P022

HIV pre-exposure prophylaxis failures in a large observational cohort from Poland with expansion of A6 subtype transmission

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Background

PrEP efficacy relies on adherence and appropriate dosing[1,2,3,4]. As data on real-life PrEP roll-out and efficacy from Central and Eastern Europe are scarce we explored PrEP failures in an observational cohort and analysed phylodynamic information among users infected with A6 subtype to help monitor transmission networks as HIV-1 A6 subtype might influence future treatment choices for the infected population[5].

Materials and methods

Between 2017-2023 a cohort of 887 men having sex with men (MSM) on generic emtricitabine/tenofovir disoproxil (FTC/TDF) was followed for cumulative 2587 person-years. Patients were included in the analysis if PrEP was started in the defined period and at least one visit took place each year. Baseline visits included HIV Ag/Ab (antigen/antibody), HCV Ab, HBs Ag or HBc Ab, HBs Ab, syphilis serology, blood morphology and creatinine and other tests if clinically indicated. The one month visit included HIV Ag/Ab, syphilis serology, creatinine and other tests if clinically indicated. Further 3-monthly visits included HIV, HCV, syphilis testing and other tests if clinically indicated. Blood morphology and creatine were performed once a year unless otherwise indicated. All tests were performed locally without outside referral. As part of adherence counselling, during each visit patients were asked about their dosing schedule (continuous or on demand) and were prescribed TDF/FTC accordingly for up to four packages (30 tablets/package). Unscheduled visits were prompted by symptoms or exposures suggestive of sexually transmitted infections (STIs) or acute retroviral infection. Patients had online access to their results and were instructed to schedule visits without any delay in case need be and not to use PrEP and avoid risk in the meantime. The waiting time for unscheduled visits was 0-1 days and only extended to 2-3 days during weekends or holidays. In newly infected users acquisition of HIV was confirmed using molecular and immunoassays, with subtype and genotyping performed at diagnosis. Following baseline assessment (HIV viral load, CD4 and CD8 cell counts, HIV genotyping, HBV/HCV/syphilis serology, general blood exam, Neisseria gonorrhoeae and Chlamydia trachomatis PCR from pooled urethral/rectal/oropharyngeal smears) and initiation of cART HIV viral load was re-tested 4-8 weeks and 12 weeks later according to Polish AIDS Scientific Society and EACS guidelines [1,2] – see details in Table 1. For phylogenetic analysis we used 2,087 HIV-1 sub-subtype A6 partial pol sequences from Poland as background, with a two-state asymmetric discrete trait analysis model to infer the geographic node locations.

Results (see Table 1)

Nine (1.01%) PrEP users acquired HIV infection during the follow-up with one user diagnosed at baseline and excluded from incidence analysis. Estimated HIV incidence was 0.347/100PY with the relative risk reduction of 90,86%. All users who acquired HIV were cis-gendered white MSM of European origin (median age: 35.5 (IQR 33-37.75) years) with infections due to inadequate PrEP dosing/exposure. Most users (8/9) dosed PrEP on demand: seven skipped doses while one user dosed TDF/FTC on demand but only prior to receptive sexual contacts. Genotypic data were available for all cases: in five (55.6%) subtype B and in four (44.4%) A6 variant was acquired with no transmitted drug resistance mutations. Phylogenetic analysis revealed that each of the four PLWH with the A6 sub-subtype belongs to distinct clusters, with no connections to other individuals followed up locally (Figure 1A) three of which had distinct regional origins within the country, and one of a foreign ancestry, as confirmed by modelling probability of at least 0.94 (Figure 1B). All A6 sub-subtype infections in the Wroclaw cohort were detected after 2021 and are classified into different clusters with distinct ancestral locations.

Users were started on tenofovir alafenamide/emtricitabine/bictegravir in the median of 10.5 (IQR: 7-21) days from diagnosis with undetectable viral load after median of 63 (IQR: 28-84) days.

