Long-term protection from HIV infection with oral HIV pre-exposure prophylaxis in gay and bisexual men: findings from the expanded and extended EPIC-NSW prospective implementation study

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Summary

Background Daily pre-exposure prophylaxis (PrEP) is effective in preventing HIV, but few long-term data are available on effectiveness and adherence in real-world settings. Here, we report trends in HIV incidence over 3 years in individuals at high risk who were prescribed PrEP in New South Wales (NSW), as well as adherence before the transition to subsidised PrEP.

Methods Expanded PrEP Implementation in Communities–New South Wales (EPIC-NSW) was a pragmatic, prospective, single-arm, implementation study of daily, oral PrEP in 31 sites (sexual health clinics, general practices, and a hospital) in NSW, Australia. Eligible participants were HIV-negative adults (aged ≥18 years) who were at high risk of HIV infection as defined in local PrEP guidelines. Participants were prescribed coformulated (once-daily, oral tablet) tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg) as HIV PrEP and were followed up with HIV testing, sexually transmitted infection testing, and PrEP dispensing. Originally planned for 3700 participants followed for 1 year, the study was expanded so that all eligible participants in the state could obtain PrEP and extended until publicly subsidised PrEP became available in Australia. The primary outcome was new HIV infection among all participants who were dispensed PrEP at least once and had at least one follow-up HIV test result. Adherence was estimated by medication possession ratio (MPR), defined as the proportion of PrEP pills dispensed in 90 days, assuming daily dosing. This study is registered with ClinicalTrials.gov, NCT02870790.

Findings Between March 1, 2016, and April 30, 2018, we enrolled 9709 participants. 9596 participants were dispensed PrEP, of whom 9448 (98·3%) were gay or bisexual men. Participants were followed up until March 31, 2019, with at least one follow-up HIV test available in 9520 (99·2%) participants. Mean MPR declined from 0·93 to 0·64 from the first to the ninth quarter. There were 30 HIV seroconversions over 18 628 person-years, an incidence of 1·61 per 1000 person-years (95% CI 1·13–2·30). Being younger, living in a postcode with fewer gay men, reporting more risk behaviours at baseline, and having an MPR of less than 0·6 were each univariately associated with increased HIV incidence. In the final year of follow-up, when PrEP was mostly purchased rather than provided free by the study, HIV incidence remained low at 2·24 per 1000 person-years (1·46–3·44).

Interpretation HIV incidence remained low over up to 3 years of follow-up, including during a transition from study-provided to publicly subsidised PrEP. In a setting of affordable PrEP and associated health-care services, very low HIV incidence of 1 to 2 per 1000 person-years can be maintained in gay and bisexual men who were previously at high risk.

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Introduction

Oral HIV pre-exposure prophylaxis (PrEP) consisting of coformulated tenofovir and emtricitabine is highly effective in preventing HIV infection in adherent gay and bisexual men.[1–3] In New South Wales (NSW), Australia, large-scale roll-out of PrEP started on March 1, 2016, through a state-wide implementation research study, the Expanded PrEP Implementation in Communities (EPIC-NSW) study. The project aimed to provide rapid high-level PrEP coverage to those at high risk, predominantly gay and bisexual men. In the 12 months after the initial recruitment target was met, the incidence of

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Research in context

Evidence before this study

We searched PubMed for studies published in English from Jan 1, 2010, to July 31, 2020, with the terms "HIV", "pre-exposure prophylaxis", "men who have sex with men", and "long term impact". Randomised controlled trials have shown that HIV pre-exposure prophylaxis (PrEP) using coformulated tenofovir disoproxil fumarate and emtricitabine is close to 100% effective in preventing HIV in adherent men who have sex with men. PrEP adherence tends to decline with time after the first receipt of PrEP, and it has been widely suggested that this might compromise long-term efficacy. Studies reporting PrEP efficacy in men who have sex with men have been randomised trials or relatively short-term, open-label extension studies with up to 18 months of follow-up. No published data exist on the efficacy of PrEP in large samples of men who have sex with men receiving PrEP for longer periods of time, and few data are available on the continuing efficacy in men who have sex with men who transition to receive PrEP in real-world clinical settings.

