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Letter to Editor

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# Unmasking the microbial drivers of HIV−associated diarrhea: Diagnostic and therapeutic insights from *16S* profiling

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Chronic diarrhea remains a frequent and debilitating complication among individuals living with HIV, particularly in the context of advanced immunosuppression. Its multifactorial nature often complicates both diagnosis and treatment. We present insights from our recent study investigating gut microbial alterations using *16S* rRNA sequencing in HIV-positive patients with diarrheal syndrome of unclear etiology.

Among 80 HIV-infected patients admitted with diarrhea, conventional diagnostics revealed herpesviruses (CMV, EBV, HHV-6) as the primary cause in 58.8% (47/80) of cases, aligning with prior findings on viral gastrointestinal pathology in immunocompromised hosts[1]. However, 22.5% (18/80) of patients had no identifiable pathogen despite comprehensive testing.

To investigate further, we performed *16S* rRNA gene sequencing on fecal samples from 10 patients—five receiving antiretroviral therapy (ART) and five ART-naïve. This approach, which allows genus- and species-level identification of bacterial communities[2], revealed severe dysbiosis and notable differences based on ART status.

As shown in Figure 1, ART-naïve patients showed a striking expansion of Proteobacteria (55.22%) as compared to 75.70% in healthy subjects, and severe depletion of Bacteroidetes: 0.17%, *vs*. 75.70% in healthy controls[3,4]. Key commensals such as *Bifidobacterium breve* and *Lactobacillus rhamnosus* were nearly absent, while opportunistic genera like *Enterococcus*, *Klebsiella*, and *Escherichia coli* dominated—consistent with prior reports of HIV-linked microbial imbalance[5–7].

In another important discovery, the study found that bacteria from the order Clostridiales were significantly more abundant in patients receiving ART. As these microbes produce butyrate and have anti-inflammatory effects, their enrichment (18.3% *vs*. 8.8% in ART naive patients) implies that ART may foster a more resilient gut environment. This finding is crucial because HIV infection typically predisposes individuals to harmful *Clostridiales* species (*e.g.*, *Clostridiales difficile* and *Clostridiales paraputrificum*), which can cause severe infections due to compromised immunity and frequent antibiotic exposure[8].

A striking uniformity across all patients was the presence of Enterotype 3, dominated by *Ruminococcus*, which is rare in healthy individuals and may indicate long-term restructuring of the gut ecosystem in chronic HIV[9,10].

These findings emphasize several clinical implications:

-Herpesviruses are a leading, underdiagnosed cause of diarrhea in advanced HIV[1].

-HIV-driven dysbiosis, particularly in ART-naïve patients, may exacerbate gastrointestinal symptoms[6,10].

-ART contributes to partial microbial recovery, especially of beneficial taxa like nonpathogenic *Clostridiales* strains (*e.g.*, *Clostridium butyricum*) and *Akkermansia*[7,8].

-*16S* rRNA sequencing holds diagnostic value in cases where standard microbiological tests yield no result[2].

-Microbiota-based therapies—such as probiotics or phage interventions—may offer new treatment avenues alongside ART[5,9].

In light of these observations, we advocate for the integration of microbiome profiling into HIV care pathways, particularly for patients with unresolved gastrointestinal symptoms.

## Conflict of interest statement

The authors declare no potential conflicts of interest.

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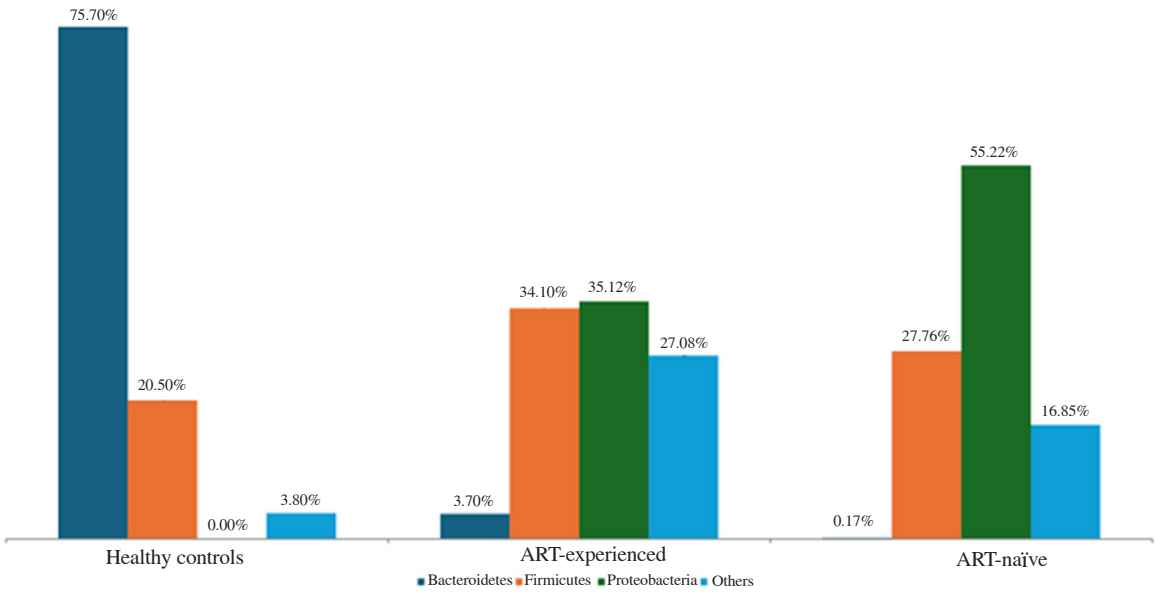


**Figure 1.** Gut microbiota composition in healthy individuals compared to HIV-infected patients with and without antiretroviral therapy (ART). This figure compares the relative abundance of major microbial taxa in the gastrointestinal tracts of three groups: healthy controls, HIV-positive patients receiving ART (ART-experienced), and HIV-positive patients not on ART (ART-naïve). The comparison underscores shift in microbial diversity and composition associated with HIV infection and ART status.

## Ethical considerations

No ethics committee review was conducted because the study only involved analyzing pre-existing, de-identified biological samples, collected according to standard protocols.

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## Authors' contributions

M.D. and V.S. conceived of and designed the study, performed the literature search and study analysis, and revised the manuscript for important intellectual content. E.K. and M.D. generated the figures, performed background research, and assisted in drafting. M.D. and V.S. edited the manuscript. E.K. and M.D. drafted the manuscript. All authors have read and approved the final version of the manuscript.

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