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Highlights of the first edition of the European Conference on Microbiota & Virology: A hybrid event, Paris, 23 March 2023☆

1. Introduction: the microbiome in HIV

Ivan Vujkovic-Cvijin (Los Angeles, USA) introduced the Conference by discussing the advances and challenges in terms of the microbiome in HIV. The microbiota comprises bacteria, fungi, protozoa, unicellular products, and commensal viruses that inhabit our various body surfaces. Many distinct communities are on body surfaces, uniquely impacting on host physiology.

The densest bacterial one resides in the colon. Indeed, the colon microbiota is particularly relevant in the context of HIV infection as it could be a source of inflammation through the translocation of bacteria or microbial products across the tight epithelial gastro-intestinal barrier into the systemic circulation. It may also participate in the metabolic processes that are harmful to the host (e.g., tryptophan, short chain fatty acids).

The rectal, vaginal, and penile microbiota are implicated in the susceptibility to HIV infection and its transmission. The vaginal microbiome can catabolize antiretroviral drugs (ART). In addition, specific patterns in microbiota composition correlate with relevant inflammatory prognostic markers. Indeed, an enrichment of Proteobacteria and depletion of Ruminococcaceae and Lachnospiraceae have been described in people living with HIV (PLWH), but sexual behavior, in men who have sex with men (MSM), can also influence the gut microbiome. Indeed, researchers have shown that the MSM microbiome signature, with depletion of Bacteroides and enrichment of Prevotella, may be a confounder for the HIV gut microbiome signal. Microbiota, however, differs in PLWH compared to seronegative controls and this independently of sexual behavior, even if MSM-associated microbiome signature is more robust than that of an HIV status.[1]

The American Gut Project (n = 5878 gut microbiota samples) has studied the effects of confounding variables in microbiome science. This project individualized ten non-redundant variables that had the highest impact on gut microbiome: age, sex, body mass index (BMI), quality of bowel movement, frequency of alcohol consumption, frequency of meat/egg, dairy, whole grain, vegetable, and of salted snacks. Matching for confounding variables reduces microbiota differences for most diseases.[1] Thus, confounder matching reduces false positives in microbiome-associated studies.

2. Transmission

The role of the microbiome in HIV transmission was extensively presented and discussed in the first part of the meeting.

Beyond the gut, emerging microbiomes in human body sites influence overall health and well-being.[2] The penile microbiome, for instance, as described by Philippe Halfon from Marseille, France, may impact HIV seroconversion, inflammation, and immune cells recruitment via the creation of an anoxic micro-environment that activates Langerhans cells to present HIV to CD4 T cells. Penile circumcision has indeed been shown to dramatically reduce the risk of contracting HIV in men.

Microbial dysbiosis is associated with many diseases. Nichole Klatt (University of Minnesota, Minneapolis, USA) gave an overview of the vaginal microbiome dysbiosis, which can be related to vaginosis, sexually transmitted diseases (STIs), yeast infection, preterm birth, and HIV transmission. Microbial dysbiosis interacts with systemic inflammation, mucosal dysfunction, immunity, and inflammatory responses. This interplay is important in multiple diseases, even when excluding HIV.

Bacterial vaginosis (BV) is a highly prevalent vaginal disorder and found in 40–60% of women. It can be asymptomatic and responsible for increased complications in pregnancy, STIs, and pelvic inflammatory disease. Low diversity is more beneficial in terms of vaginal microbiota, with a dominance of Lactobacillus, low pH ($<$4.7), and a Nugent score of 0. On the contrary, BV is defined by the dominance of polymicrobial anaerobic bacteria (Gardnerella, Prevotella, Atopobium, Mobiluncus), a high pH ($\geq$4.7), and Nugent score (7-10), a marker of inflammation and barrier damage. Polymicrobial communities facilitate the acquisition of HIV infection.

