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Review

The impact of HIV antiretroviral therapy on gut microbiota: the need for well-designed longitudinal studies

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Abstract

Introduction: Human immunodeficiency virus (HIV) infection remains a major public health concern despite a significant decline in HIV-related mortality and morbidity. These significant advances are linked mostly to effective antiretroviral therapy (ART). However, these treatments are not without consequences on other microorganisms in our body, especially when they must be used for life. Balanced gut microbiota is essential for maintaining human health through symbiotic relationship with the host cells.

Aims and methodology: This review focuses on ART and its potential impact on the intestinal microbial population of HIV-infected individuals. Therefore, we retrieved studies focusing on the impact of HIV ART on the gut microbiota, that were published from 2010 to 2021.

Results: It was observed that most studies on HIV ART and associated gut microbiota have been cross-sectional, and the findings, in general, showed significant damages caused by the ART to the gut microbial community (dysbiosis), with the impact varying in different studies. These changes also revealed dysfunction in microbial translocation and some immune markers, including T lymphocyte rates and the overall inflammation balance.

Conclusions: There are significant gaps in our understanding of the impact of HIV ART on gut microbiota. Thus, a longitudinal study is likely needed with a considerable sample size from different settings and classes of ART to better understand the impact of HIV ART on the gut microbiota, and develop remedial (restorative) and adjunctive host-directed strategies during HIV ART.

Key words: HIV antiretroviral-therapy; microbiota dysbiosis; longitudinal studies.

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Introduction

Human immunodeficiency virus (HIV) infection is a chronic infectious disease resulting in gradual decline of CD4+ T lymphocytes and chronic immune activation [1]. Despite considerable efforts in the fight against the HIV epidemic, uncontrolled HIV infection can induce the disruption of the gut microbiota (dysbiosis) in the intestinal immune barrier and systemic chronic inflammation and translocation of immune-stimulating microbial products [2]. These elements may persist despite the virus being "suppressed" during antiretroviral therapy (ART) maintaining a level of chronic inflammation even when ART is effective.

Changes to the microbiome have been associated with dysregulation of the inflammatory response, which is associated with several pathologies such as obesity, diabetes, inflammatory bowel disease, inflammatory cardiovascular diseases, and infectious diseases such as tuberculosis and malaria [3]. Alterations in the gut microbiota during HIV infection and treatment may lead to the development of non- acquired immunodeficiency syndrome (AIDS)-related infections [4]. Several observational studies have been carried out on the gut microbiota of HIV-infected patients, which often show the following features: decrease in α diversity, replacement of *Bacteroides* by *Prevotella*, protective effect against the decrease in CD4 counts for Bacteroidaceae, and Bactobacillales enriched cases [5,6].

HIV ART is a triple combination therapy and according to the therapeutic guidelines it generally consists of two nucleosides/nucleotides reverse-transcriptase inhibitors (NRTIs) plus one molecule from a different class: either a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or an integrase strand transfer inhibitor (INSTI) or a protease inhibitor (PIs) [7]. It should also be noted that new guidelines tend to move towards long-term therapeutic reduction by combining molecules from different classes or by using a single molecule (NRTI, NNRTI, PI, or INSTI) [8]. The impacts of ART with these new regimens on the gut microbiota remain largely unexplored. Several studies have been conducted over the past decade and have led to a better understanding of this topic, although many questions remain. Some believe that long-term therapy only partially alters the composition of the gut microbiota to a level that is not much different from uninfected individuals [2,6] while others suggest that ART may have an intermediate impact or even disrupt the gut microbiota significantly [9,10]. Therefore, it is interesting to review this aspect of HIV treatment and its role in changes in chronic inflammation.

The pharmacological role of ART is to first block viral replication, which in turn preserves many CD4 cells and increases their number to reinforce the host immune defense line [8]. However, in some HIV-infected individuals, the increase in CD4 count remains significantly low despite the effective use of ART. Dysbiosis from the use of antimicrobials such as ART drugs may play an important role in this process [11]. Therefore, we focused on reviewing the use of ART and its potential impact on the intestinal microbial population of HIV-infected individuals.

Literature search strategy

Search engines, such as PubMed and Google Scholar were used to identify relevant literature published from 2010 to 2021. Search articles were retrieved with the following search terms: "impact", "HIV", "antiretroviral therapy", "gut microbiome", "gut microbiota", and/or "long term study". The articles were then collated and reviewed. These search terms allowed us to specifically select studies related to the impact of HIV infection and ART on the gut microbiota.

Effects of microbiota products on host immunity

Bacteria contribute to the regulation of the host immune system through the synthesis of metabolites. Studies showed that certain microbial metabolites strongly control the immune system through host receptors and other target molecules [1,12]. The metabolites and receptors work together to generate a wide range of signals that are responsive to changes in health circumstances, nutritional status, and immunological control. These signals help collect nutrients from diets, regulate host metabolism, and strengthen the immune system. Products of the microbiota, which are regarded as microbial metabolites in this context, support host immunity and tolerance to manage infection without causing inflammatory illnesses [13]. It is well known that bacteria express carbohydrate-active enzymes to break down long carbohydrate fibers into simple sugars and create short-chain fatty acids (SCFAs), which cause colonic fermentation of carbohydrates [14]. The buildup of specific microbial metabolites, particularly SCFAs, in the colon lowers pH, regulates the composition and activity of microorganisms, satisfies nutritional requirements, and strengthens the immune system. Numerous chemicals generated by the human microbiota affect the host's innate immune system [15]. According to the studies, HIV infection causes changes to the architecture of lymphoid tissue after the depletion of gastrointestinal CD4+ T lymphocytes, which compromises the integrity and functionality of the mucosal barrier [16,17]. Bacterial translocation could persist throughout viral infection and contribute to immune activation during chronic phases of the disease. Nevertheless, a few studies have demonstrated that mucosal injury and gastrointestinal tract inflammation continue despite the use of successful ART. It was revealed that the same changes observed in the gut microbiome of HIV-positive individuals receiving no treatment were also reported in HIV patients who had been successfully receiving ART for several years. This is probably related to the way bacteria metabolize drugs or the antimicrobial qualities of these ARTs, especially since the antiretrovirals (ARVs) may possess antibacterial, antifungal, and anticancer activities [5,8].

