

ISSUES IN MEDICINE

Truvada (emtricitabine/tenofovir) pre-exposure prophylaxis roll-out among South African university students: Lots of positives, but let us keep an eye on possible surprises

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Antiretroviral therapy (ART) has fundamentally altered the natural history of HIV/AIDS, sharply reducing HIV-related morbidity and prolonging longevity. However, there seems to be a resurgence in HIV infection rates in some parts of the world that has prompted consideration of pre-exposure prophylaxis (pre-EP) and vaccination. Despite their good viral suppression profiles, most drugs used as part of ART also have unwanted adverse drug reactions/effects (ADRs). In this article we acknowledge the utility of pre-EP in combating HIV transmission, but we also highlight the need to prepare for management of other unexpected outcomes such as ADRs and viral resistance, to ensure the success of the programme.

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Truvada is an antiretroviral (ARV) pill that combines two ARV drugs, tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), and has well-established efficacy in reducing the risk of contracting HIV if taken daily. Data from the South African (SA) Human Sciences Research Council show that women aged 15 - 25 years are most at risk of contracting HIV.^[1] This report appears to have been one of the catalysts in prompting the Higher Education and Training HIV/AIDS Programme (HEAIDS) and the National Department of Health to roll out Truvada to university and college students, because of the overlap with this high-risk age group. It is important to note that many studies with Truvada and preventive vaginal gels, involving thousands of women, have failed in SA and other Southern African Development Community countries.^[2,3] These studies include trials such as FACTS and VOICE,^[4-6] and it is thought that failure was due to lack of adherence and not ineffectiveness. The roll-out of Truvada therefore aims to offer protection to students at risk of HIV infection, in the hope that they will have better adherence, and has been extended to HIV-negative students across nine institutions of higher learning across SA. According to the director of HEAIDS, university students represent a group in which high rates of transactional sex occur, coupled with a low uptake of condoms (HEAIDS press release, 27 September 2017).

It has been noted that transactional sex with so-called 'sugar daddies'/'blessers' is a significant risk factor and social driver in the context of HIV infection among young people.^[7] Relationships marked by age and material differences are increasingly common among university students and may involve exposure to unsafe sexual practices, among other things.^[8] Truvada intervention will empower mostly young women to be in control of their infection status, as HIV prevalence and incidence rates remain disproportionately high in females than in males.^[9] However, as much as Truvada is

a potentially useful intervention, little is known about the drivers of product acceptability to end-users of such methods for HIV prevention. In a study that explored the end-user's product preference for multipurpose prevention technology delivery forms in SA and Kenya, it was found that only 27% of women aged 18 - 30 years preferred the Truvada.^[10] This is the age group into which most of the college and university students who are the target for Truvada roll-out fall. It is evident that we need to ask some questions: (i) is there sufficient evidence that college and university students will have better adherence than participants enrolled in previous studies in this country? (ii) since one of the drivers of uptake and adherence is perception of HIV risk, how certain are we that the college and university students perceive their risk as high? and (iii) lastly, as evidence shows that pre-exposure prophylaxis (pre-EP) is more likely to succeed if its roll-out is combined with interventions that target social drivers of HIV vulnerability specific to college and university students, will such interventions also be rolled out?

There has been particular interest in Truvada since announcement of the roll-out, owing to its effectiveness profile. There is no doubt that if it is taken correctly, with optimal adherence, there is a huge potential to reduce numbers of new infections, estimated as more than 250 000 in the year 2016.^[11] What this article seeks to highlight is that, despite the many positives, we should also be aware of possible surprises consequent to Truvada roll-out in healthy, HIV-negative young people. These are some of the questions we need to ask: (i) what are the possible effects of non-compliance with Truvada? (ii) what would be the consequences to participants who start off negative and are then infected, but continue to take Truvada intermittently? (iii) what are the possibilities of inducing resistance to Truvada in this young sexually active population? and (iv) what effect is Truvada pre-EP likely to have on attitudes of sexually

active people to other sexually transmitted diseases or infections? Furthermore, how prepared is our healthcare system to handle and manage the multifaceted challenges that will potentially arise from the roll-out in the nine institutions? Massive simultaneous roll-out of awareness programmes to educate on possible consequences of non-adherence, and training of healthcare practitioners to handle this new phenomenon of Truvada preEP, are necessary.

