kynurenine pathway is a possible contributing factor to the alterations of tryptophan in HIV-1 seropositive individuals as reductions in the ratio of plasma kynurenine/tryptophan have been reported and are associated with the severity of cognitive impairment (Keegan et al., 2016). Further, a positive association (r=0.421) between plasma butyrate and 5-HT has been reported in chronically infected HIV-1 seropositive individuals (Ghare et al., 2022). In preclinical biological systems, constitutive expression of HIV-1 viral proteins in the HIV-1 Tg rat induces decreased serotonergic release and reuptake in the prefrontal cortex (Denton et al., 2019) and hippocampus (Denton et al., 2021). To date, only one study has systematically investigated the direct relationship between reductions in 5-HT (or tryptophan) and HIV-1-associated neurocognitive and/or affective alterations, whereby a statistically significant association between higher tryptophan and lower depression levels was observed in chronically infected HIV-1 seropositive individuals (Vadaq et al., 2022).

Pharmacological agents (e.g., SSRIs) that exert their therapeutic effects by increasing 5-HT, therefore, may be clinically relevant in this population. SSRIs, the first of which was developed and evaluated in the late 1970s (i.e., fluvoxamine; Claassen et al., 1977; Saletu et al., 1977), exhibit a selective affinity for 5-HT reuptake sites, thereby increasing extracellular 5-HT concentration. Seven SSRIs (e.g., fluvoxamine, escitalopram, sertraline)

are currently approved by the United States Food and Drug Administration for the treatment of a variety of psychiatric conditions (e.g., Major Depressive Disorder; Obsessive-Compulsive Disorder; Post-Traumatic Stress Disorder; Chu & Wadhwa et al., 2022). Indeed, SSRIs are the most commonly prescribed pharmacotherapy for adults with depression (Marasine et al., 2021). Therefore, therapeutically targeting the hypo-serotonergic tone induced by chronic exposure to HIV-1 viral proteins via SSRIs may afford a readily available pharmacotherapy for HIV-1-associated affective alterations.

Indeed, given the prevalence of psychiatric comorbidities (i.e., depression, apathy; for review, Cysique & Brew, 2019) in HIV-1 seropositive individuals, the therapeutic utility of SSRIs in this population has been widely evaluated. In patients naïve to antiretroviral therapies, both open-label (e.g., Levin et al., 1990) and case-controlled studies (e.g., Elliott et al., 1998) observed moderate to strong (i.e., 50–100% of the sample responded to treatment) efficacy of SSRIs for the treatment of depression in HIV-1 seropositive individuals. The efficacy of SSRIs for depression generalizes to samples including HIV-1 seropositive individuals taking antiretroviral therapies (e.g., Ferrando et al., 1997; Rabkin et al., 1999; Currier et al., 2004; Tsai et al., 2013) and preclinical biological systems (i.e., HIV-1 Tg rat) resembling HIV-1 seropositive individuals on cART (Denton et al., 2021). The beneficial effects of SSRIs may extend beyond affective alterations in this population, as they also selectively improve neurocognitive performance (Sacktor et al., 2018) and increase adherence to antiretroviral therapies (Horberg et al., 2008).

Although SSRIs have significant therapeutic potential for HIV-1-associated affective alterations, a few considerations must also be taken into account. First, there is a minor risk for drug-drug (i.e., SSRI-cART) interactions in this population. The metabolism of nearly all SSRIs relies, at least in part, on cytochrome P450 enzymes (e.g., Obach et al., 2005; for review, Mandrioli et al., 2006); enzymes which are also responsible for metabolizing some antiretroviral medications (e.g., protease inhibitors; Chiba et al., 1996; Kumar et al., 1996). Indeed, a few HIV-1 seropositive individuals taking both fluoxetine and antiretroviral therapies known to inhibit P450 enzymes exhibited symptoms of 5-HT syndrome (DeSilva et al., 2001; Lorenzini et al., 2012), a potentially life-threatening complication resulting from the overstimulation of 5-HT (Sternbach, 1991). Second, it remains unknown as to whether SSRIs exert their therapeutic effects in HIV-1 seropositive individuals by enhancing 5-HT. Chronic escitalopram treatment, for example, likely mitigated apathetic and anxiolytic behaviors in the HIV-1 Tg rat by restoring synaptic dysfunction in the nucleus accumbens, as treatment failed to enhance hippocampal 5-HT kinetics (Denton et al., 2021).