Added value of this study

To our knowledge, this is the first large-scale study to show efficacy of PrEP over a follow-up period of up to 3 years. The EPIC-NSW study was a prospective implementation study in New South Wales, Australia, of HIV PrEP in almost 10 000 people at high risk of HIV infection, of whom 98·5% were gay or bisexual men and 0·9% were transgender. Participants were followed up for a median of 1·98 years (IQR 1·38–2·63). The final year of follow-up was a period of transition from PrEP that was provided free by the study to PrEP provided through Australia's health-care system, requiring a copayment of approximately AU$40 per month. Mean medication possession ratio (MPR) during the time in which participants received study drug declined from 0·93 to 0·64 from the first to the ninth quarter. 30 men became HIV infected, an overall incidence of 1·61 per 1000 person-years, and all were non-adherent to daily PrEP at the time of infection. At the individual level, low MPR, younger age, reporting more risk behaviours, and living in a postcode with a lower proportion of gay men were related to higher HIV incidence. Despite declining mean MPR, HIV incidence increased only minimally, and was 2·24 per 1000 person-years in the third year of follow-up. Overall incidence was 92% less than the historically expected incidence of at least 20 per 1000 person-years in the absence of PrEP. In participants who maintained a mean MPR of 1·0 over follow-up, HIV incidence was zero over almost 5000 person-years.

Implications of all the available evidence

In our setting, with universal health care, highly subsidised availability of PrEP, and health literacy built and maintained by a gay community organisation (ACON), PrEP remained highly effective over a follow-up period of up to 3 years, including during a period of transition to purchased PrEP. Although low MPR was associated with increased HIV risk at the individual level, HIV incidence in the cohort overall did not increase as overall mean MPR declined, suggesting that most men who stopped using PrEP were no longer at risk of HIV. The study provides reassuring real-life data that the efficacy of long-term daily oral PrEP is close to 100% in adherent gay and bisexual men.

HIV infection in 3700 participants at high risk was 0·48 per 1000 person-years, which was 98% lower than the expected incidence of at least 20 per 1000 person-years.[4]

Published longer-term data on PrEP adherence and efficacy in real-world settings are scarce. Concerns have been raised that longer-term protection from HIV might be compromised by high rates of PrEP discontinuation.[5–11] After publication of the initial EPIC-NSW results in 2018, study recruitment and follow-up was extended to ensure that NSW residents who met eligibility criteria could access PrEP. Recruitment continued for a further 18 months, and the final number of participants was 2·5 times greater than in the original study cohort. Recruitment ceased on April 30, 2018, which was after subsidised PrEP became available through the Australian Government Pharmaceutical Benefits Scheme on April 1, 2018. After April, 2018, study participants who wanted to continue PrEP were transitioned to subsidised PrEP. Follow-up of EPIC-NSW study participants ceased on March 31, 2019.

Here we report trends in HIV incidence over 3 years in individuals at high risk who were prescribed PrEP in NSW, as well as adherence before the transition to subsidised PrEP. The final year of follow-up was after the date that PrEP was subsidised through Australia's public health-care system.

Methods

Study design and participants

EPIC-NSW was a pragmatic, prospective, single-arm, implementation study, the design of which has been described previously.[4,12] In brief, the study enrolled patients at 31 sites, including sexual health clinics, general practices, and one hospital, at urban and regional locations across the state of NSW and in the Australian Capital Territory (ACT). Eligible participants were HIV-negative adults (aged ≥18 years) who were at high risk of HIV infection as defined in local PrEP guidelines.[12]

The initial EPIC-NSW study protocol specified a sample size of 3700 people,[12] which was reached after 8 months of recruitment on Oct 31, 2016. As specified in the protocol, the primary outcome paper reported HIV incidence in the cohort in the 12 months after recruitment.[4] Leading up to October, 2016, the weekly recruitment rate remained high,[4] showing continuing demand for PrEP from gay and bisexual men with high risk of infection at study clinics.

