

Four cases of HIV infection in men taking pre-exposure prophylaxis in Singapore

Dear Editor,

Pre-exposure prophylaxis (PrEP) with co-formulated tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) is an effective prevention strategy against sexual transmission of human immunodeficiency virus (HIV) in at-risk populations.¹ It can be taken daily, or on-demand for cisgender men who have sex with men (MSM) and transwomen who have sex with men.² In spite of this, breakthrough infections have still been reported.^{3,4} Additionally, despite PrEP being available in Singapore for several years, accurate Singapore data on its utilisation is lacking.⁵ A Singapore study in February 2018 found that only 15% of MSM on a geosocial networking application (Grindr) had used PrEP.⁶ However, to our knowledge, there are no published Singapore cases on PrEP failures. We present 4 such cases (Table 1).

Chart review of cases of PrEP failures in a tertiary hospital infectious disease clinic was conducted. These cases of PrEP failures were identified when newly diagnosed persons with HIV were screened for recent or current PrEP use. Assessment of a patient's adherence to PrEP and understanding of PrEP dosing regime was qualitatively determined by the attending physician after each clinical encounter.

Case 1. In March 2020, an MSM in his 30s was started on daily TDF/FTC PrEP by a sexual health clinic after a negative 4th generation point-of-care (POCT) HIV test. He purchased the generic TDF/FTC formulation online. In June 2020, he underwent his last non-reactive HIV test. In September 2020, he switched to event-driven PrEP, around when he experienced an extended

period of fever and sore throat but did not seek medical attention. He was then diagnosed to have HIV seroconverted during POCT routine testing in November 2020. His adherence to event-driven PrEP dosing was confirmed again, and he reported no condomless anal sex without PrEP.

Case 2. An MSM in his 50s self-initiated daily PrEP without consultation with a healthcare provider for several years. In March 2021, he switched to event-driven PrEP on his own. He reported good understanding of PrEP dosing regimen and demonstrated adherence. He regularly performed self-testing for HIV using unvalidated POCT kits purchased online, with his last negative test in March 2021. However, in July 2021, during syphilis testing at a sexual health clinic, he was found to have HIV seroconverted on POCT testing.

Case 3. An MSM in his 40s was initiated on daily PrEP in 2018 by a private medical provider. However, he discontinued follow-up after a few months and obtained medications online. In May 2021, he self-switched to event-driven PrEP, taking 2 tablets before sex, followed by 2 tablets 24 hours later, only occasionally taking an additional single tablet 48 hours after sex. His last negative POCT HIV test was in March 2021. He subsequently only underwent POCT HIV testing inconsistently when offered by anonymous community testing sites. He continued using PrEP until he tested HIV-positive on POCT in August 2021. At the time of diagnosis, he exhibited a limited understanding of event-driven PrEP dosing.

Case 4. An MSM in his 30s was first seen in 2018 for treatment of syphilis and was found to be eligible to start PrEP but did not return for follow-

Table 1. Characteristics of PrEP failure cases at time of HIV seroconversion.

Case no.	Age and gender	PrEP regime at seroconversion	At point of diagnosis			
			Good understanding of dosing and adherence	Follow-up with PrEP provider	Resistance-associated mutations	Coinfection
1	30s M	TDF/FTC (event-driven)	Yes	Yes	M184V, V106I	Syphilis Hepatitis C
2	50s M	TDF/FTC ("do-it-yourself" event-driven)	Yes	No	M184V	Syphilis
3	40s M		No	No	M184V	Syphilis Hepatitis B (natural immunity)
4	30s M		No	No	M184V	Syphilis

M: male; PrEP: pre-exposure prophylaxis; TDF/FTC: co-formulated tenofovir disoproxil fumarate and emtricitabine

up. Instead, he obtained TDF/FTC online without prescription. In August 2022, he self-initiated event-driven PrEP using incorrect dosing schedules—taking only 1 tablet prior and 1 tablet after sex; or taking a single tablet after sex only. His last non-reactive POCT HIV test was in 2021. He presented again in November 2022 complaining of a rash where investigations confirmed secondary syphilis and HIV seroconversion.