The effectiveness of pre-exposure prophylaxis (PrEP) is highly variable in women, and outcomes were first attributed to adherence to medication. In the CAPRISA 004 trial, Klatt et al. have shown that vaginal microbial groups alter PrEP efficacy. In the healthy lactobacillus-dominant subpopulation, PrEP efficacy was evaluated at 61%, while in the non-lactobacillus-dominant subgroup with BV it was at only 18%. Dysbiotic microbiome metabolizes tenofovir diproxil and dapavirine, but not tenofovir alafenamide, a fact that should be considered when designing new PrEP strategies for women. What is causing BV and why can we not treat it better? When analyzing the alpha diversity (richness, evenness, and using the Shannon index) by time point and clearance, data has shown an increased diversity in women with recurrences as compared to those who cleared their microbiota. Moreover, alpha diversity was proportional to the number of BV recurrences. The relative abundance of differentially abundant bacteria throughout the study was proportional to when BV reoccurred. BV-associated microbiota was associated with inflammatory cytokines (IL1-beta) and the number of recurrences. Alpha- and beta diversity

☆ The first European Conference on Microbiota & Virology (ECMV) was held in Paris as a digital event. It assembled many European and international researchers working in this field and other medical specialties.

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show significant differences between individuals with different BV recurrence status.

When considering the rectal microbiome, Roger Paredes (Barcelona, Spain) described multiple factors as influencers of HIV rectal transmission. First, the constitutive risk: the rectal mucosa from young MSM supports higher peak of HIV p24 production following *ex-vivo* challenge in comparison to older MSM because of distinct cellular immune phenotype among younger MSM compared to older males.[3] *Ex vivo* viral replication levels from rectal tissues following HIV challenge correlated with microbial abundance, especially Prevotella, Peptoniphilius, and Lawsonella species. Secondly, the rectal microbiome composition is also essential. Low microbial richness was linked to HIV infection and nadir CD4 T cell count. Importantly, beyond the healthy or dysbiotic microbiome, its composition is also a result of the adaptation to oxidative stress, in turn implying a possible influence of both HIV infection and ART on the microbiome.[4] Thirdly, the microbiome likely affects local inflammation. For example, condomless rectal anal intercourse was associated with tissue inflammation and Prevotellaceae abundance. Fourth, the differential fecal virus shedding is also crucial in HIV infection such as adenovirus in all the stages of HIV infection and cytomegalovirus or enterovirus in chronic, ART-naïve infection. Lastly, specific bacteria-derived metabolites can have a strong impact. For example, bacteria secrete factors that promote immune activation and upregulate viral replication.

3. Pathogenesis and comorbidities

During the Conference, we next addressed the issue of how the microbiome shapes pathogenesis and comorbidities. Giulia Marchetti (Milan, Italy) presented an interesting overview of the role of gut damage and dysbiosis in response to ART. In the context of HIV infection, we all are aware that microbial translocation is a hallmark of HIV infectio[5] which contributes to immune activation and inflammation, as independent drivers of HIV disease.[6–9] Furthermore, microbial translocation *per se* drives HIV disease progression.[10,11] However, the described gut microbiota patterns in HIV varies across different studies.

We usually observe persistent microbial translocation and gut damage on long-term ART started during chronic HIV infection that never normalizes back to that of uninfected controls. In the case of immune non-responders PLWH, gut barrier disruption and dysbiosis are factors associated with this immunopathogenesis. Such patients demonstrate a low expression of junctional complex proteins, with subsequent widening of the intercellular space, lipopolysaccharides (LPS) accumulation in the colon lamina propria and increased microbial translocation. Interestingly, even though there are no apparent differences between immunological responders and non-responders regarding the microbiome species richness and evenness, taxa abundance, translocating bacteria, and gut metabolites such as ceramide seem to be different[12]

In the case of acute HIV infection, loss of cadherin expression and collagen deposition persists despite ART and occurs earlier than the loss of CD4 T cells. Treatment does not improve the trend towards a lower variability of taxonomic composition within the gastro-intestinal tract, just as in chronic HIV infection.

