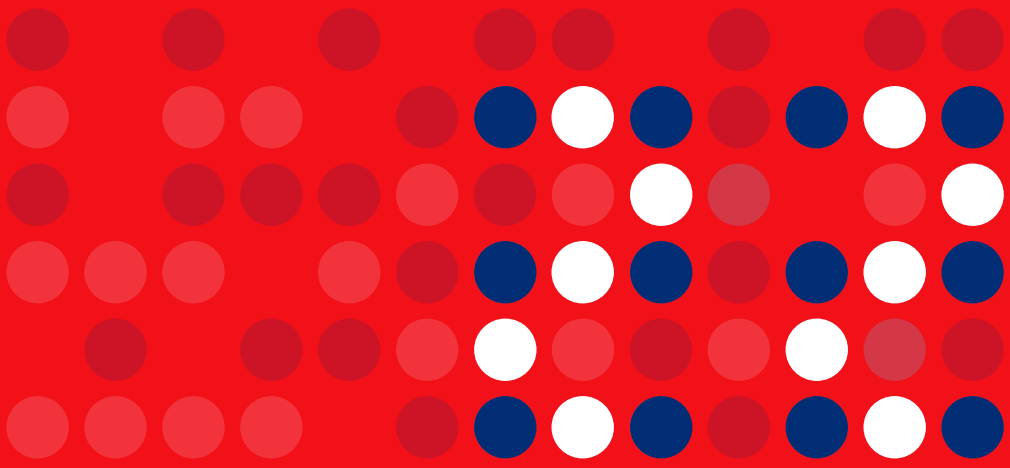
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2022

Special report 1.2:
Prior use of pre-exposure prophylaxis



Special reports

1.2 Prior use of pre-exposure prophylaxis

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Background

Pre-exposure prophylaxis (PrEP) is the use of antiretroviral drugs by people without HIV, to prevent HIV acquisition. Those at high risk of HIV acquisition in the Netherlands are eligible for the national PrEP pilot programme at the Sexual Health Centres (SHC) of the municipal Public Health Services (GGD), which was launched in September 2019. Prior to this, PrEP use prescribed by other healthcare providers (mainly general practitioners) or accessed via informal buyers' clubs, was monitored through demonstration programmes such as the AMPrEP study in Amsterdam.

Data collection

SHM has prospectively collected PrEP-related data from the electronic medical records (EMRs) of individuals with HIV first entering care, since July 2019. This is carried out in consultation and collaboration with the Dutch Association of HIV-Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB), and the Dutch Nurses Association's HIV/AIDS nurse consultants unit (*Verpleegkundigen & Verzorgenden Nederland – Verpleegkundig Consulenten Hiv*, V&VN VCH). SHM also retrospectively gathered information on prior use of PrEP by individuals who first entered into care between January 2018 and June 2019.

By 31 May 2022, data had been collected for 2,500 individuals. In 735 (29.4%) EMRs, information was available on prior use of PrEP. The proportion of individuals for whom this information was available increased from 10.6% in 2018, to 29.1% in 2019, 35.4% in 2020, 44.9% in 2021, and 56.6% in the first five months of 2022.

The demographic characteristics of the group for whom EMR information on prior PrEP use was available were largely similar to those for whom it was not (see *Table 1*). Information on prior PrEP use by MSM was slightly more likely to be available than it was for heterosexuals and other transmission categories. For transgender women however, this information was less likely to be available.

Main findings

Of the 735 individuals for whom information on prior use of PrEP was available, the majority (660, or 89.8%) reported no such use, whereas 75 (or 10.2%) reported prior PrEP use (*Table 2*). In terms of breakdown by gender:

- none of the 97 cisgender women reported prior PrEP use;
- none of the 17 transgender women reported prior PrEP use;
- 74 (12.0%) of the 616 cisgender men reported prior PrEP use; and
- one of the five transgender men reported prior PrEP use.

