Background

- A small number of seroconversions in individuals with full adherence to daily PrEP (Pre-Exposure Prophylaxis) has been reported internationally, including those where genotypic resistance has been detected.
- Seroconversions in trials and open-label extensions of on-demand PrEP have been similarly infrequent.
- Seroconversions on PrEP raise understandable concerns regarding the acquisition and potential onward transmission of drug-resistant virus.
- Scotland was the first UK nation to make PrEP available outside a clinical trial in July 2017 through existing routine clinical sexual health services.
- We describe an individual who has sex with men (MSM) who seroconverted after PrEP initiation during the first year of the programme in a single clinic.
- Investigation included DBS and segmental hair analysis, which has recently been employed to establish adherence over months prior to sampling.

Case 1:

A 25 year old white MSM eligible for PrEP and with a non-reactive HIV test was dispensed generic TD/FTC on 08/11/17. He delayed PrEP start due to perceived absence of risk and being unwell (significant flu-like illness from 12 to 16/11/17). Daily dosing began with a single PrEP dose on 16/11/17, then 2 and 4 tablets on 18/11/17, 2 and 4 tablets on 21/11/17, from which he self-discontinued due to low perceived risk. He took two further short courses (2,1,1) of on-demand PrEP in January 2018. He reported no condom use after PrEP in the intervening period. On 30/11/18 (Day 0) at routine review he tested HIV antibody positive. Quantitative viral load on Day 2 was 6,711 copies/ml, HIV subtype C. Antiretroviral therapy (ART) with TDF, Rilpivirine and Darunavir was commenced. He was enrolled in the SeroPrEP study. DBS and hair samples were taken on 19/03/18 (Day 47). Genotyping (Day 2) identified the NNRTI mutation M184V, conferring resistance to lamivudine and emtricitabine. Retrospective testing of baseline sample from 08/11/17 was negative for HIV by PCR.

The TFV-D results from DBS testing suggested an average dosing of >/= 4 doses/wk over ~8 weeks prior to draw (which included the period of 25 days on ART). Segmental hair analysis showed that drug levels in the distal hair segment (corresponding to the time of suspected seroconversion) were consistent with 3-4 doses per week of PrEP.

Despite extensive investigation of sexual contacts by both patient and clinicians, no source of HIV infection was identified. No evidence of a risk exposure immediately prior to or just after baseline HIV testing explained a possible seroconversion illness in the month before starting PrEP.

Case 2:

A 38 year old MSM attended for advice and monitoring on 08/02/2017 after having purchased PrEP from an online supplier. HIV testing was non-reactive. He commenced 2 weeks of daily dosing reducing to 4 days/wk (Tuesday, Thursday, Saturday, Sunday). TDF/FTC for 4 weeks. He tested HIV positive on 07/03/17. CD4 count was 671 copies/ml, HIV subtype C. Antiretroviral therapy (ART) with TDF, Rilpivirine and Darunavir commenced. He was enrolled in the SeroPrEP study. DBS and hair samples were taken from 04/04/17 to 27/06/18 (12 months). Genotyping showed resistance to Tenofovir and Emtricitabine. Retrospective testing of baseline sample was negative for HIV by PCR.

He reported no condom use after PrEP in all periods of ART. The TFV-D results from DBS testing suggested an average dosing of >/= 4 doses/wk over ~8 weeks prior to draw (which included the period of 25 days on ART). Segmental hair analysis showed that drug levels in the distal hair segment (corresponding to the time of suspected seroconversion) were consistent with 3-4 doses per week of PrEP.

Discussion

- Resistance is likely to have developed either as a result of acquisition of drug-resistant virus, or as a result of resistance evolution under selective drug pressure.
- Daily PrEP with lower adherence (4 doses/wk) or intermittent dosing probably requires timing of PrEP doses with sexual risk exposure by incorporation into a complex existing network of heuristics and decisions about condomless anal sex.
- In the absence of a confirmed source of HIV infection in either case, it is highly likely, but not certain, that the viruses from both individuals evolved antiretroviral resistance. The continued PrEP dosing following unrecognised seroconversion.
- The K65R mutation seen in Case 2 is rarely seen at baseline and is not thought to be easily transmitted.
- In Case 1, M184V but not K65R was identified, although the latter appears to be more likely to develop in Subtype C infection.
- Drug levels added information, but DBS were obtained after ART initiation in both cases. It is not possible to conclude (in case 2) whether dosing was maintained at 4 doses per week, or dropped below at times of risk, but it provides a useful reminder that a regimen such as TDF/TAF lowered resistance for further missed doses.
- Delay in sampling for drug level testing should be avoided in future to maximise the information to be gained from both DBS and hair samples.

Methods

PrEP was provided in integrated sexual health clinics following national Scottish eligibility criteria and protocols based on the BASHH/BHIVA Statement on PrEP and BASHH/BHIVA PrEP Guidelines 2018. 4th Generation (Architect) serological HIV antigen/antibody testing was done:

- at baseline
- at booked three-monthly appointments
- additionally at 1 month in individuals reporting risk in the 4 weeks prior to PrEP commencement.

A maximum of 90 tablets of PrEP were supplied at each visit. Verbal advice was given on daily and on-demand (following a ‘2:1:1’ [IPERGAY regimen] dosing, supported by the patient guide ‘PrEP in Scotland’, derived from the I-Base Guide to PrEP. Genotypic resistance testing was performed locally by Sanger sequencing. DBS and hair samples were obtained for TDF/FTC drug level analysis following institutionally approved protocols for the SeroPrEP study. Liquid chromatography-tandem-mass-spectrometry (LC-MS/MS) analysis in 1 cm scalp hair segments was performed.