Despite the potential utility and clinical relevance of SSRIs, it is notable that there is some, albeit not comprehensive, evidence for targeting HIV-1-induced 5-HT reductions with supplements (e.g., probiotics) and lifestyle changes (e.g., aerobic exercise). Treatment with a probiotic supplement (in addition to cART) significantly increased the serum concentration of serotonin in a small sample (n=8) of male HIV-1 seropositive individuals (Scheri et al., 2017); whether these neurochemical changes are sufficient to ameliorate neurocognitive and/or affective alterations, however, has not yet been systematically evaluated. Further, participation in an aerobic exercise and/or resistance training program significantly reduces depressive symptoms in adults living with HIV-1 (e.g., Neidig et al., 2003; Jaggers

et al., 2015; Dianatinasab et al., 2018). It again, however, is unknown as to whether aerobic exercise and/or resistance training exerts its therapeutic effects by increasing 5-HT concentrations in HIV-1 seropositive individuals. Taken together, evidence supports the therapeutic utility of targeting HIV-1-induced reductions in 5-HT for affective alterations; additional research, however, is necessary to more comprehensively evaluate whether these therapeutic effects also mitigate HIV-1-associated neurocognitive impairments.

CONCLUSIONS

1. Gastrointestinal microbiome dysbiosis in HIV-1 seropositive individuals is characterized by decreased α diversity, a decreased relative abundance of bacterial species belonging to the *Bacteroidetes* phylum, and geographic-specific alterations in *Bacillota* spp.
2. Significant inter-study heterogeneity, characterized by inconsistent findings in α and β diversity, was observed in case-control studies of chronically infected (treated or untreated) HIV-1 seropositive individuals. Low statistical power and biological factors (e.g., sexual orientation, geographic location) may lead to inter-study heterogeneity, necessitating careful consideration of experimental design and reporting practices. Further, preclinical biological systems may be fundamental to elucidating the unique role of chronic HIV-1 viral protein exposure to gastrointestinal microbiome dysbiosis.
3. HIV-1-induced alterations in the relative abundance of *Bacteroidetes* and *Bacillota* spp. may underlie, at least in part, deficits in inhibitory (i.e., GABA) and excitatory (i.e., 5-HT) neurotransmission. In addition, the increased abundance of Gram-negative *Prevotella* spp. in chronically infected HIV-1 seropositive individuals likely induces a cascade of molecular signaling events that may underlie the prominent neuronal injury and/or synaptodendritic alterations commonly observed in this population.

Outstanding Questions and Future Directions

1. Neurocognitive and/or affective alterations in HIV-1 seropositive individuals may be mitigated by therapeutically targeting either synaptodendritic dysfunction or 5-HT reductions. Albeit, to date, the most comprehensive evidence supports early treatment with the phytoestrogen SE to ameliorate both HIV-1-associated neurocognitive and affective alterations across the factor of biological sex. Indeed, SE affords high translational relevance and promising clinical utility.
2. One of the largest barriers to understanding the gut-brain-microbiota axis and how the gut microbiome modulates the brain is the variability present among clinical populations. Another barrier is the amount of environmental factors (e.g., diet, exercise, medications, geographic location) that can impact the composition of the gut microbiome. Limitations in experimental control of clinical populations or even healthy control populations and the environmental factors that can impact the composition of the gut microbiome necessitate the development of preclinical biological systems. Development and use of

preclinical biological systems allow for far better control of confounding variables, which in turn, would allow for a better understanding of HIV-1-associated dysbiosis and aid in developing novel adjunct therapies for HIV-1 associated neurocognitive and/or affective disorders.

