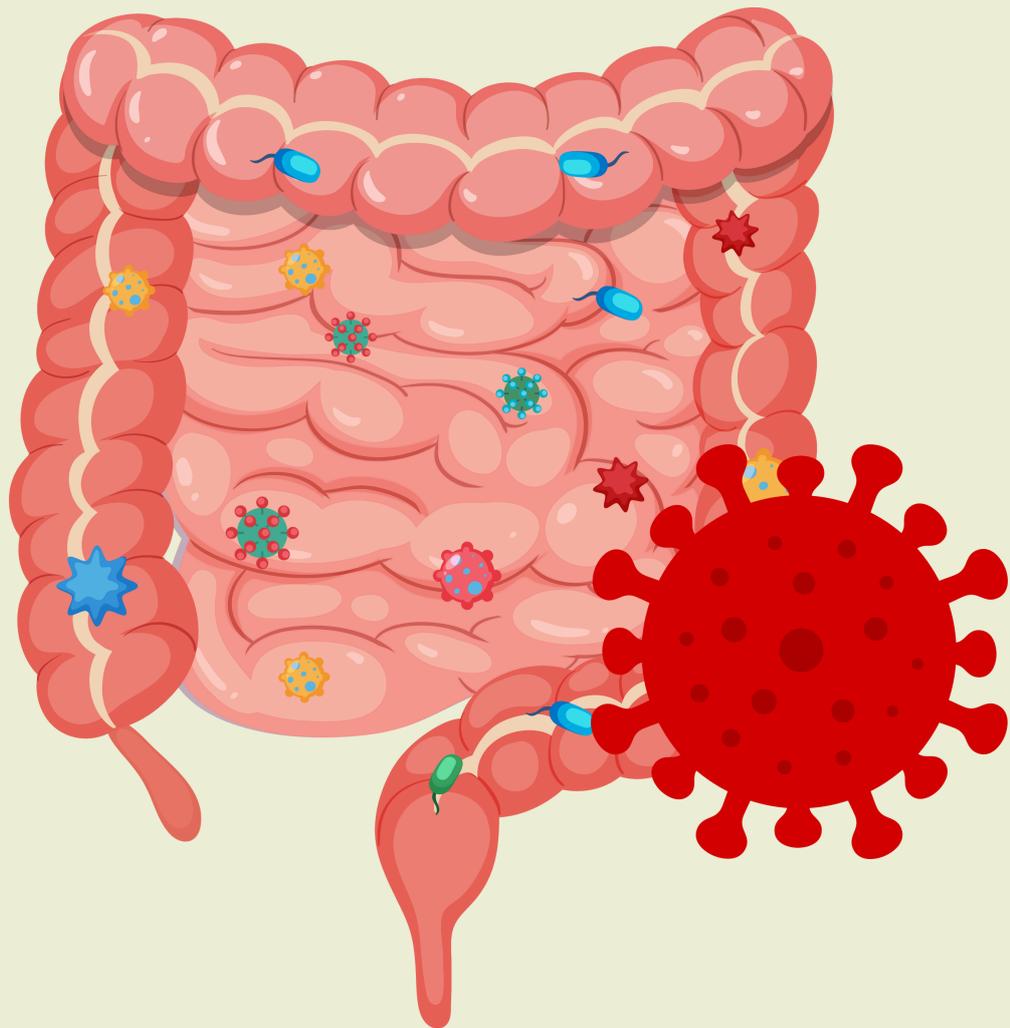


# ***GUT BACTERIA AND HIV***

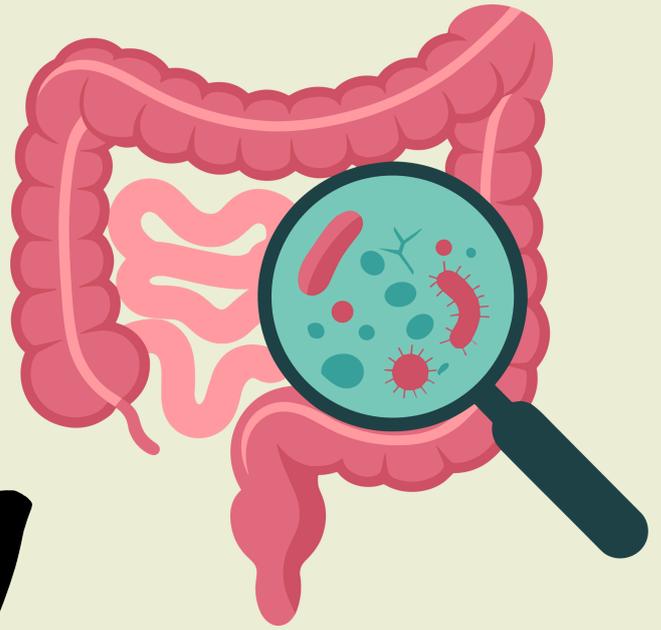


**Outcomes of**  **MISTRAL**



# Why the **Gut Matters** in HIV

The **microbiome** is home to **trillions of bacteria**, which help the body **fight infections** and keep your immune system strong.



But how is the **microbiome** linked to **HIV pathogenesis** and cure?



This question is what  **MISTRAL** set out to address **over five years of research**, and this brochure summarizes its main findings.



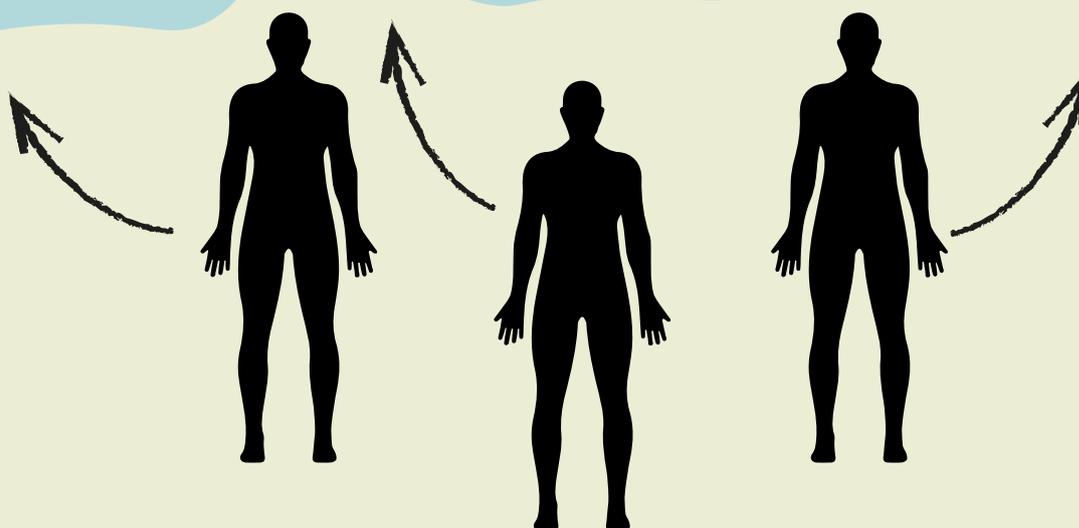
# Gut Microbiota and HIV Resistance in different HIV Patient Groups

There are different types of HIV patients:

**Highly exposed but HIV negative:** remain uninfected despite repeated exposure.

**HIV controllers:** get infected but naturally keep the virus at very low levels without treatment.

**Chronic HIV patients:** the majority of patients which typically require treatment to manage viral levels.



MISTRAL aimed to **identify gut bacteria** that may **contribute to natural resistance to HIV infection** or to **better control of the virus once infected**. Researchers **compared the microbiomes of highly exposed but negative HIV or HIV controllers** to those of **typical chronic patients**.



Early findings show that **some bacterial strains can reduce HIV activity**, suggesting they may play a role in natural protection or viral suppression.