Of the 74 cisgender men and one transgender man, 71 men (94.7%) reported sexual contact with other men as the most likely mode of HIV acquisition. One man (1.3%) reported this to be sexual contact with women, while three men (4.0%) reported this to be another acquisition category or unknown.

The 75 individuals who reported prior use of PrEP were younger (median 31.2, IQR 26.2-40.9 years) than individuals who did not (median 38.0, IQR 29.7-49.7 years). They also had much higher median (IQR) CD4 counts (570 (360-740) vs. 360 (170-584) cells/mm^3). Individuals who had used PrEP were also less likely to be born outside of the Netherlands.

PrEP awareness and uptake

For 292 (44.3%) of the 660 individuals who reported no prior PrEP use, information was available on why they had not done so. 'Not knowing PrEP existed' (13.9%) and 'presumed to be at low risk for HIV' (13.2%) were the most commonly reported reasons.

Those who said that they did not know PrEP existed were of a similar age, but less likely to be of Dutch origin (33.7%) and more likely to have acquired HIV through heterosexual contact (52.2%).

In total, 39 (5.9%) individuals had wanted to start using PrEP but tested HIV-positive at screening before entry into a PrEP programme. Of these 39 individuals with high CD4 counts (median 510, IQR 370-770), 94.5% were MSM and 61.5% had evidence of recent HIV infection, as the majority frequently underwent HIV testing. Four individuals (0.6%) reported that they tested HIV-positive while on a PrEP programme waiting list.

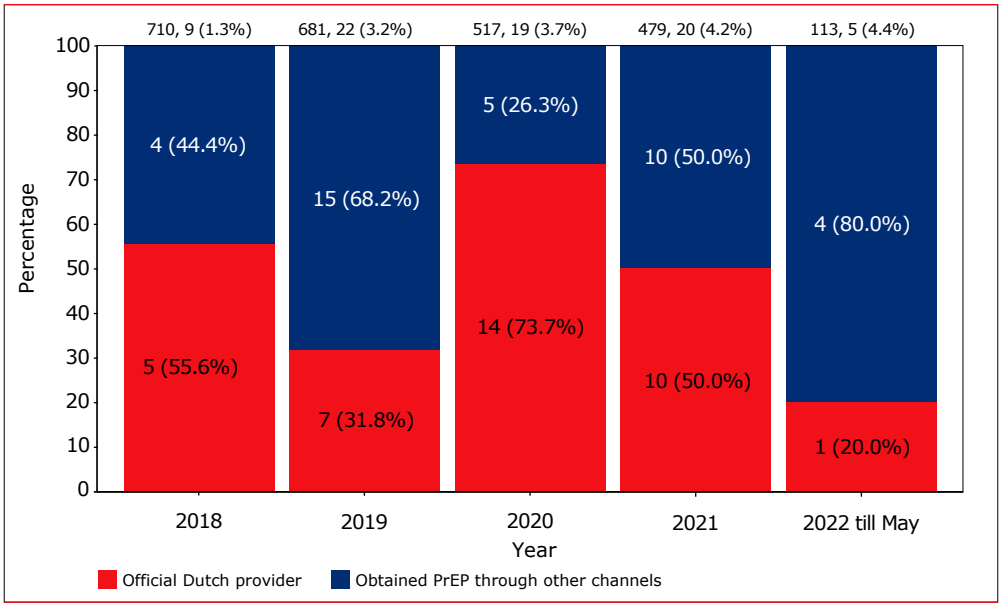
Prior use of PrEP upon entry into care

The percentage of people entering into care who reported prior PrEP use has remained stable since 2019 (P_{trend}=0.35, see Figure 1), with:

- 1.3%, or 9 out of 710 individuals, in 2018;
- 3.2%, or 22 out of 681 individuals, in 2019;
- 3.7%, or 19 out of 517 individuals, in 2020;
- 4.2%, or 20 out of 479 individuals, in 2021;
- 4.4%, or 5 out of 113 individuals, up to 31 May in 2022.