Piotr Nowak (Solna, Sweden) described interactions between the microbiota and the HIV reservoir. He showed that 98,4% of HIV RNA positive cells are in lymphoid organs, 62% in the gut before therapy, 98% after treatment initiation, and only 0,2% in blood.[13] Elite controllers (EC), representing less than 1% of the total HIV-1 population, display a richer gut microbiota with a distinct metabolic profile when compared with age/gender/sexual practice and BMI-matched untreated PLWH and negative controls.[14] They also display a higher abundance of Succinivibrio and Sutterella while viremic progressors show an enrichment of Blautia and Anaerostipes and a depletion of Anaeofilum, Oscillospira, and Rhizobium. Differences are present at the richness, diversity and compositional levels and may be involved in virological control.

Gut microbiome signatures are linked to the HIV-1 reservoir size in the BCNO1 study, a Spanish "kick-and-kill" strategy which showed a direct correlation between Bacteroidales/Clostridiales ratio and the HIV-1 reservoir size and viremic control after ART interruption.[15] Thus, the microbiome modulation could be a way to disrupt latent HIV reservoirs.

Camilla Tincati (Milan, Italy) presented the microbiome in HIV-exposed uninfected (HEU) children. Fifteen million HEU children are experiencing ongoing health disparities, such as increased mortality/morbidity, undernutrition, stunting, and impairment in early child development.[16] Breastfeeding seems to be a protective factor in terms of clinical vulnerability. Immune changes in the HEU infants include increased Treg frequency, reduced perforin-positive and activated natural killer cells, a proinflammatory cytokine milieu, and reduction in maternal transplacental antibodies, which all constitute the immune footprint of intrauterine HIV exposure.[17] The first study evaluating the gut microbiome in HEU has concluded to a lower alpha diversity in stool microbiomes in HEU versus HIV-unexposed uninfected (HUU) infants.[18] In addition, bacterial diversity was associated with maternal CD4 T cell count and HIV viral load. The data is dependent on the settings, but microbiome differences converge over time.[19,20] Factors that shape the microbiota are the mother's microbiome (vagina, milk, and skin). The effect of breast milk on the infant gut microbiota is mediated by its biochemical and immunologic properties rather than by direct seeding of the infant gut with breast milk bacteria.[21] Tincati et al. showed no microbiome differences in HEU and HIV-exposed infected (HEI) children but various abundances of specific taxa. Interestingly, in their research, two taxa were related to protection (*Lactobacillus gasseri* and Lachnospiraceae family), which is in line with data showing an inhibitory *in vitro* effect on HIV of these taxa, probably through the production of the tryptophan metabolite, indole-3-lactic acid, which inhibits HIV-1 replication.[22] Further data is needed regarding, for instance, the possible lower alpha diversity of HEI compared to HEU infants. Could that be linked to the maternal HIV infection stage? And how could we explain the fact that microbiome signatures in stool composition are predominant in early infancy while they are less pronounced with age? Are they relevant to the immune system development and the infection vulnerability of HEU infants?

Marius Tröseid (Oslo, Norway) presented data about the microbiome, cardiovascular risk, and HIV infection. Studying the microbiome in the ageing HIV population can be relevant because of its potential role in cardiovascular (CV) risk, which could lead to identifying people at risk, and potentially finding new treatment targets. In the general population, the gut microbiota dysbiosis in coronary artery disease (CAD) is represented by a decrease of *Roseburia intestinalis* and *Faecalibacterium prausnitzii*, which are butyrate-producing microbes or microbes producing short-chain fatty acids (SCFA). Depletion of Ruminococcaceae, Faecalibacterium, and Lachnospiraceae is present in all cohorts of CAD and heart failure in the general population.[23–26] The HIV-related microbiome confounded by sexual practice (Prevotella in particular) but adjusted for MSM status displays the same profile as in CV disease, namely depletion in Ruminococeae and Lachnospiraceae, enrichment of Gammaproteobacterial which is linked to a lower nadir CD4 T cell count, systemic inflammation, and increasing inflammatory-driven comorbidities.[1] Gelpi et al. have found the same pattern of dysbiosis with an increase in Gammaproteobacterial/Desulfovibriceae and decrease in Lachnospiraceae and Ruminococcaceae). This increase was associated in multivariate analysis with a metabolic syndrome (aOR = 2) and even more strongly with a low nadir CD4 T cell count (aOR = 8.5 for CD4 T cells below 50/mm3).