ACKNOWLEDGEMENTS

This work was supported in part by grants from NIH (National Institute on Drug Abuse, R01-DA013137 to R.M.B. and C.F.M.; National Institute on Drug Abuse, K99-DA056288 to K.A.M.; National Institute on Drug Abuse, R01-DA054992 to M.S.; National Institute of Allergy and Infectious Diseases, R01-A155887 to J.L.K.; National Institute of Mental Health, R01-MH106392 to C.F.M. and R.M.B.; National Institute of Neurological Disorders and Stroke, R01-NS100624 to C.F.M. and R.M.B.) and the interdisciplinary research training program supported by the University of South Carolina Behavioral-Biomedical Interface Program (T32-GM081740).

ABBREVIATIONS

5-HT	Serotonin
BBB	Blood-Brain Barrier
cART	Combination Antiretroviral Therapy
DAI	Daidzein
ERβ	Estrogen Receptor β
GABA	γ-aminobutyric Acid
GAD	Glutamate Decarboxylase
GPCR	G Protein-Coupled Receptors
HAND	HIV-1-associated neurocognitive disorders
HDAC	Histone Deacetylase
HIV-1	Human Immunodeficiency Virus Type 1
IPSC	Inhibitory Postsynaptic Currents
LPS	Lipopolysaccharides
mRNA	Messenger RNA
NCI	Neurocognitive Impairments
PERMANOVA	Permutational Multivariate ANOVA
PSA	Polysaccharide A
SE	S-Equol
SSRI	Selective Serotonin Reuptake Inhibitors
Tat	Transactivator of Transcription

Tg	Transgenic
TPH1	Tryptophan Hydroxylase 1
ZPS	Zwitterionic Polysaccharides
α	Alpha
β	Beta

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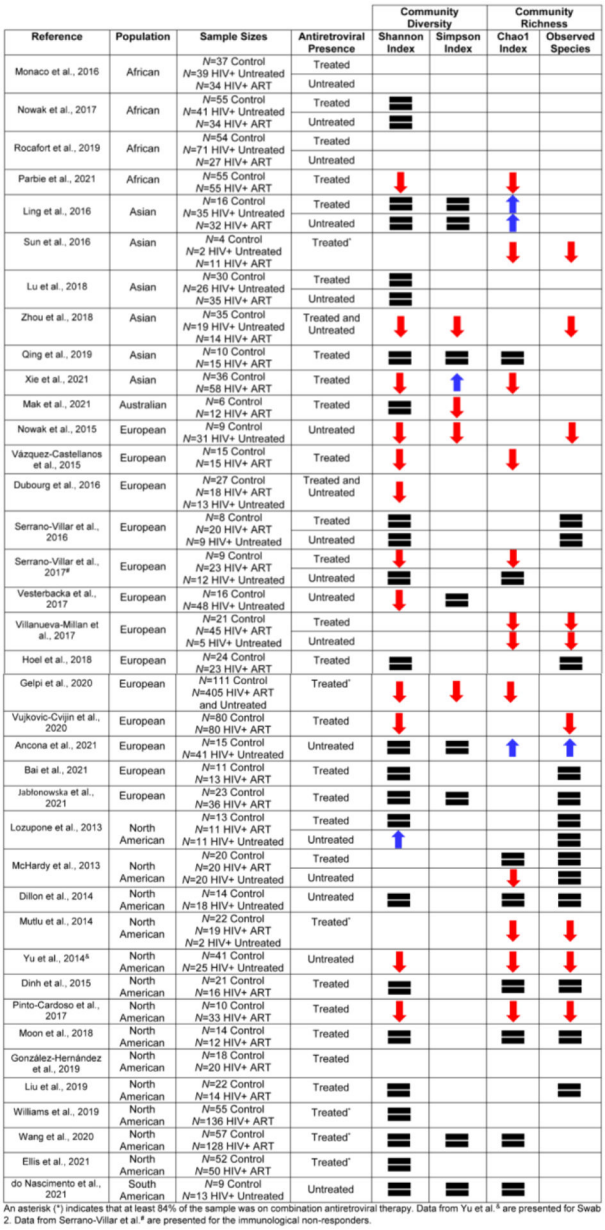