The characteristics of the 75 individuals who reported prior use of PrEP are shown in *Table 3*, with a stratification by calendar period. They do not differ significantly between those who entered into care before and after the start of the national PrEP pilot program.

Figure 1: *Time trends in the number and proportion of individuals with HIV first entering into care reporting prior use of PrEP, stratified by PrEP provider.*



Access to PrEP and usage patterns

Of the 75 individuals who reported prior PrEP use, 37 (49.3%) obtained it from a healthcare provider in the Netherlands, comprising:

- family practitioners (18, or 24.0%);
- the Municipal Health Service (15, or 20.0%); and
- HIV treatment centres (3, or 4.0%).

There was no further detailed information available for 1 individual (1.3%). The remaining individuals for whom this information was recorded, obtained their PrEP:

- from a buyers' club/internet/store outside of the Netherlands (16, or 21.3%);
- from a healthcare provider outside of the Netherlands (7, or 9.3%); or
- from a friend living with HIV who had donated some of their own medication (2, or 2.7%).

There was no information available for the remaining 13 (17.3%) individuals.

Just over half (40) of the 75 individuals who reported using PrEP, did so in the form of co-formulated tenofovir disoproxil / emtricitabine. One man used the drug Genvoya as PrEP (obtained through an unspecified route). For the remaining 34 men there was no further information available on the specific antiretrovirals used.

Dosage schedule information was available for 45 individuals (60.0%):

- 17 men (22.7%) reported on-demand use
- 20 men (27.7%) reported daily use
- 5 men (6.7%) reported intermittent use (i.e. a fixed schedule but not seven days a week)
- 3 men (4.0%) reported having used PrEP less than a week

For the remaining 30 men (40.0%), no dosage schedule information was available.

Of the 75 men who reported prior PrEP use, 19 (25.3%) had regular medical check-ups by the Public Health Service during that period. Five men (6.7%) attended an HIV treatment centre, 11 (14.7%) were seen by a family practitioner, and two men (2.7%) were checked by a medical specialist other than HIV treatment centre staff. Thirteen men (17.3%) did not have any medical check-ups, and there was no information available for the remaining 25 men (33.3%).

Forty-two (56.0%) of the 75 individuals were known or presumed to have HIV-seroconverted in the Netherlands, while 18 (24%) were known or presumed to have HIV-seroconverted before migrating to the Netherlands. For the remaining 18 (24%) this was unknown.

The median number of days between the last dose of PrEP and testing HIV-positive increased to 104 (0-232) days in the period after September 2019, up from a median of 39 (1.5-107) days in the period prior the September 2019. The number of individuals who tested HIV-positive while still using PrEP decreased from 14 (46.7%) in the period up to September 2019 to 14 (31.1%) in the period after September 2019.

In terms of demographic and HIV-related parameters, the 28 men who tested positive while still using PrEP were very similar to the total group of 75 men who reported prior PrEP use, although they were more likely to have evidence of HIV drug resistance. Of the 47 men who did not test HIV-positive while taking PrEP, 21 (44.7%) reported having tested HIV-seronegative after their last use of PrEP, while 22 (46.8%) did not have an HIV-test shortly after discontinuing the use of PrEP. There was no information available for 4 (8.5%) men.