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 847943.



**MISTRAL**

## Modulation of HIV-1 Immunotherapy: **HIV T cell vaccine in mice**

How could gut bacteria influence the immune response to the **T-cell HIV therapeutic vaccine**? Does this vaccine alter the gut microbiota?



The T-cell HIV therapeutic vaccine is an experimental treatment designed to **help people living with HIV strengthen their immune system** so it can better keep the virus under control.

Researchers carried out experiments in mice. They were given **antibiotics to eliminate their microbiota, or live therapeutic products to modify their microbiota composition**, and they were **vaccinated with the HIV T-cell vaccine**. Their goal was to see **how the immune response changed**, whether **depleting the microbiota altered vaccine response** or **probiotics could improve vaccine effects**, and how gut bacteria evolved over time.



Antibiotics



Live biotherapeutic products

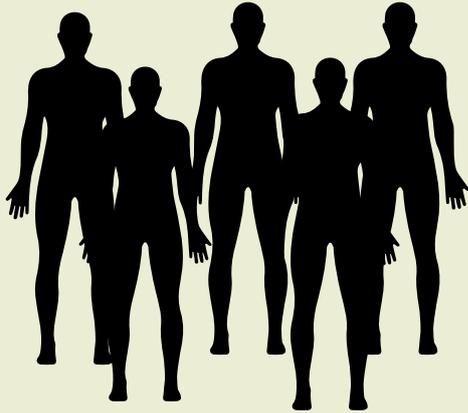


Results show that **the vaccine still gives an immune response even when the gut microbiome had been depleted**. Furthermore the **immune response is also increased with specific probiotics**; called bacteroidales, and **decreased with others**; named clostridiales.



## HTI vaccine randomized clinical trial

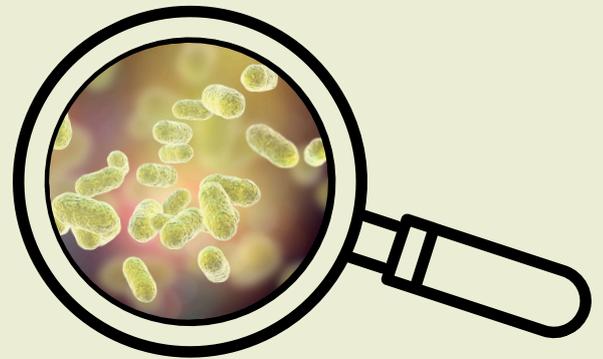
This part aimed to investigate whether the **HIV T-cell vaccine affects the gut microbiome** and whether a **person's existing microbiome influences** how well the **vaccine** works.



Researchers analyzed **participants who stopped their HIV treatment** for a total of 24 weeks, after receiving a combination of HTI vaccines or placebo.



Results reveal **differences in specific microbial communities and metabolites associated with the timing of treatment interruption.**



*For example, certain gut bacteria with known immunomodulatory properties (*Bacteroides* and *Parabacteroides*) remain stable during vaccination.*

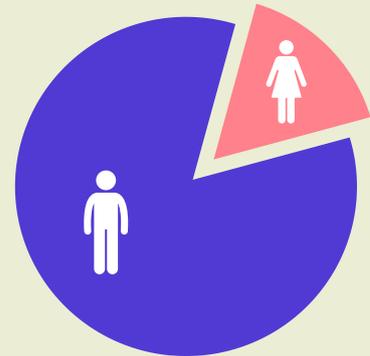
**Patients with higher levels of these bacteria** tend to have a **stronger immune response to the vaccine** and are able to **control the virus replication for longer time** during the HIV treatment interruption.



## Gut microbiome correlates of serious AIDS/non-AIDS events

MISTRAL has established a **European supercohort of 1,000 people** with HIV.

- 991 participants living with HIV.
- 50-86 years old.
- 84.1% males and 15.8% females.

