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Probiotics and HIV

Probiotics, defined by the World Health Organization as "live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host[1], have been ascribed numerous health benefits from augmenting the immune system to improving liver function and bowel function. The majority of sales are poorly regulated as most probiotics are classed as foodstuffs rather than drugs. Probiotics are finding their way into dietary supplements, toothpastes and even chewing gum.[2] Sales of probiotic products worldwide continues to increase. In 2014, Western Europe led consumption with USD 8 billion spend, followed by the Asia-Pacific region (7 billion) and Japan alone with USD 5.4 billion spend[3]. Probiotics may be single bacteria such as *Lactobacillus acidophilus*, fungi such as *Saccharomyces boulardii*, or a combination of any number of microorganisms.

Refinement of product composition continues, in order to keep pace with the burgeoning research and understanding of the body's microbiota; the ecological community of commensal, symbiotic and pathogenic microorganisms that share our body space. The term microbiome is used synonymously, although it technically refers to the collective genomes of microorganisms. The gut microbiota continues to receive the most attention. Functions of the microbiota include metabolism e.g., production of vitamins and co-factors, and host defense e.g., production of bacteriocins. As a generalization, the healthy state is marked by a diverse microbiota. The adult gut contains in the region of 10^{14} microorganisms (95% bacteria), and the total body microbiota comprises over 1000 bacterial species with differing compositions at different sites. Crohn's disease and obesity are just two examples where large research efforts are focused in characterizing alterations in the gut microbiota and how altering it, could impact on treatment.

Doctors when giving simultaneous antibiotics, commonly prescribe probiotics. The theory is that 'replacing' or 'augmenting' the microbiota that will be perturbed by antibiotics, would be protective against antibiotic-associated diarrhoea (AAD) and *Clostridium difficile* associated diarrhoea (CDAD). A Cochrane review showed a 64% reduction in CDAD with simultaneous use of probiotics[4], yet analysis of some of the key studies demonstrates concern in their interpretation. Furthermore, the largest study to date, an RCT of 2941 hospitalised patients in the UK, aged ≥65 years that was published after the publication of the Cochrane Review, showed no significant differences in AAD or *Clostridium difficile* infection between probiotic and placebo groups. For this reason, probiotics are not currently recommended routinely in conjunction with antibiotics in most guidelines. The success of the 'ultimate probiotic', faecal transplant in treating recurrent CDAD[5], and early reports of it clearing multi-drug resistant bacteria colonizing the gut, suggests that the field of 'bacteriotherapy' is an evolving one, and that it is possibly the composition and delivery of the probiotics currently in use that may need optimizing to function.

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So what additional functions might probiotics have in HIV-infected persons and are they safe to use? During early HIV infection and subsequently, massive loss of intestinal CD4 T lymphocytes in conjunction with alteration in the intestinal epithelium leads to an increase in movement (translocation) of bacterial products into the bloodstream. This in part, drives chronic immune activation[6], with generation of increased pro-inflammatory cytokines and procoagulants, which are implicated in long-term inflammatory consequences of HIV, such as increased cardiovascular risk, neurocognitive defects and malignancies. Microbial translocation is also associated with failure of CD4 count reconstitution, potentially contributing to discordance of CD4 count and viral load responses.[7] The hypothesis that probiotics may reduce microbial translocation, and thereby improve immune function and reduce chronic inflammation has been tested.[8,9] A double-blind RCT of *Saccharomyces boulardii* versus placebo in HIV-1-infected patients with a viral load <20 copies/mm^3 for at least 2 years, showed that the probiotic group had reduced markers of microbial translocation and inflammation, which persisted for 3 months following withdrawal of the probiotic. The longer-term sustainability is unknown, and future studies will need to address longer duration of treatment and sustainability of effect.

Despite these promising results, probiotics should be used with caution in patients with severe immunosuppression. A number of cases of bloodstream infection have been documented in immunosuppressed persons using probiotics, including *Saccharomyces boulardii*[10,11] and *Lactobacillus acidophilus*[12]. Hence, patients with low CD4 counts should discuss the use of probiotics with their care provider before starting.

