PrEPping for a healthier future – a concise update of current pharmacological HIV-prophylaxis practices

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Introduction

Pre-exposure prophylaxis (PrEP) refers to the use of antiretroviral drugs to *prevent* one from acquiring human immunodeficiency virus (HIV) infection when engaging in high-risk sexual behaviour. Adequate PrEP initiation is key in the clinical outcome and survival of not only vulnerable and high-risk populations, but also to ensure that a society which is free of HIV, is built. By the end of June 2019, 24.5 million people worldwide were accessing antiretroviral (ARV) therapy, with almost two million newly infected patients reported the year before.^{1,2} Still, approximately eight million are people naïve to the fact that they are living with HIV.^{1,2} Although meta-analyses have demonstrated a significant reduction in new HIV infections as a result of proper medication adherence,²⁻⁵ resistance towards antiretroviral (ARV) drugs remains a relevant health consideration. This is of note since an optimal functioning immune system is critical during times of a pandemic, such as the current global COVID-19 crisis. Due to the rapid nature of this review, a detailed overview of the complete pharmacological profile of and viral resistance mechanisms towards ARVs falls beyond the current scope. Rather, we will focus on current treatment guidelines, most frequently reported side-effects and novel alternatives of PrEP, and whether viral resistance towards ARVs is significantly affected by PrEP in populations with yet undiagnosed HIV.

Current PrEP guidelines

Importantly, individuals initiated on PrEP should be HIV-negative, willing and able to adhere to the treatment regimen, undergo quarterly HIV testing and should not portray symptoms of acute HIV infection.⁶ Proper PrEP use has been shown to reduce the risk for acquiring HIV infection by between 70–92% across all populations (including pregnant and lactating women, as well as those who become pregnant whilst on PrEP) with a side-effect profile comparable to that of placebo.^{4,5,7} To quote Dr Anthony Fauci of the US National Institute of Allergy and Infectious Diseases (NIAID): “The argument is over about PrEP. If you take the drug, it works.”⁸ Conversely, improper use offers no significant protective effects.⁴

Current South African and international guidelines recommend a fixed-dose combination of 300 mg tenofovir (TDF) and 200 mg emtricitabine (FTC) daily, adenosine and cytosine analogue

nucleoside reverse transcriptase inhibitors (NRTI), respectively. This should preferably be offered as an *additional* prevention method.^{5,6} However, unintended high-risk incidents, e.g. needle prick incidents aside, the ultimate goal of PrEP is to prevent the acquisition of HIV under high-risk circumstances. Hence, it should be considered that PrEP users may practise unprotected sex.⁹ In general *uninterrupted* treatment periods of at least seven days (before anal intercourse) and 20 days (before vaginal intercourse) are recommended to reach adequate protective tissue levels.⁶ This is based on the fact that TDF/FTC demonstrate significantly different pharmacokinetic profiles in colorectal vs vaginal tissue.^{10,11} Indeed, TDF/FTC penetrates colorectal tissue between 10–100 times more effectively and reaches peak concentrations quicker, compared to its uptake in vaginal and cervical tissue.¹⁰ However, recent World Health Organization (WHO) dosing regimens for men who have anal sex with men (MSM), suggest a loading dose of 600 mg TDF and 400 mg FTC 24 to two hours before sex, which should be followed by a single daily dose every 24 hours thereafter for two days.¹² Further, if individuals continue to engage in high-risk sexual practices after this time, dosing should continue every 24 hours until at least two doses, i.e. for 48 hours, following the last high-risk episodes have been taken; on average, this approach results in an 86% reduction in the risk for HIV infection.⁵