PrEP and possible drug resistance

Genotypic resistance test results were available for 46 (or 61.3%) of the 75 men who reported having used PrEP when first entering HIV care. Reverse transcriptase (RT) resistance-associated mutations (RAM)[a] were detected in 14 (30.4%) cases. In nine men (19.6%), these may be associated with the use of PrEP:

- Nine individuals harboured an M184VI RT RAM (which decreases susceptibility to lamivudine and emtricitabine)
  - One of these also harboured a K65R RT RAM (which is selected for by tenofovir and decreases susceptibility to tenofovir, abacavir, lamivudine and emtricitabine)
- Four individuals harboured an E138A RT RAM (a known RT RAM that can be selected for by the use of rilpivirine but is also known to occur as a natural polymorphism, especially in non-B HIV-1 subtypes)
  - Two of the four were known to harbour HIV-1 subtype B and an M184V/I RT RAM[b]
    - One of these two individuals also harboured a K65R and a V108I RT RAM
- One individual was found to harbour a V103R (which may be a naturally occurring polymorphism) and no other RT RAM
- One individual was found to harbour an L74I (which decreases susceptibility to abacavir and didanosine) and no other RT RAM
- One individual was found to harbour an L74I, V103R, and V108I RT RAM (which is a non-polymorphic accessory mutation conferring decreased susceptibility to nevirapine and efavirenz)

It is worth noting that eight of the nine men in whom M184VI RT RAM (with or without K65R RT RAM) had been detected, said they had continued using PrEP for a while after their last HIV-negative test. Four of these men had acquired HIV in the Netherlands, three in another country in western Europe, and one in Colombia. The nine men last used PrEP in 2018 (n=2), 2019 (n=2), 2020 (n=3), and 2021 (n=2).

a *All RT RAMs mentioned in this chapter start and end with capital letters; i.e. M184VI ends in the capital letter 'i' and should not be confused with the number 1.*

b *M184VI and M184V/I are used interchangeably here: they are a mixture of M184V and M184I in a single blood sample. They result in the same level of resistance as samples in which only M184V is detected.*

For the two individuals with HIV-1 subtype B and an M184V/I RT RAM, the results suggest that they may have acquired HIV from a person on a failing rilpivirine-containing regimen. However, it is not possible to determine whether the observed M184VI and K65R RAMs were also transmitted, or were selected for by their use of PrEP. One of the two tested HIV positive while still using on-demand PrEP. The other tested HIV positive on his first HIV test a few months after discontinuing on-demand PrEP. Both men are Europeans who tested HIV positive before migrating to the Netherlands.

The remaining 37 genotypic resistance tests exclusively yielded wild-type RT or naturally occurring polymorphisms that are probably unrelated to the prior use of PrEP. No major protease or integrase resistance-associated mutations were observed.

Prior use of PrEP and antiretroviral therapy (ART)

Data on the first-line ART and subsequent virological treatment response was available for 74 of the 75 individuals who reported prior use of PrEP. This includes the nine men with M184V/I (with or without K65R RT RAM), all of whom started a regimen containing an integrase inhibitor. Six of these combined the integrase inhibitor together with a protease inhibitor. The remaining three combined the integrase inhibitor with two nucleoside-analogue reverse transcriptase inhibitors, or NRTIs (tenofovir and emtricitabine, with either dolutegravir [n=2] or bictegravir [n=1]).

Of the remaining 65 individuals with no baseline resistance test results, or whose test showed no evidence of M184VI (with or without K65R RT RAM), 64 initiated a first-line regimen containing two NRTIs plus one of the following:

- an integrase inhibitor (n=39)
- a protease inhibitor (n=3)
- an integrase inhibitor plus a protease inhibitor (n=20)
- a non-nucleoside RT inhibitor (n=2)

Additionally, one individual initiated ART with lamivudine / dolutegravir.

In one of the nine individuals with an M184V (but without K65R) RT RAM, the first-line regimen was discontinued due to a persistent suboptimal virological efficacy. This individual's plasma viral load had initially become undetectable three months after starting on Biktarvy. However, in the following two-year period all eight recorded viral load measurements showed detectable viremia. The highest recorded value was 253 copies/ml. After this, ART was switched to another regimen, during which the viral load eventually became undetectable again.