To ensure additional individuals in NSW who were at high risk were able to receive PrEP in this setting where PrEP had not yet been approved for public funding, the study team elected to continue recruitment without limiting numbers. The formally amended protocol was approved by the St Vincent's Hospital (Darlinghurst) human research ethics committee. Recruitment continued until April 30, 2018, and after that date participants who wanted to continue PrEP were transitioned from free drug provision by the study to PrEP subsidised by the Australian Government, requiring a monthly copayment of approximately AU$41 ($6·50 for pensioners and unemployed people). For participants who wished to continue PrEP but who were not permanent residents of Australia and who, therefore, were not eligible for government-subsidised PrEP, continuing free PrEP access was arranged through the EPIC-NSW study, or personal importation of affordable generic PrEP was facilitated by clinic sites. Follow-up for the primary outcome of HIV infection continued until March 31, 2019, representing a maximum of 3 years and 1 month follow-up of individuals dispensed PrEP. The final year of study follow-up was thus a period during which participants mostly received subsidised PrEP rather than free study PrEP. Participants provided written, informed consent.

Procedures

Participants were prescribed coformulated (once-daily, oral tablet) tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg) as HIV PrEP. Follow-up was based on NSW PrEP guidelines.[4] Visits for HIV testing, sexually transmitted infection testing, and PrEP dispensing were required at 1 month, 3 months, and every 3 months thereafter. Sites kept written logs of the number of PrEP pills dispensed at each visit for the period that participants received study drug, but dispensing data were not available for subsidised PrEP, which occurred after April 30, 2018. The monthly number of dispensed study drug pills had declined by 42% by July, 2018, and by 97% by December, 2018.

Outcomes

The primary outcome was new HIV infection among all enrolled participants who were dispensed PrEP at least once and had at least one follow-up HIV test result. The method of data collection for HIV infections in EPIC-NSW has been described previously.[4] Briefly, data on new HIV infections were comprehensively obtained from new HIV infections notified to the study coordinators as a protocol-defined serious adverse event, electronic medical records, and data linkage with the NSW State HIV register in 7448 consenting participants (78% of 9520 total participants included in the cohort analysis; appendix p 1).

Statistical analysis

To measure adherence, medication possession ratio (MPR) was based on dispensing logs of study medication. Quarterly MPR was calculated as the number of PrEP pills dispensed in a quarter, plus the number of pills carried over from the previous quarter assuming daily dosing, divided by 90 days, to a maximum value of 1. Although dispensing logs for study medication were kept throughout the study, after April 30, 2018, and increasingly over the subsequent year, it was possible that participants received subsidised PrEP, which was not recorded by the study. Therefore, it was only possible to measure adherence accurately for the period March 1, 2016, to April 30, 2018. For HIV seroconverters, we collected data on recent adherence through reports of serious adverse events.

For HIV incidence, we calculated person-years at risk from the date of first PrEP dispensing until the first of either the date of a confirmed HIV-positive test or the last HIV-negative test. In addition, in participants who gave consent to data linkage, we set their last day of follow-up as March 31, 2019, on the basis that new HIV diagnoses made in the state of NSW in these individuals would have been detected by data linkage. Participants who formally withdrew from the study were censored at their date of withdrawal. We did a prospective analysis of HIV incidence, which included all participants who were dispensed at least one dose of study drug. No imputations were made for ongoing use of PrEP or other missing data.