Reference	Population	Sample Sizes	Antiretroviral Presence	Community Diversity: Shannon Index	Community Diversity: Simpson Index	Community Richness: Chao1 Index	Community Richness: Observed Species
Monaco et al., 2016	African	*N*=37 Control *N*=39 HIV+ Untreated *N*=34 HIV+ ART	Treated				
			Untreated				
Nowak et al., 2017	African	*N*=55 Control *N*=41 HIV+ Untreated *N*=34 HIV+ ART	Treated	=			
			Untreated	=			
Rocafort et al., 2019	African	*N*=54 Control *N*=71 HIV+ Untreated *N*=27 HIV+ ART	Treated				
			Untreated				
Parbie et al., 2021	African	*N*=55 Control *N*=55 HIV+ ART	Treated	↓		↓	
Ling et al., 2016	Asian	*N*=16 Control *N*=35 HIV+ Untreated *N*=32 HIV+ ART	Treated	=	=	↑	
			Untreated	=	=	↑	
Sun et al., 2016	Asian	*N*=4 Control *N*=2 HIV+ Untreated *N*=11 HIV+ ART	Treated*			↓	↓
Lu et al., 2018	Asian	*N*=30 Control *N*=26 HIV+ Untreated *N*=35 HIV+ ART	Treated	=			
			Untreated	=			
Zhou et al., 2018	Asian	*N*=35 Control *N*=19 HIV+ Untreated *N*=14 HIV+ ART	Treated and Untreated	↓	↓		↓
Qing et al., 2019	Asian	*N*=10 Control *N*=15 HIV+ ART	Treated	=	=	=	
Xie et al., 2021	Asian	*N*=36 Control *N*=58 HIV+ ART	Treated	↓	↑	↓	
Mak et al., 2021	Australian	*N*=6 Control *N*=12 HIV+ ART	Treated	=	↓		
Nowak et al., 2015	European	*N*=9 Control *N*=31 HIV+ Untreated	Untreated	↓	↓		↓
Vázquez-Castellanos et al., 2015	European	*N*=15 Control *N*=15 HIV+ ART	Treated	↓		↓	
Dubourg et al., 2016	European	*N*=27 Control *N*=18 HIV+ ART *N*=13 HIV+ Untreated	Treated and Untreated	↓			
Serrano-Villar et al., 2016	European	*N*=8 Control *N*=20 HIV+ ART *N*=9 HIV+ Untreated	Treated	=			=
			Untreated	=			=
Serrano-Villar et al., 2017#	European	*N*=9 Control *N*=23 HIV+ ART *N*=12 HIV+ Untreated	Treated	↓		↓	
			Untreated	=		=	
Vesterbacka et al., 2017	European	*N*=16 Control *N*=48 HIV+ Untreated	Untreated	↓	=		