Table 2. Patient characteristics and results

	Age strata [years]	PrEP dosing	Year of HIV infection	Reason for missed/incorrectly dosed PrEP	PHI symptoms	CD4 cell count at diagnosis [cells/mcl]	HIV viral load at diagnosis [copies/ml]	HIV genotyping (protease, reverse transcriptase, integrase)	HIV subtype	Time from previous negative HIV/p24 result [weeks]	Fiebig stage	Time to cART from the first positive result [weeks]	cART used	Time to the first undetectable viral load or <200 copies/ml [weeks]	anti-HCV	anti-HBs post vaccination	Other STIs
1	30-39	on demand	2020	COVID-19 restrictions, risk unplanned - missed PrEP	No	405	29	not available – viral load too low	NA	35	VI	6	FTC/TAF/BIC	12 (no earlier sample)	negative	positive	CT at diagnosis
2	30-39	on demand	2020	missed PrEP (COVID-19 restrictions, risk unplanned, left PrEP at home)	No	422	42.470	WT	B	8	V	1	FTC/TAF/BIC	2	negative	positive	past TP and NG
3	30-39	daily	2020	no PrEP (did not restart dosing after COVID-19 lockdown)	No	1174	113.000	WT	B	12	V	2	FTC/TAF/BIC	12 (no earlier sample)	negative	positive	past TP
4	20-29	on demand	2020	missed PrEP (chemsex)	No	344	115.000	WT	B	10	V	1	FTC/TAF/BIC	12 (no earlier sample)	positive (HCV-RNA positive)	positive	NG at diagnosis
5	30-39	on demand	2022	no PrEP during insertive sex (only receptive seen as risky)	No	417	1.260.000	WT	B	16	V	4	FTC/TAF/BIC	20 (no earlier sample)	negative	positive	past TP, CT, NG
6	30-39	on demand	2022	missed PrEP (chemsex/slam sex); infection probably 4 weeks before diagnosis	Yes	603	6.300	WT	A6	8	V	3	FTC/TAF/BIC	4	negative	positive	past TP; NG and CT at diagnosis
7	50-59	on demand	2023	no PrEP (known partner but not exclusive)	Yes	347	303.000	WT	B	8	V	3	FTC/TAF/BIC	6	negative	positive	past TP
8	30-39	on demand	2023	missed/no PrEP (chemsex, known partner but not exclusive)	No	897	32.500	WT	A6	31	VI	1	FTC/TAF/BIC	4	negative	positive	past TP; NG at diagnosis
9	30-39	on demand	2023	infection confirmed during 1st visit but patient took PrEP for one month; infection probably 4 weeks before diagnosis	No	636	396	WT	A6	100	V	1	FTC/TAF/BIC	12 (no earlier sample)	negative	positive	past TP
10	30-39	on demand	2023	missed PrEP on one occasion; infection probably 4 week before diagnosis	No	453	4.960	WT	A6	16	V	1	FTC/TAF/BIC	4	negative	positive	NG at diagnosis

cART – combined antiretroviral therapy, TAF/FTC/BIC – tenofovir alafenamide/emtricitabine/bictegravir, PHI – primary HIV infection, WT – wild type, WB – Geenius HIV-1/2 blot, anti-HCV- hepatits C virus antibodies, anti-HBs – hepatitis B surface antigen antibodies, STIs – sexually transmitted infections, CT – Chlamydia trachomatis, NG – Neisseria gonorrhoeae, TP – Treponema pallidum, NA – not available