In targeted metabolomics, the trimethylamine-N-oxyde (TMAO) is a biomarker of CV disease which is oxidized in the liver from trimethylamine (TMA) produced by microbes from L-carnitine and choline of Western-type of food. In the COCOMO cohort, the kynurenine tryptophan ratio (KTR) mediated 10% of the association between HIV-related dysbiosis and visceral adipose tissue accumulation. The PLWH with

stenotic CAD had a lower alpha diversity, with a decrease of Lachnospiraceae and Ruminococcaceae and an increase of Veillonella and *Ruminococcus gnavus*, which produces imidazole propionate, a histidine metabolite. Imidazole propionate is increased in diabetes and associated with dietary patterns and altered microbial ecology with an increase of *Ruminococcus gnavus*.[27] Imidazole propionate separates stenotic CAD from non-stenotic one and the absence of CAD.

Globally, HIV cohorts have unique confounders such as sexual practice and ART and thus require separate studies with these groups.

Andrea Ticinesi (Parma, Italy) gave an insight into the aging gut microbiota and the gut-muscle axis. The adult gut microbiota is characterized by a relative stability of its diversity and resilience to stressors. In an Irish study, Claesson MJ et al. have demonstrated that clusters of microbiotas are significantly related to place of residence, diet, and physical performance.[28] In centenarians Bizgi et al.[29] demonstrated that high biodiversity indexes and abundance of health-promoting taxa persist, namely Akkermansia, Bifidobacteria, and Christensenellaceae. Furthermore, sarcopenia depended on the age-related derangement of anabolic/catabolic balance, increased insulin resistance, reduced protein intake, and increased chronic inflammation. Thus, age-related changes in gut microbiota can influence aging patterns. In mouse models, age-related gut microbiota dysbiosis could reduce the bioavailability of dietary amino acids and other nutrients involved in muscle protein synthesis.[30] Age-related gut microbiota dysbiosis may be associated with reduced production of SCFA (acetate, propionate, butyrate), which can influence skeletal muscle anabolism and response to inflammation.[31] In mice models, fecal microbiota translocation influenced mouse skeletal muscle functioning. In human microbiota and sarcopenia studies, differences in biodiversity and beta diversity between sarcopenia and average muscle mass and function were inconsistent among studies. Probiotics may be positive regulators of muscle mass and muscle strength, mainly observed with Bifidobacterium but less pronounced in ≥70 years old individuals.

4. Diagnosis and therapeutics

Sergio Serrano-Villar (Madrid, Spain) opened the next session of the meeting, which addressed the microbiome as a diagnostic and therapeutic tool. The microbiome is linked with chronic inflammation, HIV risk acquisition, response to vaccines, CV risk, HIV persistence, oncogenic risk, and lung diseases such as chronic obstructive pulmonary disease and tuberculosis. The cervico-vaginal microbiota influences the risk for HIV acquisition in women with BV or up-regulated cervicovaginal cytokine concentration but also affects PrEP strategies.[32–34]

The human papilloma virus (HPV) physically interacts with the microbiome, even if it is exclusively intraepithelial. The low number of "core species", i.e., those shared across individuals, limits using the microbiome signatures as a diagnostic tool.[35] Multi-kingdom microbiome analyses have identifed biomarkers of colorectal cancer, for instance, better than single-kingdom approaches.[36] Therefore, we need a better understanding of the temporal variation of predictive microbial signatures and the microbiome variability at the sub-species and functional levels.[37–39]

In the SCRATCH European Network and prospective study, anal microbiota composition did not consistently persist in high-grade intraepithelial lesions (HSIL). Still, a group of microbiome-encoded proteins belonging to the glycolysis, gluconeogenesis, and cobalamin synthesis pathways, was significantly associated with HSIL. Targeted metabolite such as succinyl-CoA and cobalamin analysis directed by the proteomic findings showed an increase of these metabolites in anal cytologic samples from HSIL patients. Measuring succinyl-CoA and cobalamin outperformed anal cytology, the reference test, as it increased specificity and diagnostic accuracy.