Villanueva-Millan et al., 2017	European	*N*=21 Control *N*=45 HIV+ ART *N*=5 HIV+ Untreated	Treated			↓	↓
			Untreated			↓	↓
Hoel et al., 2018	European	*N*=24 Control *N*=23 HIV+ ART	Treated	=			=
Gelpi et al., 2020	European	*N*=111 Control *N*=405 HIV+ ART and Untreated	Treated*	↓	↓	↓	
Vujkovic-Cvijin et al., 2020	European	*N*=80 Control *N*=80 HIV+ ART	Treated	↓			↓
Ancona et al., 2021	European	*N*=15 Control *N*=41 HIV+ Untreated	Untreated	=	=	↑	↑
Bai et al., 2021	European	*N*=11 Control *N*=13 HIV+ ART	Treated	=			=
Jablonowska et al., 2021	European	*N*=23 Control *N*=36 HIV+ ART	Treated	=	=		=
Lozupone et al., 2013	North American	*N*=13 Control *N*=11 HIV+ ART *N*=11 HIV+ Untreated	Treated	=			=
			Untreated	↑			=
McHardy et al., 2013	North American	*N*=20 Control *N*=20 HIV+ ART *N*=20 HIV+ Untreated	Treated			=	=
			Untreated			↓	=
Dillon et al., 2014	North American	*N*=14 Control *N*=18 HIV+ Untreated	Untreated	=		=	=
Mutlu et al., 2014	North American	*N*=22 Control *N*=19 HIV+ ART *N*=2 HIV+ Untreated	Treated*			↓	↓
Yu et al., 2014§	North American	*N*=41 Control *N*=25 HIV+ Untreated	Untreated	↓		↓	↓
Dinh et al., 2015	North American	*N*=21 Control *N*=16 HIV+ ART	Treated	=		=	=
Pinto-Cardoso et al., 2017	North American	*N*=10 Control *N*=33 HIV+ ART	Treated	↓		↓	↓
Moon et al., 2018	North American	*N*=14 Control *N*=12 HIV+ ART	Treated	=		=	=
González-Hernández et al., 2019	North American	*N*=18 Control *N*=20 HIV+ ART	Treated				
Liu et al., 2019	North American	*N*=22 Control *N*=14 HIV+ ART	Treated	=			=
Williams et al., 2019	North American	*N*=55 Control *N*=136 HIV+ ART	Treated*	=			
Wang et al., 2020	North American	*N*=57 Control *N*=128 HIV+ ART	Treated*	=	=	=	
Ellis et al., 2021	North American	*N*=52 Control *N*=50 HIV+ ART	Treated*	=			
do Nascimento et al., 2021	South American	*N*=9 Control *N*=13 HIV+ Untreated	Untreated	=	=	=	