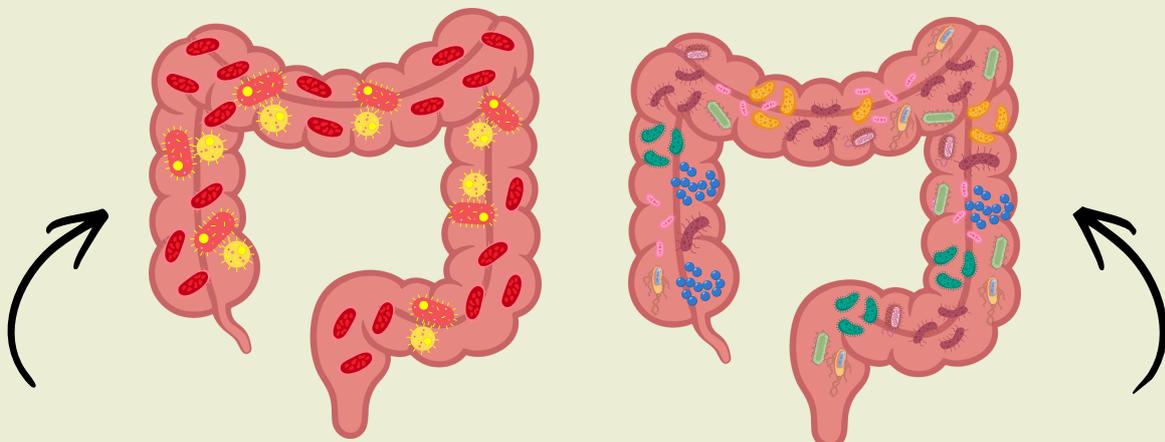


**22 clinical study sites** from **11 countries**.

The study aimed to investigate the **impact of the gut microbiome on HIV-related and unrelated diseases**. Analyses performed were focused on **gut microbiome structure** and **functional potential** in relation to **systemic inflammatory** and **coagulation markers** and validated cardiovascular risk measures, with planned integration of metabolomic and proteomic data in future work.



Preliminary findings indicate that **higher blood inflammation levels in people with HIV are associated with a less diverse gut microbiome**, characterized by fewer bacterial species that are unevenly distributed.



MISTRAL participant with low microbial diversity and high levels of inflammation

MISTRAL participant with high microbial diversity and low levels of inflammation



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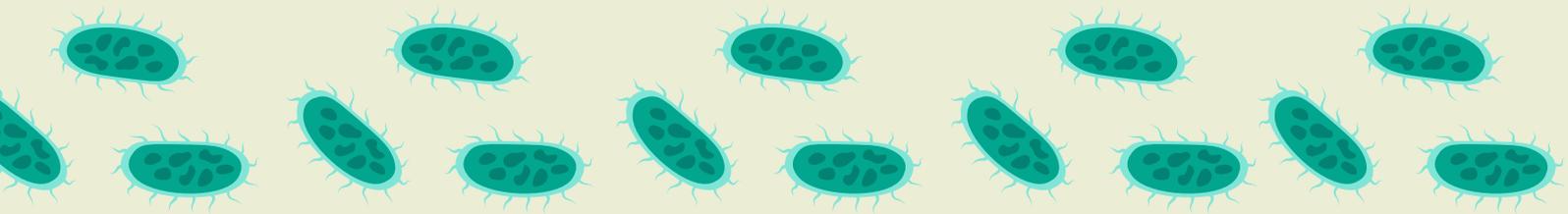


## Resistome

This part of the project examined **how HIV medicines affect gut bacteria**, including their **impact on antibiotic resistance**. It also investigates whether these **drugs can directly kill bacteria** or be **repurposed as antimicrobial agents**.