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Improved treatment outcomes in patients with XDR TB in South Africa

XDR TB is diagnosed when TB is resistant to rifampicin, INH, a quinolone and one of the second-line injectables. Pre-XDR is diagnosed when TB is resistant to rifampicin, INH and either a quinolone or a second-line injectable.

A previously published cohort study[1] conducted in South Africa (2008-2012) reported extremely poor outcomes in 107 patients diagnosed and treated with XDR TB across 3 provinces. Only 36% of patients achieved culture conversion (from sputum culture positive to negative), but around half of these patients reverted back to positive later. After 5 years, 73% of these patients had died and only 11% had a favorable outcome. These patients were treated with treatment regimens that were largely ineffective because there were insufficient active drugs available to include in their regimens.

This situation has recently changed with the availability of new and re-purposed drugs for the treatment of drug-resistant TB. One such new drug is bedaquiline that was registered by the South African Medicines Control Council in 2014. It has a completely novel mechanism of action: inhibition of *Mycobacterium tuberculosis* ATP synthase. A toxicity concern related to bedaquiline is that it prolongs the QT interval potentially predisposing to tachyarrythmias. Prior to registration by the MCC, bedaquiline was made available to patients with XDR TB and pre-XDR TB through an expanded access programme: the Bedaquiline Clinical Access Programme.[2] The preliminary outcomes of the first 91 patients treated with bedaquiline in this programme (including 59% with HIV co-infection) were recently published. Treatment responses were much improved for these patients compared with historical experience: approximately 75% of patients with both XDR and pre-XDR had converted from sputum culture positive to negative by 6 months regardless of HIV status.[3]

The antibiotic linezolid also has antimicrobial activity against TB and has been shown to improve outcomes in patients with XDR TB.[4] The SA National Department of Health has now made both bedaquiline and linezolid available for the treatment of patients with XDR and pre-XDR TB. Access to these drugs is carefully regulated and monitored at a provincial and national level to ensure they are used within appropriate TB regimens to minimize the risk of amplifying resistance to these drugs.

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Aid for AIDS is delighted to announce we have been appointed as the HIV disease manager for the South African Police Service Medical Scheme (POLMED) as of 01 January 2016

HIV tests in children on ART

It is already well described that children with HIV infection confirmed by HIV DNA PCR can lose antibodies to HIV and even have a negative HIV DNA PCR after being on effective ART for 18 moths or more.[1] This scenario also occurred in the well-described Mississippi baby, who was treated from the 2nd day of life until approximately 18 months of age when the mother discontinued ART. When retested 6 months later, standard HIV DNA PCR and plasma viral load assays were negative, as was the standard test for antibodies to HIV. However, virological relapse occurred after approximately 2 years off ART.[2]

The final results of the Children with HIV Early Antiretroviral (CHER) trial were recently reported and confirmed that the benefits of early ART persisted over time.[3] Decay of antibodies to HIV measured by rapid test and standard commercial EIA assays was recently described in infants randomised to deferred ART or on continuous ART until 2 years of age. Forty-six percent of those commencing ART before 12 weeks of age were seronegative versus 11% who started ART later.[4]

There are a number of lessons to be learned from these data:

1. It is essential to confirm the HIV status at baseline by at least 2 virological assays (HIV DNA PCR and viral load).
2. Loss of antibodies against HIV occurs commonly after 2 years of suppressive therapy and suggests good adherence, but is NOT an indication to discontinue ART.

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0199 Tariff Claiming Process

Certain schemes allow the payment for tariff 0199 for full clinical completion of the Aid for AIDS application form for the initial registration of a patient onto the HIV programme. These payments have traditionally been processed on the providers' behalf. However this process must be changed with immediate effect due to legislation and scheme rules.

As of 01 October 2015 all providers who register new patients onto the HIV programme will be required to submit a paper claim via post, fax or email to Aid for AIDS using the tariff code 0199 as well as the ICD10 code of B24. These claims will be processed and verified by Aid for AIDS.