Possible long-term effects

It is important to note that both TDF and FTC have documented adverse effects (adverse drug reactions, or ADRs). A meta-analysis by Siemieniuk *et al.*^[12] showed that TDF/FTC was associated with stillbirth/early neonatal death and early premature delivery in HIV-positive participants, although there were no data on HIV-negative participants. Several studies have reported that another effect of the two drugs is lowering bone mineral density,^[13,14] so an additional concern is the possible long-term effects of Truvada pre-EP on the general health of the population. Surveillance of ADRs and related toxicities remains a challenge in the public health sectors of developing countries,^[15] mainly owing to lack of coherent structures or systems for pharmacovigilance and drug surveillance that track, assess and monitor safety profiles of ARVs. Patients on ARV therapy (ART) are usually monitored through a spontaneous surveillance method that is currently inefficient in detecting ADRs.^[15] In resource-limited health sectors like that of SA, pre-EP for healthy individuals will compete for scarce resources that are failing to contain a growing disease burden.

What about the cost?

In September 2016, SA started to implement the World Health Organization (WHO) evidence-based guidelines for universal test and treat (UTT). This strategy aims to test 90% of infected people, treat 90% of those tested, and have viral loads suppressed in 90% of individuals treated. SA already has one of the biggest ART programmes in the world, mostly funded by the fiscus, and implementation of UTT will significantly increase the number of people on ART. An increase in the budget will therefore be required in an already unfavourable economic climate. UTT will undoubtedly push demand for healthcare services in a context of a double burden of disease, high demand for medical personnel, and inadequate infrastructure. Public hospitals are already barely coping with the influx of patients, with complaints including medication stock-outs and sluggish financial support from donors, whose contribution has flatlined for the past 6 years.^[16] To add a huge number of sexually active but healthy people to this overburdened healthcare platform would hasten its further deterioration.

TDF has been associated with severe nephrotoxicity, changes in markers of renal function, serious renal adverse events, and decreases in bone mineral density.^[17] It should also be taken into consideration that most data on TDF ADRs are from controlled trials in populations that are genetically different from much of SA's student population. Furthermore, many individuals in resource-limited settings use a dual system of healthcare, traditional and conventional. With an estimated 26.6 million users of traditional medicine in SA,^[18] new drug-herb interactions are likely to emerge.

The challenges that policies such as UTT pose for developing countries have been well outlined, and have been predicted for sub-Saharan Africa (SSA).^[19,20] The same challenges outlined by Bigna and colleagues^[19,20] are applicable in the roll-out of Truvada to healthy individuals in SA. It was concluded that SSA cannot afford UTT, and in this case it is our submission that SA cannot afford the cost and implications of Truvada roll-out. SSA should always

strategise in implementing WHO policies, factoring in local resource constraints.^[19] We do not want to believe that Truvada roll-out is influenced by pharmaceutical companies that stand to gain regardless of the consequences to the country.

There is no doubt that Truvada roll-out will require additional resources, so for a successful outcome, funds need to be made available in a sustainable manner. Total health expenditure is predicted to reach almost 10% of the gross domestic product in SA by 2017/18, amounting to a staggering USD12 billion (ZAR178 billion).^[21] In the 2017 budget, the SA National Treasury allocated an additional USD63 million (ZAR885 million) to the response to HIV, in particular the implementation of UTT.^[22] However, SA still faces a flood of new HIV infections, with an estimated 266 618 in 2016.^[11]

Conclusion

Generally, ART has been associated with ADRs, and exposing healthy individuals to Truvada could put them at risk of renal failure and other complications.^[20] It is our opinion that, as we look at the positive side of Truvada roll-out, due care should be taken in its implementation, as there are environmental and genomic factors specific to SA populations. We write this letter in the hope that as the Truvada pre-EP programme is rolled out, appropriate preparations are made to ensure its success and possible mitigation measures put in place to ameliorate the negatives.

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