Impact of HIV infection on the gut microbiota

HIV infection may have an impact on the composition of the gut microbiota [18]. HIV, responsible for AIDS, is a retrovirus that is able to integrate its own DNA into the genome of the host. The genomes of retroviruses are transcribed into DNA by a RNA dependent DNA polymerase which synthesizes DNA on a genomic RNA template by the process of reverse transcription (RT) [19]. This makes the virus extremely difficult to eliminate with existing therapies [20]. HIV is one of the rare pathogens known so far to

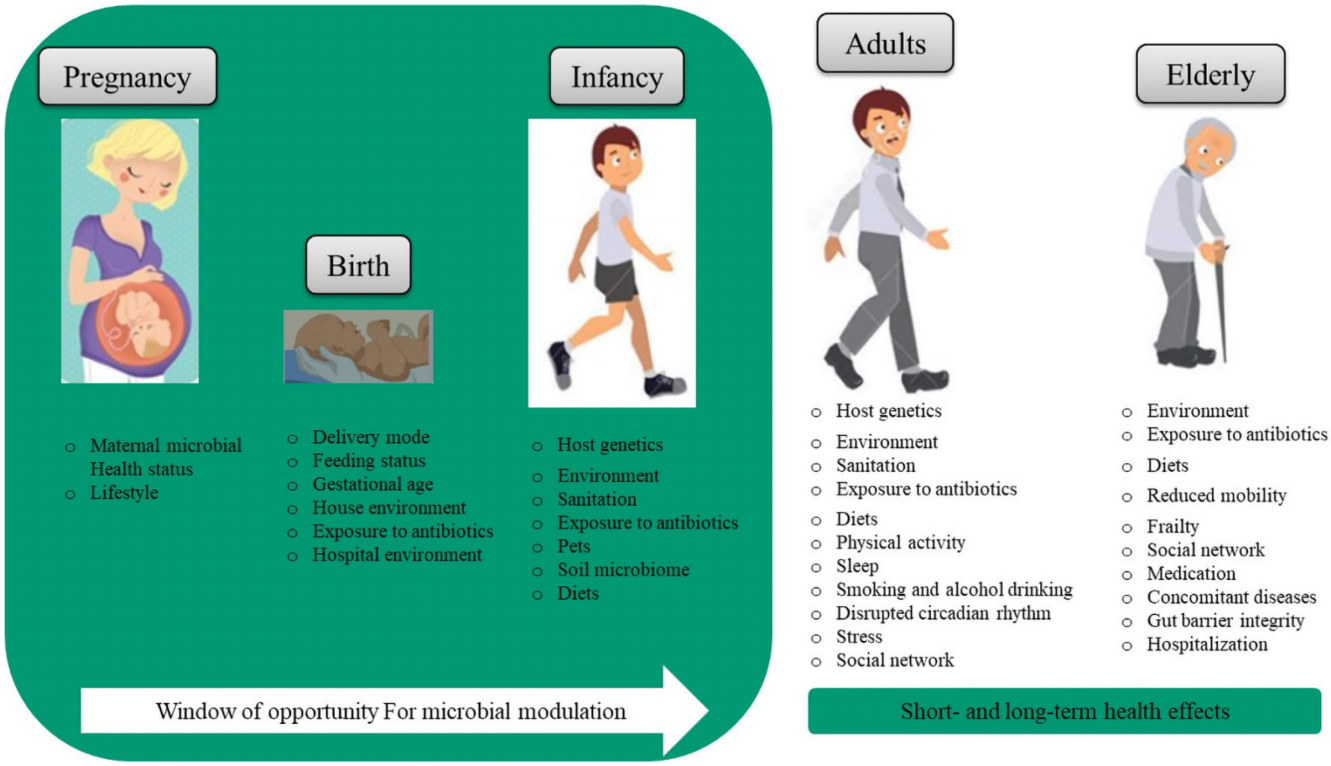
attack the immune system directly. Cells that are subject to HIV infection express CD4 receptors on the surface of their membranes [21]. The CD4 receptor was discovered in 1984 and it is insufficient to allow entry of the virus into the host organism [22]. Ten years later, the chemokine receptors, CXCR4 and CCR5, were identified as essential co-receptors for HIV to enter host cells [23]. Among these cells are mainly CD4 helper T lymphocytes, but also antigen-presenting cells, such as macrophages, dendritic cells, Langerhans cells, and microglial cells of the brain [24]. The majority (99%) of infections occur in the activated CD4+ lymphocyte cells in lymphoid organs, which are the main reservoirs of the virus [17]. Microbial colonization of the body, including the gut, begins immediately at birth. Although influenced by a variety of stimuli, namely diet, physical activity, lifestyle, diseases including chronic diseases such as cancer and HIV infection, hormonal cycles, therapies, genetics, and environmental changes; the acquired profile remains largely stable in healthy adults (Figure 1) [25]. Figure 1 demonstrates the factors influencing gut microbiota in humans throughout life [25].

