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HIV and the risk of COVID-19 and its complications

Prior to the first cases of COVID-19 in South Africa, there were serious concerns expressed that people living with HIV (PLHIV) could be at much heightened risk for acquiring SARS-CoV-2, developing more severe disease and dying. With almost 8 million PLHIV in South Africa and without any data at that stage to inform us on these issues, there was understandably great anxiety about the consequences of this pandemic for PLHIV.

There have now been a number of studies published that inform our understanding of the impact of HIV on SARS-CoV-2 risks.

The most relevant to our setting is a study conducted using the Western Cape provincial electronic health database. Among 3.5 million patients on the database (16% HIV positive), 22,308 were diagnosed with COVID-19 in the initial months of the South African epidemic (March-June 2020), of whom 625 died. COVID-19 death was associated with male sex, increasing age, diabetes, hypertension and chronic kidney disease. After adjustment for other factors, HIV was associated with a moderately increased risk of COVID-19 death (adjusted hazard ratio = 2.14 – in other words, a roughly two-fold increase in risk for COVID-19 death relative to HIV-negative individuals with similar demographic and health characteristics). The elevated risk for COVID-19 was similar across strata of HIV viral load. However, recent unpublished updated analysis of the same data with more patient numbers does suggest that patients with advanced HIV and high viral loads do have higher mortality than patients on ART with suppressed viral loads. A greater proportion of COVID-19 deaths were in patients aged <50 years in those with HIV compared to those without HIV (39% vs 13%). A substantial proportion of PLWH who died due to COVID-19 had diabetes (50%) and hypertension (42%). However, diabetes and hypertension were even more common in people without HIV who died (62% for each condition). HIV accounted for 8.5% of COVID-19 deaths in the Western Cape during this time period.

By contrast, there did not appear to be an increased risk of severe COVID-19 outcomes in two studies from the US. Whereas a study from Wuhan, China, did report a higher risk of severe cases and death in PLHIV.

In terms of risk of acquiring SARS-CoV-2 infection, two studies from Spain suggested there were lower rates in PLWH than the general population, whereas other studies in the US and Europe have suggested similar incidence in PLHIV compared to the general population. No study has suggested a markedly higher risk for SARS-CoV-2 infection in PLHIV.

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Managing Weight Gain Associated with Dolutegravir

Dolutegravir and other integrase strand transfer inhibitors have recently been associated with more weight gain in people living with HIV (PLHIV) starting antiretroviral therapy (ART).[1,2] The ADVANCE study, conducted in South Africa, reported more weight gain in the dolutegravir arms than the efavirenz arms at 96 weeks, especially among women.[3]

The greater weight gain with dolutegravir compared with efavirenz may be due to dolutegravir binding to host receptors affecting metabolism or increasing appetite, or efavirenz may impair weight gain through its toxicity. Understanding which of these two possible explanations is correct is essential to recommend rational management of weight gain associated with dolutegravir.

Two recent studies provide clear evidence that sub-populations on efavirenz have impaired weight gain. Efavirenz concentrations is primarily metabolised by the cytochrome P450 enzyme CYP2B6. Mutations in the *CYP2B6* gene reduce the function of the enzyme, allowing the categorisation of people into extensive, intermediate, and slow metabolisers who have progressively higher concentrations of efavirenz. *CYP2B6* slow metaboliser genotypes are more common in people of African ancestry compared with European ancestry; about 20% of the South African population are slow metabolisers. A genetic sub-study of ADVANCE found that *CYP2B6* metaboliser genotype in the efavirenz arm predicted weight gain: extensive metabolisers gained the most weight, followed by intermediate metabolisers, then slow metabolisers.[4] Weight gain was similar between *CYP2B6* extensive metabolisers in the efavirenz arm and in the dolutegravir arm with the same nucleoside reverse transcriptase inhibitors (NRTIs): tenofovir disoproxil fumarate (TDF) and emtricitabine. A cohort study from the USA reported that *CYP2B6* slow metabolisers gained the most weight after switching from efavirenz to integrase inhibitors when virologically suppressed.[5] A possible explanation for the weight gain differences by *CYP2B6* metaboliser status is that efavirenz causes mitochondrial toxicity and impairs adipocyte differentiation in a concentration-dependent way.[6]

Antiretroviral drugs that have more metabolic toxicity are associated with less weight gain in randomised controlled trials[1], suggesting that, like efavirenz, they impair weight gain. One example is the NRTIs: weight gain is progressively higher with zidovudine, TDF, abacavir, and tenofovir alafenamide (TAF)[1]; a ranking of drugs with most to least metabolic toxicity would follow the same order. Newer, safer antiretroviral drugs are associated with more weight gain because they allow a better return to health, which could include excessive weight gain for PLHIV with unhealthy lifestyles.

PLHIV who experience marked weight gain on dolutegravir-based ART should be screened for other features of the metabolic syndrome and treated accordingly. The weight gain should be addressed by appropriate lifestyle interventions. Switching to more toxic antiretrovirals is not evidence-based and could cause harm.

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All your gut wants for Christmas is for you to stay away from your in-laws

In the August 2019 edition of the AFA newsletter, we delved into the importance of the gut microbiota to health in HIV. Now we take a festive peek into how sensitive your gut microbes are to the formidable external force that is, your in-laws.

Clerq and colleagues[1] studied the gut microbiota of Dutch adults between the ages of 20 and 40 years with a normal body mass index. Faeces was collected before and after Christmas. A total of 16 adults visited their in-laws during Christmas while the remaining eight visited their own families. There was no significant difference in dietary macronutrients or alcohol consumption between the 2 groups.

The team found 2 distinct biomarker signatures containing seven species of bacteria that distinguished participants who had visited their in-laws rather than their families. One bacterial genus, *Rumminococcaceae_UCG-009,* showed the most divergence, decreasing in those participants who visited their in-laws, and increasing in those visiting family. Previous studies have found mice that are exposed to chronic stress have reduced levels of *Rumminococcaceae_UCG-009,*[2] as do humans with major depressive disorders.[3]

With multiple limitations of the study, the authors correctly call for a large randomised controlled study to determine whether findings can be reproduced in different settings and to confirm whether visiting in-laws is to be added to the risk factors for microbial dysbiosis in the festive season.

May you (and your trillions of microbes) have a very merry festive season!

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