An asterisk (*) indicates that at least 84% of the sample was on combination antiretroviral therapy. Data from Yu et al.[8] are presented for Swab 2. Data from Serrano-Villar et al.[#] are presented for the immunological non-responders.

Figure 1.

Characteristics of the 38 case-control studies comparing the gut microbiome in HIV-1 seropositive individuals with chronic infection and well-matched controls. Results from four alpha (α) diversity indices measuring community diversity (Shannon Index, Simpson Index) and community richness (Chao1 Index, Observed Species) are utilized to illustrate the significant inter-study heterogeneity observed within the field. The = indicates no statistically significant difference between HIV-1 seropositive individuals and controls, whereas the ↑ and ↓ illustrate significant decreases and increases, respectively, in α diversity in HIV-1 seropositive individuals relative to case-controls.

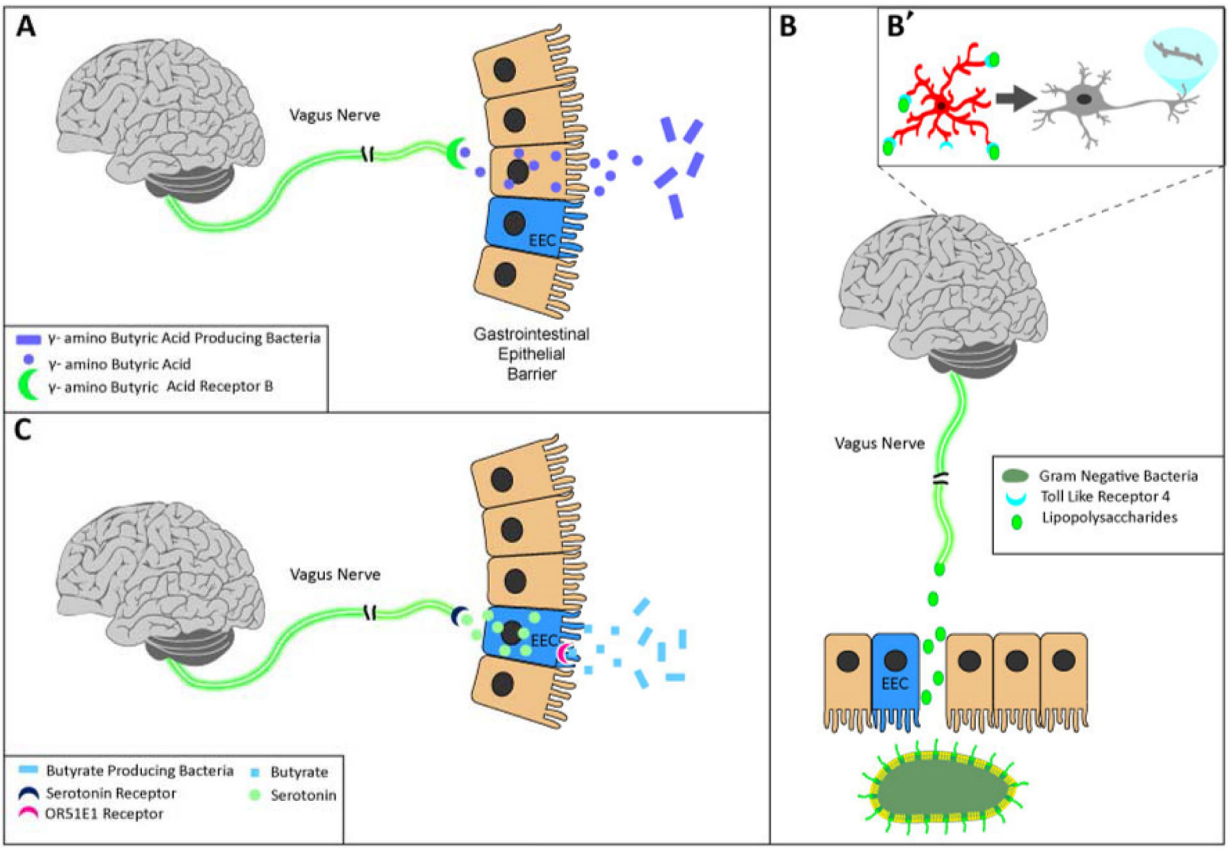

Figure 2.

Graphical illustration of how alterations in the prevalence of Bacteroides (**A**), Prevotella (**B**), and Faecalibacterium (**C**) may alter brain function. (**A**) Decreased production of *Bacteroides* species in HIV-1 seropositive individuals may result in decreased production of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). *Bacteroides* spp. produce GABA via the glutamate decarboxylase system. GABA is subsequently transported from the gastrointestinal system to the brain via vagal pathways, which express a high density of $GABA_B$ receptors. (**B**) A higher concentration of lipopolysaccharides (LPS) is one of the consequences of the increased prevalence of *Prevotella* spp. in chronically infected HIV-1 seropositive individuals. LPS can leak into circulation via the impaired gastrointestinal barrier or be transmitted to the brain via the vagus nerve. Upon entering the brain (**B'**), LPS binds to microglia, leading to their activation and/or dysfunction, which may subsequently underlie neurite and/or synaptic damage. (**C**) *Faecalibacterium* spp. serve as one of the main producers of butyrate, which is involved in the production and/or release of the neurotransmitter serotonin (5-HT) in a dose-dependent manner. Alterations in *Faecalibacterium*, as observed in HIV-1 seropositive individuals, support decreased production and/or release of 5-HT.