The microbiome has an essential role in maintaining a state of good health. An unbalanced microbiome is prone to many diseases; therefore, having a healthy microbiota would be a key factor in being healthy [26]. Recent studies have highlighted the essential role of these microorganisms in human physiology, health, and disease [27,28]. The microbial population in the gastrointestinal tract is mainly composed of 6 phyla; notably, Firmicutes, Bacteroidetes, Actinobacteria, Virrucomicrobio, Proteobacteria and Euryarchaeota phyla (Figure 2) [29].

The influences of commensals on health and disease through the regulation of immune function have become an area of scientific and clinical importance. Recent studies have characterized the gut microbial communities and have shown a profound effect on the host's immune mechanisms. Various factors, such as genetic and environmental factors, can also play an important role in gut dysbiosis. These factors need to be carefully monitored since inappropriate practices such as overuse of drugs, especially antibiotics, may increase autoimmune disease risk as a result of dysfunction of the gut microbiota [30].

Disruption of the intestinal immune system at the intestinal mucosa is correlated with microbial intestinal dysbiosis. Despite success in managing HIV infection, many HIV-infected patients have persistent inflammation and immune activation leading to the development of co-morbidities such as cardiovascular disease, osteoporosis, neurocognitive decline, cancers, as well as significant associated mortality [31]. Several

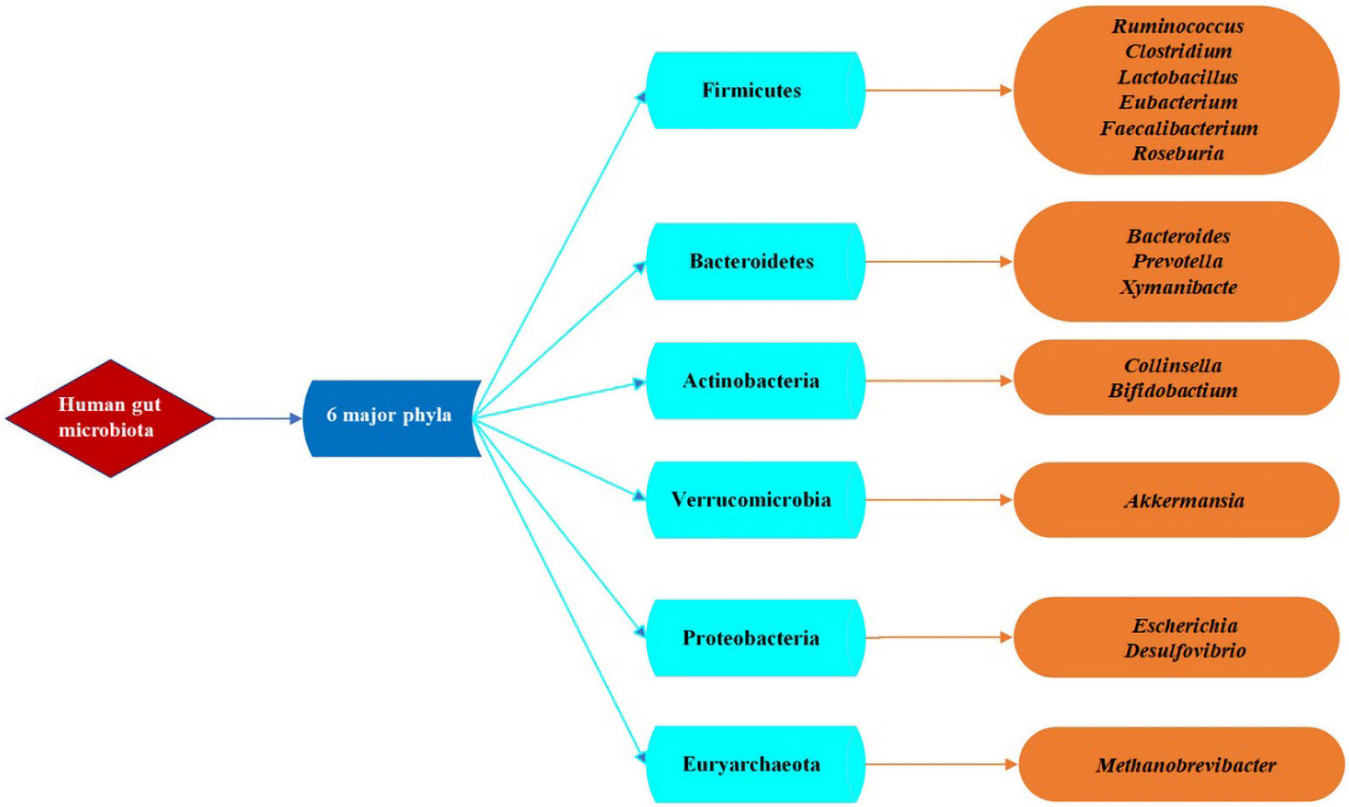
Figure 1. Factors influencing the gut microbiota in humans throughout life [25].