During the meeting Therapeutics round table, Netanya Utay (Dallas, US) discussed the microbiome therapeutic modulations. Fecal microbiota transplantation (FMT) was recorded as early as the Western Zhou Dynasty in China in the 10th century BC and was maintained over centuries. In 1958, four patients with pseudomembranous colitis were successfully treated with fecal enemas in Colorado. *Clostridium difficile* infection is a medical condition enhanced by different risk factors such as antibiotic use, gastric acid suppressants, healthcare exposure, and older age with comorbidities. The loss of intestinal microbiome diversity can precipitate it, and FMT is a recommended treatment option, bringing in healthy species that will out-compete *C. difficile* and prevent re-colonization.

In the first randomized controlled trial of FMT by naso-gastric tube, FMT resulted in a significantly higher cure rate than vancomycin with microbiota species diversity restored towards that of healthy donors.[40] In a recent study, Khanna S et al presented the results of a randomized placebo-controlled study of RBX2660 (Rebyota™) or saline enema in adults with ≥1 number of *C. difficile* recurrences.[41] A treatment effect of 13.1% (95% CI 2.3, 24.0) was observed and it was concluded that RBX2660 by enema after standard treatment resulted in a significantly higher cure rate than standard treatment alone. RBX2660 was FDA approved in November 2022. FMT by oral capsules has also proven to have a significantly higher cure rate when compared to vancomycin alone and displays easier administration and comfort.[42] Since FMT is a biological product, there are multiple issues with the screening of transplant donors and safety issues, regarding not only infection risks (HIV or viral hepatitis exposure, use of illicit drugs, risk factors for multi-drug resistant organisms) but also potentially for microbiome-mediated conditions (inflammatory bowel disease, atopic or autoimmune conditions, metabolic conditions, malignancy). Fewer than 3% of potential donors are selected after review of these criteria. OpenBiome, which is one of the FMT principal suppliers in the US, has published real-world data on a 5344-person cohort of immunocompromised patients who had received FMT for *C. difficile* infection, among which only six had serious adverse events, possibly related to FMT.[43] In total, studies have shown in *C. difficile* its efficacy, particularly in recurrent infections, regardless of the mode of delivery.

The inflammatory bowel disease (IBD) gut microbiome has lower diversity and fewer Firmicutes and Bacteroidetes, but it is still unclear whether this is a cause or consequence. In a randomized controlled trial in this context, FMT by colonoscopy/enema resulted in a significantly higher response rate than standard treatment alone and responders displayed a higher microbiota diversity than non-responders.[44] Another study has suggested that antibiotics were associated with improved donor microbiota uptake, mainly Firmicutes.[45]

In terms of HIV infection, in a small single-arm study (n = 6), FMT by oral capsules increased diversity in PLWH on ART with low diversity and decreased intestinal fatty-acid binding protein (I-FABP), sCD14, soluble tumor necrosis factor receptor type II (sTNFRII), and sTNFRSF8 levels with change in diversity.[46] In a randomized, double-blind, placebo--controlled trial of OpenBiome oral capsules (donors with high Bacteroides, Faecalibacterium, Butyrate, and low Prevotella concentrations), the microbiota diversity showed a transient increase that was donor-dependent and enhanced in people with recent antibiotic exposure, while the intestinal fatty-acid binding protein (I-FABP) decreased with FMT.[47] Overall, FMT is safe and well-tolerated, even if there are still unresolved questions and a challenge to find suitable donors. As of March 2023, 63 interventional studies of FMT and infections have been registered at clinicaltrials.gov. Nevertheless, there is insufficient evidence to state that pro- and prebiotics supplementation have enough effect on preventing or treating infectious diseases.