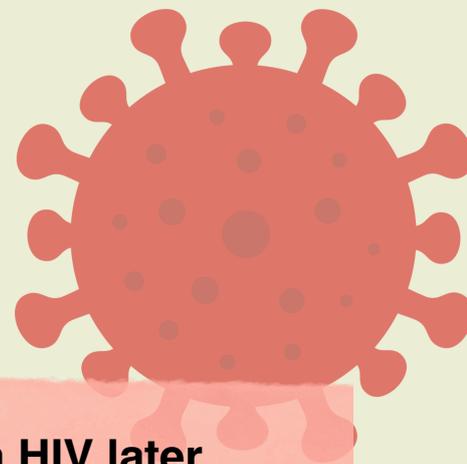
One finding is the **discovery of a high burden of antibiotic resistance** in the gut microbiota of **people with advanced HIV infection**. Many individuals carry **multidrug-resistant bacteria**, with resistance genes. This pattern suggests that **prolonged prophylactic treatments** may **help maintain reservoirs of resistant bacteria** in the gut. However, the **presence of these multidrug-resistant organisms is not associated with a higher risk of developing infections**.



The second main result is the identification of **direct antibacterial activity** from **certain HIV medicines**. MISTRAL shows that some antiretroviral drugs, with a particular candidate identified for reprofiling, are capable of killing bacteria that are difficult to treat, including those **responsible for severe infections**. These findings raise the possibility that existing **HIV drugs could be repurposed as antimicrobial agents**, offering a promising new strategy to address challenging bacterial infections.

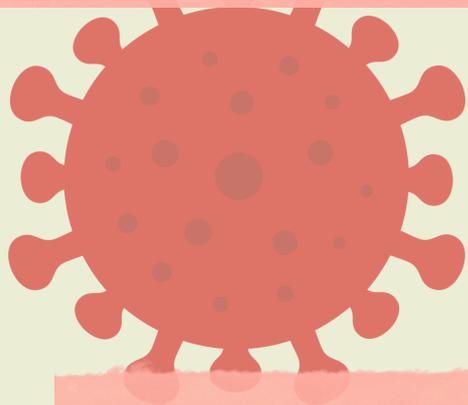


## Randomized Clinical trials



MISTRAL has had several clinical trials on HIV-1:

**Advanz-4:** has focused on **people diagnosed with HIV later than usual**, when their **immune system** is already **weakened**. MISTRAL looked at **how the gut microbiome recovers** when people **start different HIV treatments**. Results show that treatments known as **integrase inhibitors help the gut microbiome recover better** than other therapies.



**RECOVER:** explored if supplements such as **probiotics and prebiotics** can **support the immune system** and **help control the virus** in **people with HIV** who have low immune cell counts. Researchers found that a **combination of probiotics and prebiotics** was safe and **led to small but measurable improvements** in some immune markers. However, **taking probiotics alone did not show clear benefits**. While these changes were modest, the findings help researchers understand how the gut microbiome responds to treatment and may guide future strategies.





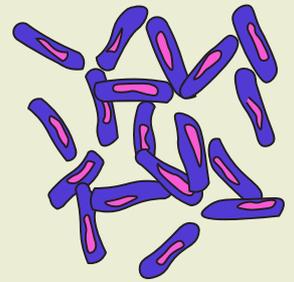
The main goal of this work was to integrate high-dimensional biological data to understand why some people are able to better control HIV after vaccination or treatment interruption, while others are not. To address this, researchers looked beyond the virus itself and focused on small molecules in the blood, known as **metabolites**, which actively shape interactions between host immunity and the gut microbiome.



A major finding was that **individuals who controlled HIV more effectively after vaccination** exhibited a **distinct metabolic signature associated with viral control**. Specifically, these individuals had **lower levels** of circulating **ceramides** and reduced markers of immune overactivation. These results suggest that persistent inflammation, driven by upstream metabolic states following vaccination, can undermine effective immune control of the virus and lead to poorer virologic outcomes.