studies suggest that HIV infection has an impact on the richness and diversity of the gut microbiota [10,32]. Reduced immunity (CD4+ less than 300 cells/mm^3) is linked to an unbalanced microbial composition, and subjects with a CD4+ count greater than 300 cells/mm^3, in turn, have an unbalanced microbial composition compared to HIV-negative individuals, but slightly improved compared to immunocompromised subjects (CD4+ less than 300 cells/mm^3). This indicates that the initial impact on the gut microbiota composition and microbial diversity, despite adequate immune recovery, is linked to HIV infection, suggesting that HIV infection remains consistently associated with reduced microbial diversity (compared to HIV negative people) [32,33]. Systemic immune activation is increased in people infected with HIV; although many factors can contribute to it, and microbial products have recently emerged as potential drivers of this immune activation [33]. Noguera-Julian *et al.* and *Ji et al*., reported that the gut microbiota was altered in HIV infected patients with high-viremia (viral load > 1000 copies/mL) and was associated with microbial translocation, monocyte activation, and immune dysfunction respectively [5,10].

Previously, studies have shown that alteration of the gastrointestinal (GI) tract in HIV-infected subjects is influenced in the early stages of HIV disease [34,35]. The presence of opportunistic pathogens such as *Pseudomonas aeruginosa* and *Candida albicans* is 10 times and 10,000 times higher, respectively, compared to those reported in the general population. Fewer beneficial microbial groups were found in HIV-infected patients such as *Bifidobacteria* and *Lactobacilli*, compared to the general population [36]. *Bifidobacteria* and *Lactobacilli* are known to have a positive influence on the immune function of the mucous membranes and intestinal health [37]. These results are consistent with several other studies which also confirm that there is a loss of various commensal bacterial genera in the composition of the gut microbiota of HIV-infected subjects. At the same time, there may be an addition of the genus *Prevotella*, which is generally considered to be a commensal organism rather than usually pathogenic and is frequently discovered following anaerobic respiratory infections. In addition to their well-documented presence in bacterial infections, *Prevotella* is linked to infections of the respiratory system, including aspiration pneumonia, lung abscess, chronic otitis media, and sinusitis; lung abscess around the mouth; infections of the urinary tract; brain abscesses; osteomyelitis; and periodontal disease [9,38].

Figure 2. The six main phyla of the human gut microbiota and their predominant genus [29].



Numerous similar studies have revealed that microbial alterations in the gastrointestinal tract are key factors in the pathogenesis of chronic HIV infection and can directly stimulate inflammation in the host [39,40]. The gut microbiota represents a crucial line of resistance to colonization by pathogens [41], controls the proliferation and differentiation of epithelial cells [42], and modulates the maturation and activity of the innate and adaptive immune responses [43]. This is reported on the importance of the observed abundance of various microbial taxa, including Enterobacteriaceae, a family made up of many pro-inflammatory members including *Escherichia coli*, *Salmonella*, *Pseudomonas*, *Yersinia*, and *Klebsiella*. Members of this family induce inflammation of the host upon infection and can utilize the products of this inflammation, namely reactive oxygen species (ROS) of neutrophils and macrophages as terminal acceptors of electrons in their respiratory chain [44], allowing them only to derive cellular energy from a source that members of the endogenous gut microbiota cannot easily use. This gives a growth advantage over endogenous bacteria as part of host inflammatory processes. In addition, IL-17 and IL-22 secreting T cell populations were found to limit microbial translocation and systemic T cell activation/inflammation [2]. These results were confirmed by a report published in 2016, showing increased colon proteins and decreased Firmicutes in untreated HIV-infected people, as well as an association between microbial lesions and active mucous membranes and myeloid dendritic cells [38].

Anti-retroviral drugs used in the treatment of HIV and their mechanisms of action

HIV latency, HIV-induced immunological dysfunction, and potentially ongoing low-level viral replication in compartments and reservoirs, which permit the pathogenic disease processes, are some of the mechanisms that contribute to HIV persistence during ART; even though ART is very effective in inhibiting HIV replication [46]. At the intestine level, ART can only partially and slowly replace CD4+ cells; it cannot eradicate viral reservoirs, which are also immune system resistant [47]. Furthermore, despite ART, it has been noted that HIV-positive individuals are in a state of inmunoactivation, which may be connected to the higher bacterial translocation seen in individuals with long-term HIV infection [48]. Due to the complexity of HIV persistence and treatment, various classes of antiretroviral drugs have been approved by the United States Food and Drug Administration (FDA) and more drug candidates are still under development to treat HIV/AIDS.

Nucleotide and nucleoside inhibitors (NRTIs)