For the 65 individuals with no evidence of M184VI (with or without K65R RT RAM) in the baseline resistance test or for whom no test data was available, all those with viral load measurements available at least four months after the initiation of ART showed an adequate initial virological treatment response. This is defined as a decrease to below 200 copies/ml. No subsequent viral breakthrough (above 200 copies/ml) was recorded, except in two individuals who temporarily interrupted the use of ART. They eventually re-suppressed after restarting the same ART regimen. The median duration of follow-up after the start of ART was 76.6 (IQR 33.4-126.3) weeks.

Table 1: *Characteristics of individuals with and without available information on prior PrEP use*

	Info on PrEP available	No info available	p-value
Number of subjects	735 (29.4%)	1765 (70.6%)	
Age	37.6 (29.3-48.7)	38.1 (28.9-49.6)	0.975
Gender			<.001
Cisgender male	616 (83.8%)	1406 (79.7%)	
Cisgender female	97 (13.2%)	320 (18.1%)	
Transgender male	5 (0.7%)	1 (0.1%)	
Transgender female	17 (2.3%)	38 (2.2%)	
Dutch origin	370 (50.3%)	814 (46.1%)	0.059
Transmission category			<.001
MSM	505 (68.7%)	1033 (58.5%)	
Heterosexual transmission	176 (23.9%)	454 (25.7%)	
Other transmission categories	54 (7.3%)	278 (15.8%)	
Recent HIV inf. (<365 days after last neg. test)	206 (28.0%)	335 (19.0%)	<.001
CD4 at HIV diagnosis	376 (180-600)	360 (154-557)	0.012

Table 2: Comparison of individuals with and without prior use of PrEP

	Prior use of PrEP	No prior use	p-value
Number of subjects	75 (10.2%)	660 (89.8%)	
Age	31.2 (26.2-40.9)	38 (29.7-49.7)	<.001
Gender			<.001
Cisgender male	74 (98.7%)	542 (82.1%)	
Cisgender female	0 (0.0%)	97 (14.7%)	
Transgender male	1 (1.3%)	4 (0.6%)	
Transgender female	0 (0.0%)	17 (2.6%)	
Dutch origin	34 (45.3%)	336 (50.9%)	0.395
Transmission category			<.001
MSM	71 (94.7%)	434 (65.8%)	
Heterosexual transmission	1 (1.3%)	175 (26.5%)	
Other transmission categories	3 (4.0%)	51 (7.7%)	
Recent HIV inf. (<365 days after last neg. test)	59 (78.7%)	147 (22.3%)	<.001
CD4 at HIV diagnosis	570 (360-740)	360 (170-584)	<.001
Reasons for not having used PrEP			
Did not know of PrEP		92 (13.9%)	
Wanted PrEP but had no access		44 (6.7%)	
Presumed to be at low risk for HIV		87 (13.2%)	
Knew of PrEP but did not want to use it		26 (3.9%)	
Tested positive at PrEP intake		39 (5.9%)	
Was on PrEP waiting list		4 (0.6%)	
Unknown		368 (55.8%)	

Table 3: characteristics of individuals who reported prior use of PrEP prior to or after the start of the national PrEP pilot program in September 2019