We used Poisson regression to determine predictors that were associated with incident HIV infection. Because of the small number of cases, no multivariable analyses were done. Incidence rate ratios and their corresponding 95% CIs were reported. Variables considered included age, risk assessment categories at baseline relating to study eligibility criteria and total number of categories met, country of birth, and proportion of adult male population in the postcode of residence that was gay. These postcodes were defined on the basis of a published estimate that combined Australian census data on the population of cohabiting male couples with survey data on the proportion of gay men who cohabited with a regular partner.[13] We grouped non-Australian country of birth based on the observed distribution as countries in Asia, an English-speaking high-income country (Canada, Ireland, New Zealand, the UK, and the USA), and other countries. We separately calculated HIV incidence by years since PrEP was first dispensed and by calendar year. We examined the association between HIV incidence and mean MPR between first PrEP dispensing and April 30, 2018. For adherence analyses only, we restricted analysis to those who had 6 months or more of follow-up data on adherence, comprising those who were recruited before Nov 1, 2017.

Statistical analyses were done with Stata version 16.1. The study was registered with ClinicalTrials.gov, NCT02870790. See Online for appendix

Role of the funding source

As an implementation study, the NSW Ministry of Health had a role in the study design, conduct and analysis of the

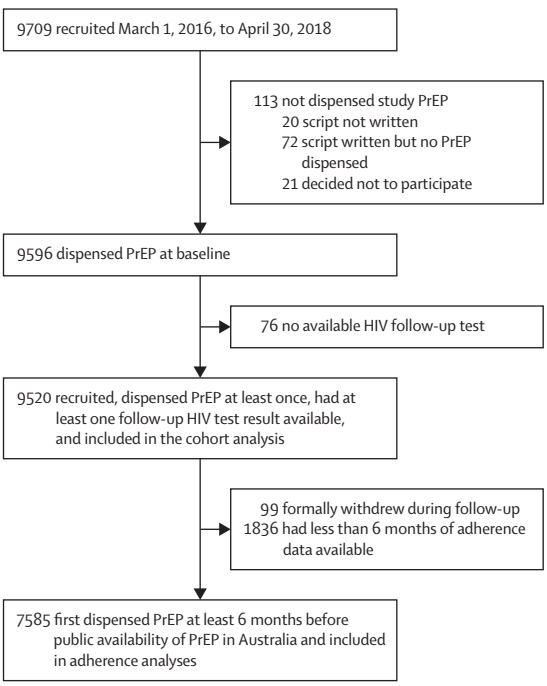

Figure: **The EPIC-NSW cohort**
Follow-up is defined as having had an HIV test or PrEP script dispensed after the baseline visit. PrEP=pre-exposure prophylaxis.

	n (%)
Age, years	
18–24	1119 (11·7%)
25–34	3853 (40·2%)
35–44	2492 (26·0%)
≥45	2132 (22·2%)
Gender	
Male	9455 (98·5%)
Female	14 (0·2%)
Transgender, female	62 (0·7%)
Transgender, male	23 (0·2%)
Other	42 (0·4%)
Sexual identity	
Gay or homosexual	8781 (91·5%)
Bisexual	667 (7·0%)
Heterosexual	51 (0·5%)
Other	97 (1·0%)
Place of birth	
Australia	5059 (52·7%)
English-speaking, high-income country*	1049 (10·9%)
Asia	1235 (12·9%)
Europe, excluding UK and Ireland	357 (3·7%)
Africa	153 (1·6%)
South America, Central America, or Caribbean	371 (3·9%)
Other countries	171 (1·8%)
Missing data	1201 (12·5%)
Proportion of adult male population of postcode who were gay	
≥20%	2912 (30·4%)
10–19%	846 (8·8%)
5–9%	1120 (11·7%)
<5%	4618 (48·1%)
Missing data	100 (1·0%)
Type of recruiting site	
Public sexual health clinic	4441 (46·3%)
Private general practice	4707 (49·1%)
Hospital	448 (4·7%)

PrEP=pre-exposure prophylaxis. *Canada, Ireland, New Zealand, the UK, the USA.