The Food and Drug Administration (FDA) approved the first class of antiretroviral medications known as nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) [49]. However, they require cellular kinases to phosphorylate for them to have an antiviral action; therefore, they are supplied as prodrugs. As a result, NRTIs are phosphorylated in the host cell to produce their active diphosphate or triphosphate metabolites, which block the viral reverse transcriptase's ability to function by either competing with the enzyme's natural substrate to prevent it from converting viral RNA into double-stranded DNA, or by incorporating into the nucleotide analog, which stops the virus from continuing to grow [46]. NRTIs are not metabolized by CYP450, which makes them less likely to cause drug-drug interactions. Currently, the following NRTIs has been approved for use: zidovudine (AZT), didanosine (ddI), stavudine (d4T), lamivudine (3TC), emtricitabine (FTC), abacavir (ABC), tenofovir disoprovil fumarate (TDF), and tenofovir-alafenamide (TAF) [50]. It is noteworthy that severe toxicities, mostly related to their effects on human cellular mitochondrial DNA, have been documented in HIV-positive patients receiving treatment with earlier NRTIs, particularly AZT and d4T [51]. These medications cause mitochondrial malfunction by inhibiting the transcription of mitochondrial RNA (mt RNA), which is caused by their inhibition of mitochondrial DNA polymerase gamma. This is linked to a rise in ROS concentrations, which encourages oxidative stress. An increase in ROS levels in adipose tissue is linked to adipocyte mortality and the loss of subcutaneous fat, which may result in clinical lipoatrophy instead of cell differentiation inhibition. In addition, hepatic steatosis and lactic acidosis are two more serious effects linked to older NRTIs [52]. This class of ART, particularly zidovudine (AZT), is implicated in the reduced α-diversity, increased ß-diversity, and radical changes in the proportions of gut microbial communities during HIV treatment [53].

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

These molecules have an entirely different chemical structure compared to typical nucleosides. They are allosteric inhibitors that are non-competitive. NNRTIs are located next to the DNA polymerase site in a hydrophobic region. Their complexation modifies the

enzyme's shape, greatly decreasing its catalytic efficiency [54].

The four NNRTIs that are currently in use are nevirapine (NVP), efavirenz (EFV), etravirine (ETR, ETV), and rilpivirine (RPV) [50]. Since NNRTIs do not require phosphorylation to be active, they differ from NRTIs in that they do not require cellular activation. Consequently, these molecules are more potent than NRTIs and permanently inhibit HIV reverse transcriptase, except for group O (outlier). NNRTIs are limited because of drug-drug interactions since CYP450 metabolizes them extensively, even though these medications generate a strong virologic suppression. Therefore, extra care should be used when these medications are provided in conjunction with other substances that are also extensively metabolized by CYP450 [55]. NNRTIs are generally well tolerated and safe, while EFV usage can have negative effects on the central nervous system and cause lipoatrophy. NVP is linked to rash and hepatotoxicity [7]. However, the antibacterial activity of this class of ARTs, particularly EFV, could aggravate alterations in the intestinal microbiota [8].

Protease inhibitors (PIs)

PIs block the late phase of viral maturation. The HIV protease cleaves the precursor polypeptides produced by the *gag* and *pol* genes encoding the virion's structural proteins and enzymes. The virions produced under PIs are then immature and cannot infect new cells [56]. Ritonavir (RTV) was the first PI to be approved; however, its side effects and high dosage requirements prevent it from being used as an anti-HIV drug at this time. It is now a PI booster that is used in small doses. The use of six PIs, including atazanavir (ATV), darunavir (DRV), lopinavir (LPV), fosamprenavir (FPV), saquinavir (SQV), and tipranavir (TPV), has been approved [56]. This is because the main enzyme involved in the metabolism of most PIs, CYP3A4 isozyme, is strongly inhibited by RTV. This molecule, therefore, inhibits the metabolism of concurrently administered PIs, increasing absorption, and extending the half-life so that lower doses and more frequent administration of the PI are possible [61]. Most common metabolic abnormalities are the negative effects linked to the use of this class of antiretrovirals, which include dyslipidemia, insulin resistance, hyperglycemia, lipodystrophy, and metabolic syndrome. Therefore, prolonged use may result in malfunction related to the heart and metabolism [59]. Research has shown that HIV PIs cause stress on the endoplasmic reticulum (ER) and activate the unfolded protein response (UPR) in various cell types. Furthermore, disruption of intestinal barrier function results from activation of the UPR caused by HIV-1 PIs [60].

Inhibitors of attachment

The only CCR5 antagonist that has been authorized for therapeutic use in individuals with R5-tropic HIV-1 infection is maraviroc (MVC). As a CCR5 antagonist, MVC attaches itself to the human CCR5 receptor on the cell membrane and subsequently prevents HIV gp120 from interacting with the CCR5 receptor to cause CCR5-tropic HIV [56]. The co-receptor use may vary during HIV infection, which is a significant drawback of MVC. For this reason, the tropism of HIV-1 should be assessed both before beginning treatment and if an antagonist of CCR5 treatment fails [56]. Since CYP3A4 is involved in the extensive metabolism of MVC, dose adjustments are necessary when administering MVC in conjunction with drugs that affect CYP3A4 activity [61]. It is not frequently used in clinical practice due to this medication interaction, the requirement to test for HIV tropism, and the pain associated with using it twice daily [56]. Furthermore, negative consequences of MVC, including fever, hepatotoxicity, allergic reactions, upper respiratory tract infections, and cardiovascular issues, have been documented in clinical trials [61]. According to a study based on an obese mouse model, MVC may lower the level of Bacteroidales while preventing obesity and related diseases in HIV patients [62].

Fusion inhibitors

The only fusion inhibitor that has been approved for use in HIV-positive individuals is enfuvirtide (ENF). According to Matos *et al*., the fusion inhibitor ENF binds to gp41 and inhibits the conformational change that is required for fusing of the viral and cellular membrane, hence preventing viral entry into host cells [63]. The fact that this medication must be taken twice daily and is only accessible in an injectable formulation is a drawback. Thus, in addition to the discomfort associated with this kind of administration, most patients experience injection site reactions such as pain, erythema, induration, etc. Regarding adverse effects, clinical studies have shown that people with HIV who are receiving ENF have a higher risk of pneumonia [56].

