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The importance of the gut microbiota to health in HIV

The collective microbial flora of the human gastrointestinal tract (gut microbiota) comprises ~10^{14} microbes including bacteria, viruses, fungi, and protozoa, that live in symbiosis with their human hosts. The explosion in research on the gut microbiota is impressive, with almost 4000 dedicated publications in 2017. Now a regular topic at the dinner table, healthcare professionals and the public alike are increasingly aware of the roles of our microbial guests, the potential for probiotics (including faecal microbiota transplant) and prebiotics as possible treatments, and the rapidly increasing number of associations identified between the gut microbiota and human disease, ranging from obesity to inflammatory bowel disease, and neuropsychiatric conditions.

Gut microbiota play critical roles in maintaining gut health, digestion, and controlling local and systemic immunity. Perturbation of the gut microbiota (termed dysbiosis) is a feature of many disease states including HIV, with loss of microbial diversity being a common theme, as well as alterations in the relative quantity of microbes and their gene expression (collectively termed the gut microbiome).

The gut is long known to be a critical organ in HIV pathogenesis. The virus targets gut-associated lymphoid tissue, which is the major site of coordination of innate and adaptive immunity, central to protection against microbes. The initial catastrophic loss of CD4 cells in the first weeks of HIV infection predominantly arises in the gut and persists throughout HIV infection. Loss of a particular subset of CD4 cells ($CD4^+$ Th17 cells) coincides with creation of a 'leaky' gut, with movement of microbial products into the systemic circulation, which in turn induces persistent immune activation at distant sites. Furthermore, microbial products set up inflammatory responses in the gut mucosa, which perpetuates gut inflammation.

Gut dysbiosis in HIV infection may further exacerbate effects on gut and systemic immunity. Dysbiosis may be caused by selection of pathogenic bacteria, expanding viral populations in the gut (adenoviruses, parvoviruses and caliciviruses) or disrupting gut fungal populations, all of which can cause further inflammation and translocation of microbial products, thereby contributing to local and systemic inflammation. Identifying which particular bacterial species alter significantly in HIV infection has been difficult to elucidate due to technical differences in sampling and assays used, differences in the stage of HIV studied (recent vs chronic infection), populations studied (men who have sex with men have distinct microbial profiles which differ from other HIV subgroups), and the fact that many of the studies have been performed with SIV in non-human primate models, which, whilst instructive about global changes, show distinct differences between species. For example, there is no strong clustering of microbial communities associated with chronic SIV infection, as there is in chronic HIV, where studies have shown increased abundance of some bacteria such as *Fusobacteria, Proteobacteria*, and *Prevotella*, and decreased abundance of others, such as *Bacteriodetes, Firmicutes,* and *Erysipelotrichaceae.*

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Long-term ART is associated with partial restoration of microbial diversity of the gut compared to healthy individuals. Certain critical bacteria, such as *Fusobacterium prausnitzii*, which helps maintain gut homeostasis were found to be reduced in studies of patients on long-term ART. There is also some evidence that type of ART regimen may influence the gut microbiota, with one comparison showing integrase inhibitors to be associated with lowest levels of systemic inflammation and gut dysbiosis (Villanueva-Millan 2017). However, further studies are needed to increase understanding of any differential antiretroviral effects before guidance can be given.

Can probiotics influence gut health in HIV? Although more studies are needed, early investigation in non-human primate SIV infection and in human HIV infection suggests that probiotics may partially repair mucosal damage. A small randomised controlled, double-blind study of 32 HIV-positive participants on ART, 15 of whom received probiotics and 9 placebo with 8 untreated controls, reported that participants in the probiotic arm had reduced C-reactive protein levels and CD4 T cell activation, although these changes were independent of changes in microbial translocation (Stiskrud et al). Observational studies have also shown changes in CD4 activation markers and pro-inflammatory cytokine production in those on probiotics; these findings have been mirrored in SIV macaque models. A study of faecal microbiota transplantation in macaques reported an increase in circulating Th17 and Th22 cells, which are responsible for epithelial homeostasis (Hensley-McBain et al). What is still uncertain is which prebiotic or set of prebiotics is optimal, and this is the focus of a number of intervention studies. However, care should be exercised in the use of probiotics in sick HIV-positive hospitalised patients or those who are profoundly immunosuppressed, among whom bacteraemia and fungaemia have been recorded following probiotic use.