The most clinically concerning side-effects associated with TDF/FTC PrEP include the TDF-induced nephrotoxicity and reduced bone mineral density. Although these effects will likely only transpire in susceptible individuals following *chronic uninterrupted use*, two recent meta-analyses found no evidence to support severe TDF-induced renal or bone damage.^{13,14} Interestingly, a recent *in vitro* study described the interaction between probenecid and TDF as well as the potential of such a combination to further reduce the risk of nephrotoxicity.¹⁵ The efficacy of TDF in HIV is partly based on the accumulation of TDF in peripheral blood mononuclear cells (lymphocytes) and the consequent prolonged exposure thereof.¹⁶ Essentially, the risk for nephrotoxicity is also increased via this prolonged exposure mechanism in kidney cells. Concurrent probenecid administration would therefore reduce the daily required TDF dose without decreasing plasma concentrations and potentially decrease the overall nephrotoxicity risk.¹⁵ Importantly, although

these findings hold promise, further validation and investigation is required. FTC is known to induce hyperpigmentation of the palms and soles with long-term use.¹⁷ Still, the prevalence of this adverse effect is relatively low¹⁸ and transient.¹⁹ Nevertheless, this should be communicated, especially to non-Caucasian patients, who appear to have an increased risk.^{19,20} Importantly, although comorbid hepatitis B (HBV) infection is not an absolute contraindication for PrEP initiation,⁶ liver function should as far as possible be monitored as abrupt treatment cessation could result in hepatitis flare-ups.¹⁸ Specialist referral should be encouraged in HBV-positive patients. Taken together, current data support the widespread use of PrEP since the benefits far outweigh the risk of potential unwanted effects.

Finally, although oral preparations are easy to use, studies have indicated that certain populations would prefer alternative dosage forms, such as long-acting injectable formulations.²¹ To this extent, bimonthly injectable cabotegravir, an investigational integrase inhibitor is currently being tested in Phase III clinical trials for the prevention and treatment of HIV in combination with rilpivirine (a second generation non-nucleoside reverse transcriptase inhibitor [NNRTI]).²² Other possible alternatives include the sustained release dapivirine, an NNRTI which is administered in the form of a monthly administered vaginal ring.²³

PrEP and ARV resistance

Regardless of PrEP regimen, antimicrobial misuse is generally associated with increased organism resistance towards treatment and consequently, poor clinical outcome. However, considering that PrEP is intended for the HIV-negative cohort, the likelihood of ARV resistance will only be of concern in those with a positive, but undiagnosed viral load.²⁴ The outcomes of PrEP use in this population will ultimately also speak to whether such prophylaxis was 'successful' or not. As alluded to earlier, current PrEP guidelines are NRTI-based, with novel alternatives under investigation also including NNRTI-based regimens. Importantly, protease inhibitors (PI), such as lopinavir and ritonavir (LPV/r) are not currently considered as part of PrEP regimens, largely due to the robust efficacy of PIs against HIV and their attractive safety profile;^{25,26} as such, PIs are reserved for HIV treatment. Nevertheless, chances that current NRTI-based regimens will induce viral resistance in patients with a positive viral load of HIV strains that are not already resistant to TDF and/or FTC, are slim. Briefly, HIV develops resistance to ARVs via various drug-specific mutations that ultimately decrease the general drug penetration and accumulation within the virus. Although viral mutation-induced resistance towards both TDF and FTC have been reported,²⁷ various studies have concluded that the benefits of properly adhered to PrEP, outweigh the possible increase in HIV drug resistance prevalence.^{3,24,27} Still, acquiring ARV-resistant HIV, despite proper PrEP adherence, remains a possibility.²⁸ Against the background of current PrEP guidelines, adherence entails more than mere daily drug use. It also includes proper social support of users and a commitment on their behalf to perform quarterly HIV testing.^{6,28} Further, users should be cognisant of the fact that PrEP is also intended for use in addition to other

healthy habits, including but not limited to condom use, sexually transmitted disease management, regular HIV screening and proper HIV counselling.⁶

Conclusion

The use of PrEP is associated with a significant reduction in the risk of acquiring HIV across all populations. Proper use of PrEP regimens is effective in preventing HIV infection and is associated with a low risk for viral resistance in the HIV-infected, but undiagnosed population. Further, the side-effect profile associated with current PrEP regimens is also attractive, with renal and bone density monitoring only being considered in high-risk individuals with underlying conditions. Overall, patient adherence to PrEP treatment appears to be the one factor that will have the most robust influence on prophylaxis efficacy, highlighting the need for adequate counselling of users prior to its initiation.

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