Integrase strand transfer inhibitors

The World Health Organization (WHO) highly recommends this family of ARVs because it is the

newest and most potent class of ARVs currently in use. INSTIs accelerate the creation of covalent connections between the host and viral DNA to prevent viral DNA from integrating into the host chromosome and to inhibit the virus integrase enzyme. In specific terms, INSTIs inhibit the strand transfer reaction selectively [46,56]. Bictegravir (BIC) is presently undergoing approval procedures, whereas raltegravir (RAL), dolutegravir (DTG), and elvitegravir (EVG) are approved for use [50]. Strong antiviral activity and relatively good tolerance characterize this family of ARVs. Therefore, INSTIs are included in the list of treatments that are advised for naive patients.

The most common adverse events of the three currently approved INSTIs are gastrointestinal side effects and headaches, which are generally well tolerated in individuals with or without prior treatment experience [64]. Patients receiving this ARV will experience greater intestinal dysbiosis than other classes of ARVs, including PIs, associated with weight gain [65].

Impact of antiretroviral therapy on the human gut microbiota

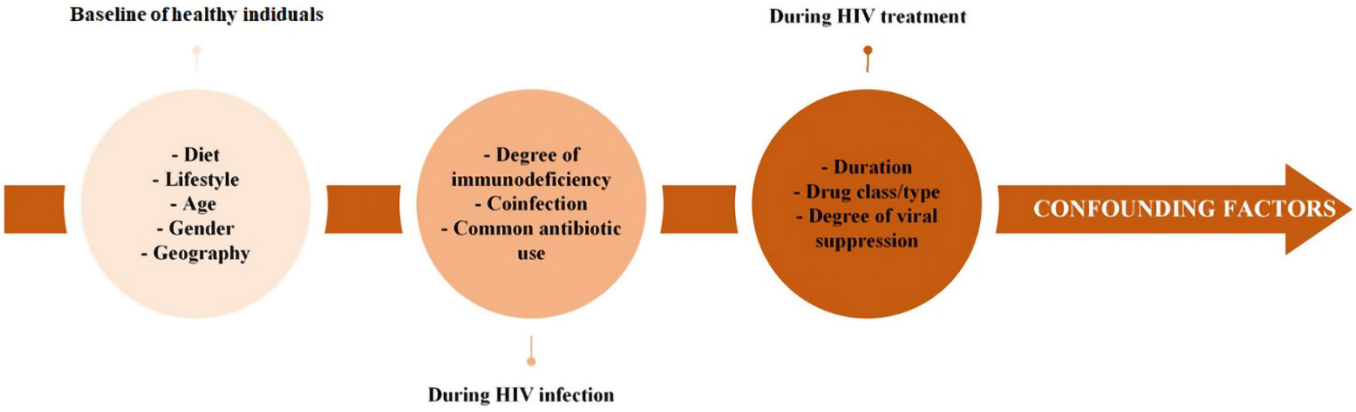
Today, ART is the only alternative that allows people living with HIV to live with their disease for life and have a life expectancy close to that of non-HIV-infected people. ART aims to reduce viral replication to the point of suppression while restoring the immune system and reducing HIV-related mortality and morbidity [66]. However, these ART molecules, which are essential for people living with HIV, are not without consequences; they have toxicities and adverse effects. These effects range from mild to severe, including gastrointestinal effects such as nausea, vomiting, diarrhea, abdominal pain, and possible intestinal disease [67]. Various factors influence the gut microbiota during HIV infection and treatment. An individual's gut microbiota initially, before infection, will influence the changes associated with HIV infection. These changes associated with HIV are themselves influenced by the course of the infection as well as by any co-infection and treatment (Figure 3) [68].

Since ART does not cure HIV infection, lifelong ART is essential for patients living with HIV. Therefore, special care is fundamental against the occurrence of side effects and/or long-term toxicities of ART to maintain patient health. One of the main side effects is gastrointestinal symptoms, such as diarrhea, nausea, and abdominal bloating [57].

Data from various research studies support the idea that chronic immune activation is a major contributor to HIV disease progression and mortality in people infected with HIV [69,70]. For any untreated HIV infection, activation of CD4/CD8 T-cells can predict the time to AIDS and is related to CD4 and CD8 counts before treatment [71]. Although ART is effective, a substantial proportion of successfully treated subjects do not show resolution of the systemic inflammation [72]. It is important to note that persistent inflammation is strongly associated with increased cardiovascular events, accelerated liver disease, impaired immune recovery, and mortality [73,74]. However, the major challenge for the scientific community is to understand and reverse persistent inflammation in order to restore the health and lifespan of people infected with HIV. Table 1 summarizes the studies on the impact of ART on the gut microbiota.

In 2021, Imahashi *et al.,* analyzed fecal samples and concluded that over time NRTIs are linked to a decrease in α-diversity and an increase in β-diversity during

Figure 3. Factors influencing the gut microbiota from health to infection and during ART [68].



ART: antiretroviral therapy; HIV: Human immunodeficiency virus.