In summary, the gut microbiota is adversely affected by HIV infection and the resulting dysbiosis contributes to gut inflammation and impairment of local and systemic immunity. ART partially restores the microbiota. The role of probiotics as adjunctive treatment looks promising, although further studies are needed before definitive guidance can be given.

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Update on risk for neural tube disorders for women on dolutegravir at conception: downgraded but real risk

In issue no. 48 (July 2018) we reported on new information from Botswana linking periconception dolutegravir exposure to an increased risk of neural tube disorders (NTD). In May 2018, the World Health Organization (WHO) released a warning based on an unplanned analysis from the ongoing Tsepamo study, which is evaluating safety of antiretrovirals in pregnancy.

The Tsepamo study began in 2014 to evaluate the NTD risk for efavirenz; Botswana transitioned to dolutegravir in 2016. Four NTD cases were identified from 426 women (prevalence 0.9%) who became pregnant on dolutegravir. In comparison, the prevalence of NTDs in women who became pregnant on other antiretrovirals was 0.1%, versus 1.2% with exposure to valproic acid, a known cause of NTD. The survey was then expanded to include 72% of all births in Botswana. The next analysis was specified to occur after March 2019 to detect dolutegravir exposures prior to June 2018, when Botswana changed their guideline to avoid dolutegravir in women wanting to conceive. One additional NTD was detected in 1683 deliveries, for a prevalence of 0.3% (95% confidence interval: 0.13 to 0.69%). This was in comparison to 15 NTDs in 14792 deliveries (prevalence 0.1%; 95% confidence interval 0.06 to 0.17%). For pregnant women starting dolutegravir after 8 weeks of gestation, 1 NTD occurred (prevalence 0.1%: 95% confidence interval: 0 to 0.15%). There were no differences in adverse birth outcomes such as prematurity, intra-uterine growth retardation and stillbirth between efavirenz and dolutegravir use at conception.[1]

In surveillance data from 22 additional facilities in Botswana between October 2018 and March 2019, 6 suspected NTDs were detected from 3076 pregnancies. One was confirmed and two were considered probable. One of these occurred in 152 women on periconception dolutegravir (prevalence 0.66%: 95% confidence interval 0.02 to 3.69%). Two NTDs were in the 2328 HIV-negative mothers (prevalence 0.09%: 95% confidence interval 0.01 to 0.31%). Together with the Tsepamo study, 90% of all births in Botswana were covered.[2]

In the Tsepamo study, between 0.1% and 0.2% of women were on folate at the time of pregnancy. Although folate fortification of foods has not been implemented in Botswana, grains imported from South Africa do have added folate. In an in vitro model, supplemental folic acid mitigates dolutegravir developmental toxicity in zebrafish embryos, possibly linking relative folate deficiency in women becoming pregnant on dolutegravir to NTDs.[3]

In conclusion, although the prevalence of NTD in Botswana was 3 times higher with dolutegravir compared with other antiretrovirals, this represents approximately 2 excess defects per 1000 exposures. Do the benefits of dolutegravir outweigh the harm in women of child-bearing potential? In a modelling study, Dugdale and colleagues show that dolutegravir in child-bearing women will be associated with fewer maternal deaths and a lower transmission rate to their babies.[4] Clearly, good contraception is essential for all women of child-bearing potential who are on dolutegravir. More data are expected from Botswana and other pregnancy registers.

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No clinically significant interaction between dolutegravir and valproate

In the previous newsletter we alerted you to an interaction between dolutegravir and valproate, resulting in a reduction in dolutegravir exposure of about 80%. The mechanism of this interaction was unexpected as valproate is not known to induce any of the metabolic pathways of dolutegravir. A follow up study has recently reported that, although total dolutegravir concentrations were reduced by valproate, free dolutegravir concentrations were not affected – this indicates that the interaction is due to displacement of protein binding of dolutegravir by valproate. As only the free drug is active, this interaction is not clinically significant. However, therapeutic drug monitoring will show lower dolutegravir concentrations as only total drug concentrations are measured.

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