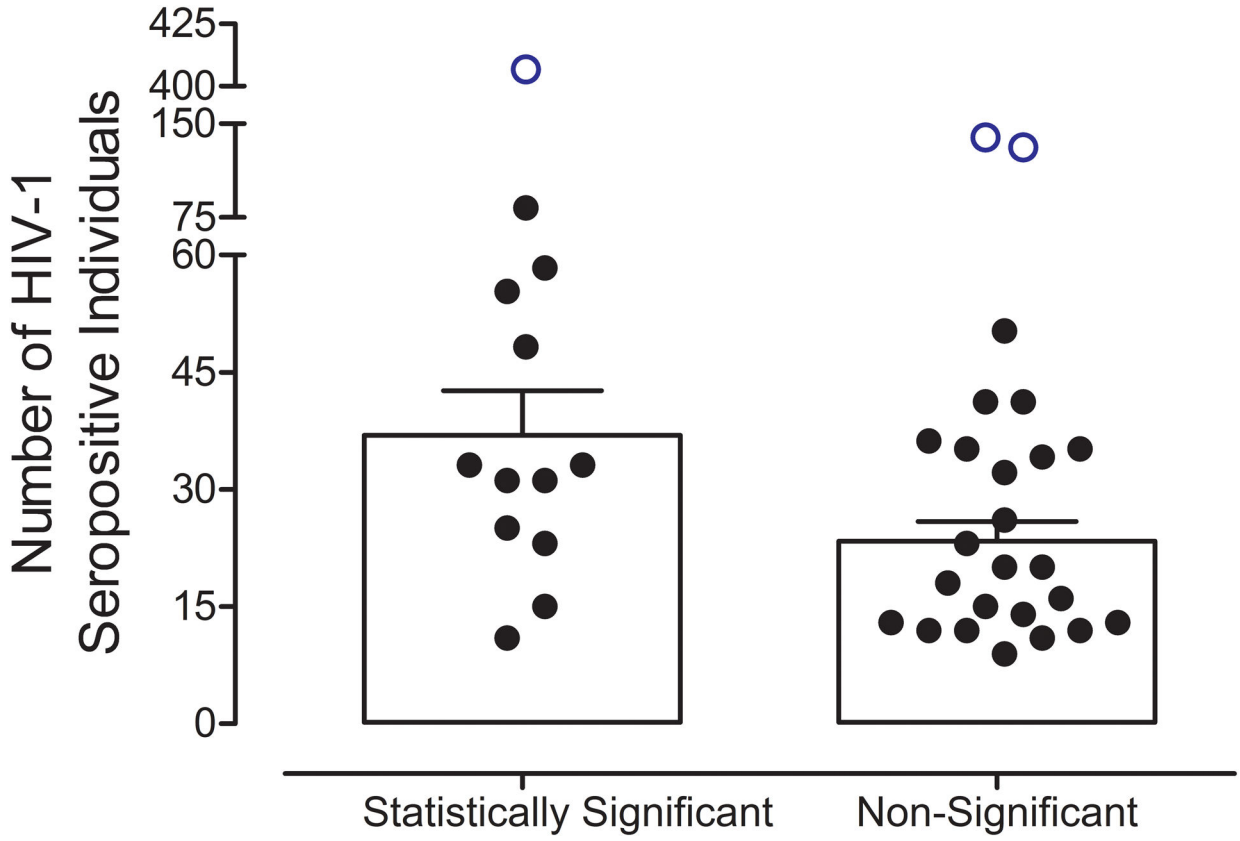

Figure 3.

Studies finding statistically significant effects of HIV-1 serostatus on α diversity, measured using the Shannon Index, evaluated a significantly greater number of chronically infected HIV-1 seropositive individuals (Main Effect of Statistical Significance, $F(1,33)=6.3$, $p<0.017$). Three outliers, defined as being greater than 2.5 standard deviations above the mean, are indicated by the open blue circles and were not included in the analysis.