ART. An enrichment of *Prevotella* and a depletion of *Bacteroides* in the genus composition in patients on ART, particularly in patients starting NRTI-based treatment, was noted. But an increased loss of *Bacteroides* and an increase of *Succinivibrio* and *Megasphaera* were observed in patients on INSTI and/or NNRTI-based ART. However, it should be noted that these were patients on ART for at least a year and had followed INTI in the past. These results suggest that NRTI-based ARTs have dysbiotic effects on the composition and diversity of the gut microbiota during ART over time. Other therapeutic classes, notably INSTIs and NNRTIs, did not show significant associations with dysbiosis. These results justify the need for new longitudinal studies to describe the effects of different classes of ART on the gut microbiota using whole genome sequencing (Table 1) [53].

A metagenome sequencing model in HIV-positive subjects on ART identified several genera of the faecal microbial community as biomarkers (systemic markers) among which we can note a high abundance of *Succinivibrio* and *Prevotella*, and a depletion of *Faecalibacterium*, *Bacteroides*, and *Roseburia*. This led to an enrichment of genes involved in several pathogenic processes, including bacterial translocation, T cell markers, and lipopolysaccharide biosynthesis associated with other inflammatory pathways. In addition, a deletion for pathways involved in energy processes and amino acid metabolism was observed in successfully treated HIV-infected patients (Table 1) [75].

Table 1. Summary of the effects of ART on the disruption of the gut microbiota during HIV treatment.

Study type	Groups (sample size)	Therapeutic classes	Summary of observed changes between groups	Impact of observed changes	Study site	References
Cohort study from (0, 1, 12, and 24 weeks after start of ART)	HAART (20) Control (13)	INSTI + NRTI (6), INSTI + NNRTI (9), INSTI + PI/r (2) PI/r + MVC (3)	↓ α-diversity, ↑ β-diversity ↑ *Prevotella* ↓*Bacteroides* ↑ *Succinivibrio* ↑ *Megasphaera*	Dysbiosis due to NRTIs INSTIs and INNTIs restores dysbiosis caused by NRTIs	Nagoya, Japan	Imahashi, M. *et al.* [53].
Case–control study	HAART (15) VL < 20 cop/mL Control (15)	Not determined	↑ *Succinivibrio* ↑ *Prevotella* ↓ *Faecalibacterium* ↓ *Bacteroides* ↓ *Roseburia*	Enrichment of genes implicated in multiple pathogenic pathways in HIV-positive patients who have received effective treatment: - Bacterial translocation, -Lipopolysaccharide biosynthesis pathway, -T cell markers -Inflammatory pathways	Madrid, Spain	Vazquez-Castellanos *et al.* [75].
Case–control study	HAART (21) VL < 400 cop/mL Control (16)	PIs (8), NNRTIs (11), PIs + NNRTs (2)	↑ *Enterobacteriaceae* ↑ *Enterobacteriales* ↑ *Erysipelotrichaceae* ↑ *Erysipelotrichi* ↑ *Gammaproteobacteria* ↑ *Barnesiella* ↓ Rikenellaceae ↓ Alistipes	-Microbial translocation EndoCAb, sCD14 -Systemic inflammation IL-1β, IFN-γ, TNF-α	Boston, USA	Dinh *et al.* [48].
Cross-sectional study	Not HAART (5) HAART (45) VL < 20 cop/mL Control (21)	NRTIs + PIs (15) NRTIs + NNRTIs (22) NRTIs + INSTIs (8)	↑ *Bacteroidetes, Proteobacteria,* ↑ *α-proteobacteria* ↓ *Firmicutes*	-Increase in intercellular adhesion molecule (ICAM) -Higher plasma sCD14 levels - Decreased inflammation and bacterial translocation	Logrono, Spain	Villanueva-Millán *et al.* [76].
Cross-sectional study	Not HAART (9) HAART (18) Control (6)	Not determined	↑ *Proteobacteries.* ↓ *Bacteroides*	-Disruption of immune markers, -T-cell activation markers and inflammation -Intermediate dysbiosis due to treatment	San Francisco, USA	Vujkovic-Cvijin *et al.* [2].
Cross-sectional study	Not HAART (20) HAART (20) Control (20)	Not determined	↓ *Alpha-diversity* ↓ *Alistipes* ↓ *Coprococcus* ↑ *Fusobacteria*	-Dysfunction in amino acid metabolism, vitamin biosynthesis, and siderophores, -Intermediate dysbiosis due to treatment	Los Angeles, USA	McHardy *et al.* [77].
Cohort study from (0, and 10 months after start of ART)	Before HAART start (16) After HAART start (16)	NRTI + NNRTI (8) NRTI + PI/r (8)	↓ *Alpha-diversity* ↓ *Prevotella*	Dysbiosis of the intestinal microbiota exacerbated in the presence of ART (notably EFV and AZT)	Stockholm, Sweden	Ray *et al.* [8].
Cohort study from (0, and 6 months after start of ART)	Before HAART start (37) After HAART start (31) Control (7)	2NRTI + EFV (31)	↓ Bacteroidetes ↑ Fusobacteria Firmicutes	Instability of soluble CD14 levels in certain bacterial taxa during ART	Bangkok, Thailand	Sortino *et al.* [79].

ART: antiretroviral therapy; EFV: efavirenz; HAART: highly active antiretroviral therapy; HIV: human immunodeficiency virus; INSTI: integrase strand transfer inhibitor; MVC: maraviroc; NNRTI: non-nucleoside reverse-transcriptase inhibitor; NRTI: nucleosides/nucleotides reverse-transcriptase inhibitors; PI: protease inhibitor ; VL: viral load. ↑: Increase; ↓: Discrease.