	2018-01 to 2019-09	2019-10 and later	p-value
Number of subjects	30 (40.0%)	45 (60.0%)	
Age	29.3 (25.6-36.3)	32.1 (27.4-46.4)	0.063
Gender			1.000
Cisgender male	30 (100%)	44 (97.8%)	
Transgender male	0 (0.0%)	1 (2.2%)	
Dutch origin	12 (40.0%)	22 (48.9%)	0.486
Transmission category			0.260
MSM	27 (90.0%)	44 (97.8%)	
Heterosexual transmission	1 (3.3%)	0 (0.0%)	
Other transmission categories	2 (6.7%)	1 (2.2%)	
Recent HIV inf. (<365 days after last neg. test)	23 (76.7%)	36 (80.0%)	0.778
Days between last neg. test and first CD4)	132 (55-216)	201 (95-347)	0.105
CD4 at HIV diagnosis	585 (420-750)	570 (347-740)	0.646
PrEP provider			0.201
Provider in the Netherlands	10 (33.3%)	27 (60.0%)	
- Public Health Service	4 (40.0%)	11 (40.7%)	
- HIV treatment center	0 (0.0%)	3 (11.1%)	
- Family practitioner	5 (50.0%)	13 (48.1%)	
- No info	1 (10.0%)	0 (0.0%)	
Provider outside of the Netherlands	4 (13.3%)	3 (6.7%)	
Buyers club/internet/store outside of the Netherlands	8 (26.7%)	8 (17.8%)	
From friend living with HIV	1 (3.3%)	1 (2.2%)	
No info	7 (23.3%)	6 (13.3%)	
ART used for PrEP			0.462
TDF/FTC	14 (46.7%)	26 (57.8%)	
Genvoya	0 (0.0%)	1 (2.2%)	
Unspecified	16 (53.3%)	18 (40.0%)	
ART schedule			0.786
On demand	5 (16.7%)	12 (26.7%)	
Daily	8 (26.7%)	12 (26.7%)	
Intermittent	3 (10.0%)	2 (4.4%)	
Unknown	13 (43.3%)	17 (37.8%)	
Used PrEP <1 week	1 (3.3%)	2 (4.4%)	

	2018-01 to 2019-09	2019-10 and later	p-value
Routine medical check-ups while on PrEP			0.754
Public Health Service	5 (16.7%)	14 (31.1%)	
Family practitioner	4 (13.3%)	7 (15.6%)	
HIV treatment center	2 (6.7%)	3 (6.7%)	
Other healthcare provider	1 (3.3%)	1 (2.2%)	
No medical check-ups	6 (20.0%)	7 (15.6%)	
No info	12 (40.0%)	13 (28.9%)	
Duration of PrEP use (days)	171 (36-428)	182 (30-599)	0.898
Days between last PrEP use and testing HIV-positive	39 (1.5-107)	104 (0-232)	0.200
Tested HIV-positive while on PrEP	14 (46.7%)	14 (31.1%)	0.225
HIV-negative test performed after last dose of PrEP			0.588
Yes	8 (50.0%)	13 (41.9%)	
No	6 (37.5%)	16 (51.6%)	
Unknown	2 (12.5%)	2 (6.5%)	
Seroconverted in the Netherlands or abroad			0.305
In the Netherlands	14 (46.7%)	27 (60.0%)	
Abroad	10 (33.3%)	8 (17.8%)	
Unknown	6 (20.0%)	10 (22.2%)	
Documented acute HIV infection (Fiebig 1-5)	2 (6.7%)	6 (13.3%)	0.464
Resistance test performed after testing HIV-positive	16 (53.3%)	30 (66.7%)	0.334
Resistance test findings in RT *			
M184V/I	4 (25.0%)	5 (16.7%)	
K65R	0 (0.0%)	1 (3.3%)	
V74I	0 (0.0%)	2 (14.3%)	
V103R	0 (0.0%)	2 (6.7%)	
V108I	0 (0.0%)	2 (6.7%)	
E138A	1 (6.3%)	3 (10.0%)	
No RT RAMs, only wild type or polymorphisms	12 (75.0%)	20 (66.7%)	
Resistance profile in RT **			
M184VI	3 (75.0%)	4 (40.0%)	
K65R,V108I,E138A,M184VI	0 (0.0%)	1 (10.0%)	
E138A,M184VI	1 (25.0%)	0 (0.0%)	
E138A	0 (0.0%)	2 (20.0%)	
V103R	0 (0.0%)	1 (10.0%)	
V74I	0 (0.0%)	1 (10.0%)	
V74I,V103R,V108I	0 (0.0%)	1 (10.0%)	

Legend: ** categories not mutually exclusive; ** complete RAM profile in RT.*