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Management of hyperlipidaemia in patients on protease inhibitors

Interpreting antiretroviral-associated changes in lipid data from clinical trials is difficult, as untreated HIV infection is associated with increases in triglycerides and reductions in cholesterol – any ART will normalise these changes. However, several protease inhibitors (PIs) may cause or exacerbate hyperlipidaemia. The currently recommended PIs are ritonavir-boosted atazanavir, darunavir, and lopinavir. Head-to-head clinical trials of these PIs have shown that lopinavir-r is associated with the greatest increase in triglycerides and cholesterol, followed by darunavir-r, then atazanavir-r. Once daily darunavir 800 mg with ritonavir 100 mg daily, which is widely used but not yet available in South Africa, is associated with less hyperlipidaemia than the doses used in salvage therapy (darunavir 600 mg with ritonavir 100 mg 12 hourly). It is important to note that PI-associated increases in triglycerides occur very early (within 2-4 weeks) and that severe hypertriglyceridaemia (>10.0 mmol/L) can cause pancreatitis, which may be life-threatening. Therefore fasting lipids should be requested within a few weeks of commencing PIs.

The following guidelines are recommended for the management of hyperlipidaemia for patients receiving PIs:

- If the patient is on lopinavir-r, switch to atazanavir-r and repeat the fasting lipogram after a month.
- Lifestyle modifications (stop smoking, weight control, regular exercise and reduce intake of cholesterol and saturated fats) are important in all cases.
- Exclude secondary causes of hyperlipidaemia (e.g. diabetes mellitus, hypothyroidism).
- Bezafibrate should be commenced urgently if fasting triglycerides are >10.0 mmol/L as there is a risk of pancreatitis. Triglycerides 2.5 to 10 mmol/L should be treated with diet, which is more effective for controlling hypertriglyceridaemia than hypercholesterolaemia.
- The following are the recommended indications for statins:
    i. Atherosclerotic disease (ischaemic heart disease, cerebrovascular disease, peripheral vascular disease) irrespective of cholesterol concentrations
    ii. Coronary heart disease "risk equivalents" (diabetes mellitus type 1 with microalbuminuria/proteinuria OR diabetes mellitus type 2 OR chronic kidney disease with GFR < 60ml/min/1.73m^2) irrespective of cholesterol concentrations
    iii. Patients with a 10-year risk of a cardiovascular disease of ≥20%
    iv. Patients with total cholesterol ≥7.5 mmol/L or tendon xanthomas or LDL-cholesterol ≥5 mmol/L are likely to have major gene defects and require further work up
- Many statins cannot be used with ritonavir-boosted PIs because of marked inhibition of statin metabolism, resulting in toxic concentrations. Simvastatin and lovastatin should not be used with PIs. Rosuvastatin is best avoided as it has a complex interaction with PIs, which reduces its efficacy. Pravastatin or fluvastatin can be used with no dose adjustment. Atorvastatin has a significant interaction with PIs, but can be used provided the daily dose does not exceed 10 mg.
- AVOID combining statins and fibrates because of the high risk of rhabdomyolysis.

Cross-reactivity between darunavir and co-trimoxazole

Both darunavir and co-trimoxazole contain a sulphonamide moiety, and there is therefore a potential risk for cross-reactivity in terms of allergic reactions. The risk of drug allergy to darunavir in patients with a history of allergy to co-trimoxazole is however not well defined.

A recently published retrospective cohort study has provided new information regarding this risk. The study included 405 HIV-infected patients all with a history of exposure to co-trimoxazole who were commenced on darunavir. In those patients with a history of an allergic reaction to co-trimoxazole a darunavir allergic reaction occurred in 4/79 (5%). In those with no history of co-trimoxazole allergy, 4/326 (1%) developed a darunavir allergic reaction. Patients with history of co-trimoxazole allergy were thus at increased risk of darunavir allergy (odds ratio = 4.29, 95%CI= 1.05-17.56). However, darunavir allergy is still uncommon (5%) in these patients. In this cohort none of the darunavir allergic reactions that occurred were severe or life-threatening.

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