A 2015 study used pyrosequencing of the bacterial gene encoding 16S ribosomal RNA (rRNA) on virologically successful HIV-infected patients (on suppressive ART) [48]. The researchers noted that gut dysbiosis was associated with increased microbial translocation, and significant correlations between markers of systemic inflammation and microbial translocation and specific taxa were demonstrated. In particular, the high level of soluble CD14 in plasma would be associated with the abundance of Enterobacteriales and Enterobacteriaceae; and low level of central endotoxin IgM was associated with the enrichment of Erysipelotrichaceae and Erysipelotrichi for microbial translocation markers. As for markers of systemic inflammation, high levels of IL-1β and IFN-γ were associated with the abundance of Enterobacteriales, Enterobacteriaceae for both, and Gammaproteobacteria for IFN-γ; whereas a low level of TNF-α was be associated with enrichment of Erysipelotrichi and *Barnesiella* (Table 1) [48].

Villanueva-Millán *et al.* found that HIV-infected individuals on INSTIs therapy have a positive impact in relation to levels of systemic inflammation, which would likely be due to almost identical microbial diversity to that of HIV-uninfected individuals, such as an increase in Bacteroidetes, Proteobacteria, and α-proteobacteria in individuals receiving this class of ART [76]. In contrast, a decrease in some species of the phylum Firmicutes was observed in individuals using NRTIs and PIs. This would have led to a significant increase in intercellular adhesion molecule (ICAM) values in these individuals. Similarly, plasma CD14 levels were significantly higher in patients using NRTIs, NNRTIs and PIs (Table 1) [76].

Vujkovic-Cvijin *et al.* used a mouse model to demonstrate that there is a link between immunopathogenesis during HIV infection and colonic bacteria, which is irreversible even with viral suppression under ART. A profound change in the gut microbiome would have resulted in an enrichment of *Proteobacteria* and degradation of *Bacteroides* with a disruption of immune markers, T-cell activation, and inflammation in HIV-infected individuals and this persists even during ART (Table 1) [2].

McHardy *et al.* reported a significant increase in *Peptostreptococcus*, *Fusobacteria*, and *Porphyromonas*; and a decrease in the genera *Coprococcus*, *Roseburia*, *Alistipes*, *Ruminococcus*, *Lachnospira*, and *Eubacterium* in treatment-naive HIV-infected individuals and these changes continue even during ART but less significantly in this group. This imbalance in gut microbiota correlates with dysfunction in amino acid metabolism, vitamin biosynthesis, and siderophores in treatment-naive HIV-infected individuals (Table 1) [77]. These results are in favor of a disruption of the gut microbiota by ART with a marked impact on certain essential markers to different degrees.

The bactericidal effect of certain ARTs has been documented since the start of the HIV epidemic [78]. In 2021, Ray and colleagues documented a marked decrease in α diversity in patients using NNRTIs, accompanied by a particularly low abundance of *Prevotella*. Furthermore, antivirals EFV and ZDV had a direct impact on intestinal bacteria, notably *Prevotella* and *Bacteroides fragilis*. They thus discovered that these antiretroviral drugs have antibacterial qualities, and are likely to exacerbate the dysbiosis of the gut microbiota induced by HIV during treatment rather than repairing it [8].

Further research is needed, as Ornella Sortino *et al*. determined the potential effects of certain HIV therapeutic drugs as well as the potential contribution of microbiome alterations to HIV-associated inflammation [79]. They also discovered dysbiosis early in acute HIV infection during their microbiota investigation, which only partially recovered after six months of ART. Additionally, even though there were unmistakable connections between pathogenic taxa and indicators of the advancement of HIV disease, the bacterial structure of the gut microbiota is typically more slightly than drastically changed in dysbiosis. It is possible that, in comparison to before ART initiation, there would be a significant decrease in Bacteroidetes and an increase in *Fusobacteria* after six months of treatment [79]. The frequencies of Firmicutes and Proteobacteria before and after the initiation of treatment did not differ, according to their observations after six months of ART. Soluble CD14 levels were adversely correlated with the relative abundance of Firmicutes in HIV-positive persons following six months of ART. On the other hand, the relative abundance of Fusobacteria and soluble CD14 levels are positively correlated [79]. Research on the effects of ART on the gut microbiota is summarized in Table 1, including the type of study, whether transversal or longitudinal, study groups, classes of ART, and the microbial changes in the gut (dysbiosis) observed, the impact of this dysbiosis at the functional level, such as for the restoration of the gut microbiota during ART, the implication of certain functional markers, and the study site in order to show the correlation between the geographic location on the gut microbiome dysbiosis [80].

Conclusions

Numerous studies conducted over the past decade have made remarkable progress in understanding the impact of HIV infection and ART on the gut microbiota. In general, they all show that ART has an impact on the gut microbiota, but to varying degrees. These changes revealed dysfunctions in some markers of microbial translocation and the overall inflammation. However, there is still a lot to be deciphered, as in this review we found that most of the studies conducted are cross-sectional, which made it difficult to draw causative links between changes observed and the effects seen. Moreover, in clinical studies, it was not possible to study the effect of single drugs or classes of ARTs on the gut microbiota. It would be interesting to conduct longitudinal studies in HIV-infected patients before and during treatment to link and confirm for instance the state of the inflammation balance that is critical for host homeostasis. The understanding of these phenomena may lead to a more effective and eventless ART using a new adjunctive host-directed therapy to support ART, including the new ones.

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