There is currently no scientific evidence to support the use of pre- or probiotics in well-treated PLWH on ART.[48] Targeted interventions in subpopulations with systemic inflammation and inadequate immune recovery are pending.

5. Innovation and perspectives

During the Innovation and Perspectives Session, Celine Ribiere

(Labège, France) presented data about targeting the gut and tumor microbiota in cancer. Intestinal and tumor microbiomes are key players in tumor progression and treatment efficacy. Metagenomic studies have revealed differences in gut microbiome diversity and functions in responding patients, especially to PD-1-based immunotherapy.[49–51] Following tumor implantation, one can observe increased gut permeability that promotes microbial translocation, systemic inflammation, dysbiosis, frequently linked to *C. difficile*, which contributes to carcinogenesis.[52] This dysbiosis is also linked to cancer and treatment prognosis. The human tumor microbiome comprises tumor type-specific intra-cellular bacteria.[53] All the bacterial diversity cannot be recovered from formalin-fixed paraffin-embedded (FFPE) samples because of technical reasons (for instance, DNA degradation from fixative agents and compliance for metagenomics). The human tumor microbiome analysis has also revealed cancer type-specific fungal ecologies and bacteriome interactions with recruitment from the local microbiome by cancer cells.[54] The microbiome has also been proven to modulate the tumor microenvironment locally or through metabolites or immune cells.[55]

Alex Mira (Valencia, Spain) discussed one of the "other microbiomes" in order to decrease biases associated with microbiome studies, namely those biased towards bacteria and probiotics development in terms of the gut microbiome. Oral diseases are due to imbalanced microbiota which influence oral and systemic health. Developing prebiotics and probiotics can help keep the microbiome homeostasis and combat viral infections.

Jo-Ann Passmore (Cape Town, South Africa) talked about geo-adapted live biotherapeutic strategies for HIV prevention. Untreated STIs and BV are the leading cause of HIV infection. In many regions of the world, with only 36% of women with symptomatic STI/BV accessing treatment. They have helped to establish a platform of collaborative vaginal microbiome studies in South Africa and African partner countries. This initiative is a partnership with the Vaginal Microbiome Research Consortium (VMRC4Africa).

Ronald Gary Collman (Philadelphia, US) gave an insight into the respiratory tract microbiome and COVID-19. SARS-CoV-2 initially replicates in the upper respiratory tract (URT), where it may remain or propagate to the lower respiratory tract. The respiratory tract microbiome could affect the outcome of viral respiratory infections through the modulation of innate immunity. The URT is characterized by a microbe-rich oropharynx and nasopharynx, while below the glottis, the lung contains bacterial DNA at a very low level compared to the URT. Lung bacteria closely match peri-glottic and oropharynx communities. Thus, the normal lung microbiome is derived passively from the URT and reflects an equilibrium between entry and local clearance. In 507 samples from 83 hospitalized COVID-19 patients who underwent 16S rRNA gene sequencing for bacterial microbiome, Merenstein C et al. have shown an association between the URT microbiome and COVID-19 in comparison to healthy individuals as well as with disease severity.[56] Moreover, lower diversity in the initial oropharyngeal community was associated with greater clinical severity throughout hospitalization (ultimate level of disease severity). There was also a lower diversity and frequent domination by specific lineages, particularly staphylococcus, in the lung microbiome of intubated patients. This endotracheal microbiome is variable and can be highly unstable. The oropharyngeal microbiome in COVID-19 correlated with the systemic immune response. Likewise, the upper respiratory microbiome has been linked with susceptibility or outcome in influenza and respiratory syncytial infections.[57,58] Beyond the respiratory tract microbiome, the gut microbiome may also impact COVID-19, possibly through systemic immunomodulation.[59,60]

In conclusion this was the first of hopefully many more meetings discussing the increasing interest in microbiome studies and its interaction with many infectious and non-infectious diseases with fascinating presentations and discussions.

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