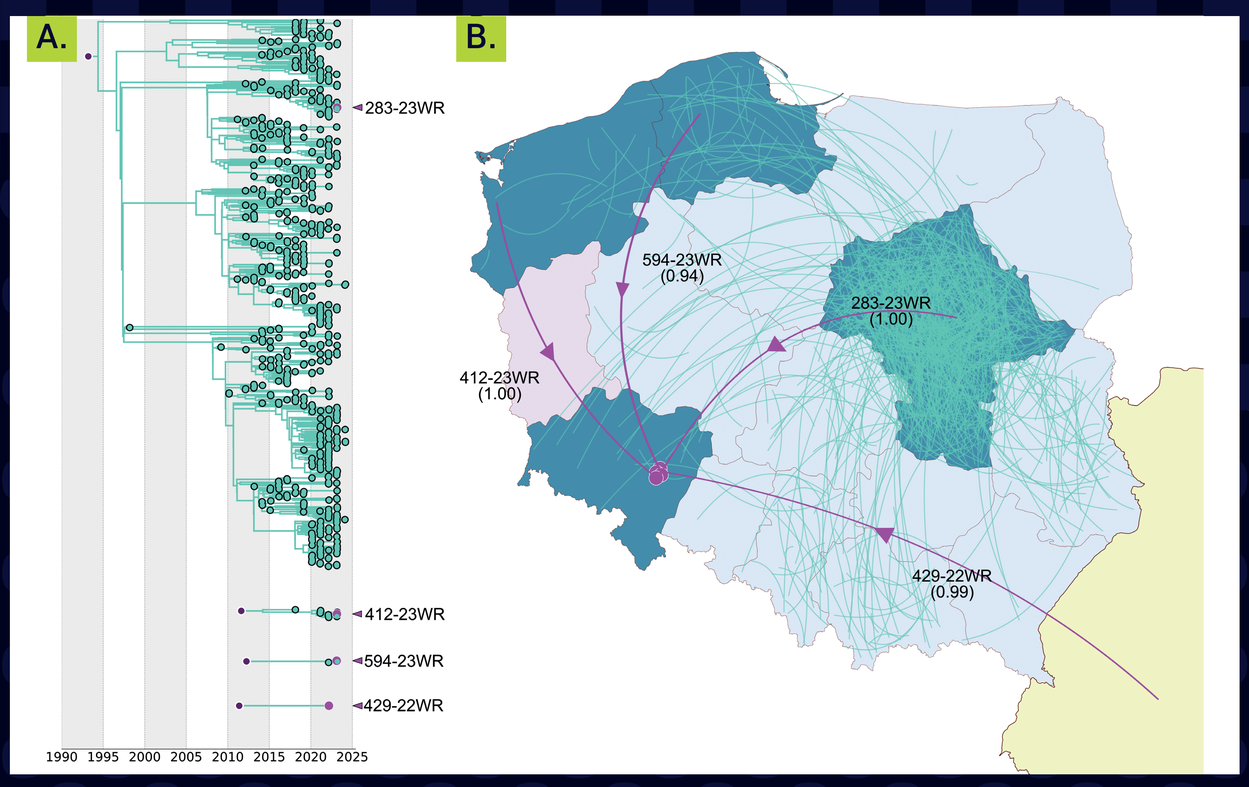

Figure 1A, B. Distribution of HIV-1 A6 infections in the Wroclaw All Saints Cohort within the Polish HIV A6 epidemic

Discussion

Continuous and on demand dosing have been shown to be equally effective in the ANRS Prevenir trial [3], however, lack of daily habit with on demand dosing might create room for mistakes as seen in our group. Only 2% of our users opted for on-demand dosing when the cohort started in October 2017 but reached 35% in 2021 and 53% in October 2023. Thus, the possibility of on-demand dosing created an additional prevention opportunity for diverse and changing needs increasing the number of PrEP users. On demand PrEP use has been less popular in Germany with only 18.9% users choosing this dosing in 2021 [6] while French experience has shown 50% of PrEP users dosing on demand [7]. On demand dosing complexity, visit adherence and stigma also play an important role in patient readiness to accept and follow PrEP schedule [23,25]. What all cohorts have shown is that baseline testing, regular follow-up, easy access to refills, rapid PrEP initiation or cART initiation in case of suspected infection as well as patient education and inclusion in the diagnostic process are paramount to a safe and efficacious roll-out of PrEP programmes [3, 8].

In case of PrEP failure, European AIDS Clinical Society (EACS) [1] and Polish AIDS Scientific Society [2] recommend cART be started without delay and HIV genotyping be performed to guide future treatment modifications. Notably, no drug resistance mutations were observed in our cohort. Despite most diagnoses made relatively late (Fiebig stage V and median time from previous negative result 98 days), this was enough to prevent resistance emergence and still inside the 3-monthly visit period. Similarly, no mutations were seen among ANRS IPERGAY trial participants who acquired HIV infection despite on-demand PrEP use also suggesting that prompt action can mitigate resistance emergence [3]. However, British 56 Dean Street Clinic experience has shown that 69% of patients who acquired HIV infection dosed PrEP daily. Higher prevalence of M184V/I mutations in this group might have been the result of longer exposure to TDF/FTC after HIV infection. There was no difference between the daily and on demand groups, however [4]. One individual (283-23WR) was part of the largest domestic cluster, which has been circulating in Poland since 1993 (Figure 1A) and included primarily MSM [9]. The other two individuals (412-23WR and 594-23WR) were associated with clusters reported in the country after 2010. Only one sequence (429-22WR) is linked to a lineage of Ukrainian origin (Fig.1B). Therefore, most A6 infections in the Wroclaw cohort arise from domestic A6 lineage circulation and are not attributed to the increase in A6 infections following the influx of war-displaced people from Ukraine [10].

The relative risk reduction of 90,86% was lower than in other clinical trials and cohorts [3, 11] despite a downward trend in new HIV infections among homosexual men in Wroclaw (in press). We think it is due to 5 out of 9 HIV infections occurring outside of Wroclaw and/or Poland (specific cities not shown for anonymisation purposes) with limited PrEP and combined prophylaxis access.

Conclusions

In this first Polish analysis of PrEP failures suboptimal PrEP adherence/exposure and engaging in chemsex use were confirmed as primary factors associated with HIV transmission among TDF/FTC users. We emphasize the necessity to reduce barriers to PrEP and the urgent need for state funded combination prevention programmes to respond to the unmet needs of LGBTQ community in Poland, local and migrant. Patients engaging in chemsex might require additional interventions to stabilize their daily routines, mitigate failures and diagnose infection early. The four cases of A6 in the Wroclaw cohort illustrate multiple introductions and widespread A6 lineage circulation across country suggestive of further spread irrespective of Ukrainian migration. Changing molecular epidemiology of HIV may limit future treatment options for newly infected patients therefore action for immediate PrEP implementation is strongly advised.

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