“Do-it-yourself” PrEP and PrEP adherence. Only 1 of the 4 cases was regularly monitored by a PrEP provider, while none obtained TDF/FTC from local pharmacies, opting for online generic versions without prescriptions. This highlights the impact of barriers, e.g. high costs and stigma on PrEP utilisation, which discourage potential users to seek PrEP from established local providers.⁶

All 4 cases utilised event-driven PrEP at the time of HIV seroconversion. Although event-driven PrEP has been proven effective in MSM,^{7,8} the dosing regimen’s complexity necessitates regular reinforcement during counselling sessions to ensure correct dosing: taking 2 tablets 2 to 24 hours before sexual encounter, then taking a single tablet each 24 and 48 hours after. Out of the 3 cases who were continuing event-driven PrEP without guidance of a medical professional, 2 (cases 3 and 4) showed poor understanding of PrEP dosing, which likely contributed to its failure.

TDF/FTC resistance. The M184V mutation, associated with emtricitabine resistance, was detected in all 4 cases upon HIV diagnosis on baseline genotype testing. Two mechanisms explain the development of drug-resistant mutations in PrEP failure. Transmitted resistance is the transmission of virus that already carries resistance-associated mutations, which may render TDF/FTC ineffective as PrEP. Acquired resistance occurs when an individual, infected with a wild-type virus due to suboptimal adherence or poor understanding of dosing, continues PrEP without a third antiretroviral agent (which is insufficient treatment for an established HIV infection). This causes selective drug pressure by TDF/FTC in the presence of unsuppressed viral load, and the initially fully-sensitive virus develops mutations associated with resistance to TDF and/or FTC.

Assuming cases 1 and 2 were fully adherent to TDF/FTC, they may have been infected with a resistant strain (transmitted resistance), while cases 3 and 4 likely acquired resistance by continuing PrEP despite being HIV-positive. Since all cases were on event-driven PrEP at the point of seroconversion, analysing tenofovir plasma levels at diagnosis did not give any reflection about their PrEP adherence.

Medication authenticity. In Singapore, Truvada (Gilead Sciences, Foster City, CA, US), the branded co-formulated TDF/FTC, can cost up to SGD 900 (about USD 680) for a 30-tablet supply, leading patients to seek cheaper, less regulated sources locally or from overseas. Counterfeit HIV medication is prevalent globally.⁹ It is hence crucial to investigate the authenticity of such medications and their contribution to PrEP failures.

Sexually transmitted infection (STI) coinfection. Contracting an STI can be a result of sexual practices associated with increased risk of HIV transmission. Active STIs are known to augment HIV transmission in seronegative individuals.¹⁰ However, this association is less clear in PrEP failure cases. All 4 cases had coinfection with syphilis and 1 with hepatitis C. It remains uncertain if STI coinfection increased risk of PrEP failure or if it stemmed from increased sexual exposures.

Barriers to accessing PrEP. It should be recognised that external factors may influence individuals’ behaviour and decisions regarding PrEP. These include limited access to reliable PrEP information, high costs of laboratory tests and PrEP, as well as stigma related to both sex and HIV among healthcare providers. All these can contribute to barriers to accessing PrEP from official sources.

A limitation of this case series is its reliance on self-reported information from patients about their sexual behaviour and medication adherence, introducing recall and social desirability biases, particularly given the stigma around discussing sex and HIV. To mitigate these biases, enhancements like using a self-reporting form instead of interviewer-administered surveys or introducing a PrEP navigator from the community to provide care coordination could be considered. Another limitation was the inability to definitively exclude that the initial negative HIV test occurred within the test’s window period, because patients either initiated PrEP on their own or had it done by a private medical provider.

In conclusion, while PrEP is highly effective, it does not eliminate the risk of HIV transmission, which should be communicated to users. Follow-up with a PrEP provider is crucial for counselling, verifying understanding of dosing, and regular HIV testing to prevent acquired resistance in case of PrEP failure. Two of the cases here could have possibly been prevented with proper provider follow-up. Better outreach and engagement with populations at risk of HIV are needed to address potential gaps in PrEP services access, and to ultimately reduce “do-it-yourself” PrEP approaches.

Disclosure

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