In parallel, researchers conducted a meta-analysis spanning more than five independent cohorts of people living with HIV to examine how metabolites involved in gut-immune crosstalk influence HIV control more broadly. They found that **individuals who naturally controlled the virus**, or who had reduced levels of latent HIV, **displayed distinct blood profiles of bile acid metabolites**. These findings were further validated in the laboratory, where experimental studies demonstrated that this bile acid profile enhances antiviral immune responses. Together, these results highlight **bile acid metabolites as key regulators of HIV persistence** and identify them as promising targets for improving therapeutic vaccine strategies.



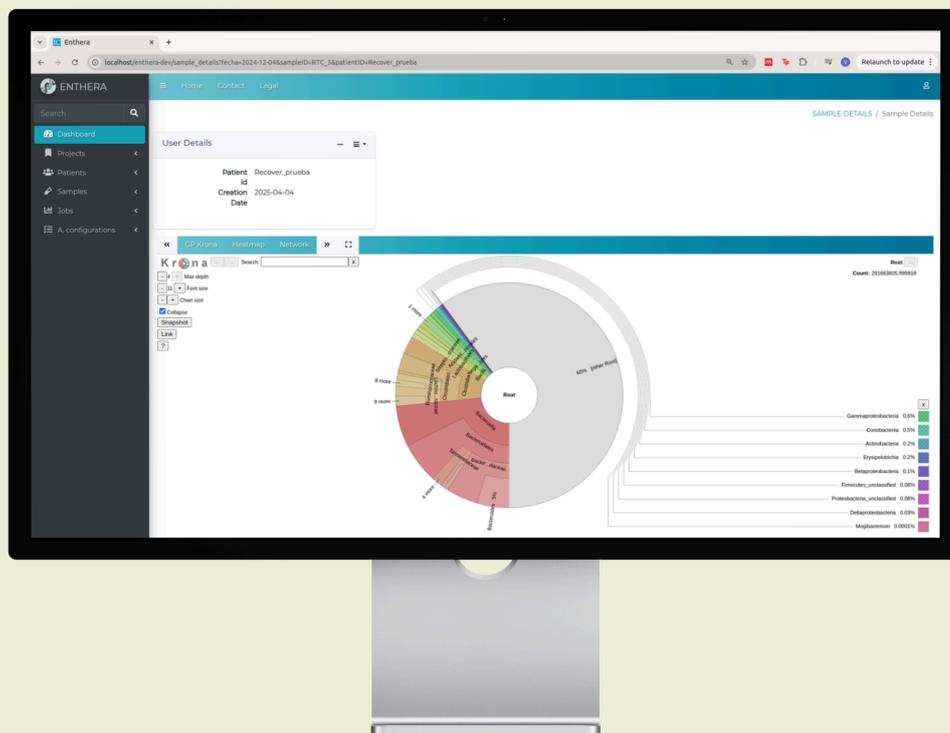


Enthera is an **online platform** developed within the project that **helps people work with microbiome data**.



Users can **upload biological samples** along with related information, and run analyses automatically, without needing special software.

The platform supports different kinds of microbiome tests. Once the analyses are finished, the results are saved securely and presented through **easy-to-use visual tools**. These tools allow users to **track changes over time, compare patients or samples**, and explore detailed information about the microorganisms present in each sample.



**Enthera also includes a reporting.** Reports can be created for one sample or for an entire patient and include summaries, trends over time, and plain-language explanations of the findings.

# WHO WE ARE

*MISTRAL has brought together a team of world-class HIV and microbiome researchers.*

## IrsiCaixa

Institut de Recerca de la Sida



**Karolinska  
Institutet**

**Projecte dels NOMS**

hispano**sida**



**EMORY  
UNIVERSITY**



**MÉDITERRANÉE  
INFECTION**

**ID | BAPS**

**ASPHALION**  
Knowledge from experience

**ÆLIX**  
THERAPEUTICS

**VEDANTA  
BIOSCIENCES**

**chip**   
Centre of Excellence for  
Health, Immunity and Infection



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