Table 1: **Enrolment characteristics of 9596 EPIC-NSW study participants who were dispensed PrEP at least once**

study, data collection, data analysis, data interpretation, and writing of the report. Gilead Science had no role study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 1, 2016, and April 30, 2018, 9709 participants were recruited, of whom 9596 (98·8%) were dispensed PrEP at least once (figure) and were followed up for 18 628 person-years. This represented an additional 5896 participants dispensed PrEP and an additional 14 528 person-years of follow-up to data previously reported.[4]

The 9596 participants (table 1) had a median age of 34 years (IQR 28–43). At baseline, eligibility criteria were available for 9553 (99·6%) participants (table 2). Most participants reported recent receptive condomless anal intercourse with a casual partner, almost one in five reported recent crystal methamphetamine use, and a similar number reported a diagnosis of infectious syphilis, anal chlamydia, or anal gonorrhoea in the past 3 months (table 2). Few participants reported condomless anal intercourse with HIV-positive partners who did not have undetectable viral loads or being a participant in the preceding PrEP demonstration project, PRELUDE.[14] 6517 (67·9%) participants reported one of the behavioural eligibility criteria, 2534 (26·4%) reported two criteria, 482 (5·0%) reported three criteria, and 62 (0·6%) reported four or more criteria.

9520 (99·2%) of those who were dispensed PrEP had at least one follow-up HIV test available and were included in the cohort analysis (figure). 99 (1·0%) of 9520 formally withdrew during follow-up, most commonly because they no longer felt at risk of HIV (n=36), they had side-effects (n=20), or they moved away from NSW (n=14). All other participants remained under follow-up, regardless of whether they continued to take PrEP or continued to attend the study clinic.

7585 (79·0%) of the 9596 participants who were dispensed PrEP were recruited before Nov 1, 2017, and were included in the adherence analysis (figure); 2011 (21·0%) participants were classified as having insufficient adherence data. For study drug dispensed

	n (%)
Receptive condomless anal intercourse with at least one casual male partner of HIV-positive or unknown status	8904 (92·8%)
Diagnosis of infectious syphilis, anal gonorrhoea, or anal chlamydia	1687 (17·6%)
Use of crystal methamphetamine	1865 (19·4%)
Condomless anal intercourse with an HIV-positive regular partner who is not on antiretroviral therapy or has detectable viral load	596 (6·2%)
Previous PRELUDE study participant	186 (1·9%)
Eligibility criteria missing	43 (0·4%)

PrEP=pre-exposure prophylaxis.

Table 2: **High risk eligibility criteria in the 3 months before enrolment in 9596 participants enrolled and dispensed PrEP in the EPIC-NSW study**

between March 1, 2016, and April 30, 2018, the mean MPR during the first quarter of dispensing was 0·93, which declined to 0·82 in the second quarter (p<0·0001). After the second quarter, MPR declined substantially less rapidly but consistently with time, reaching 0·64 by the last (ninth) quarter in which dispensing data were available (p_{trend}<0·0001).

Between March 1, 2016, and March 31, 2019, there were 30 HIV seroconversions for an HIV incidence of 1·61 per 1000 person-years (95% CI 1·13–2·30) over a median 1·98 years of follow-up (IQR 1·38–2·63). All new HIV infections occurred in men, 29 were gay and one was bisexual. Incidence did not differ significantly by place of birth grouping (table 3). Younger age was associated with higher risk of HIV infection (p_{trend}=0·029) and decreased from 4·13 per 1000 person-years (95% CI 1·72–9·91) in those aged 18–24 years to 0·78 per 1000 person-years (0·29–2·09) in those aged 45 years and older (table 3). Men who resided in a postcode with a higher proportion (5% or more) of gay men had a lower incidence (0·91 per 1000 person-years, 95% CI 0·47–1·74) compared with men who lived in postcodes with a lower proportion of gay men (<5%; 2·32 per 1000 person-years, 1·50–3·60; p=0·019). When analysed by baseline risk criteria, HIV incidence was highest (3·69 per 1000 person-years, 2·10–6·50) in those who reported a recent diagnosis of anal gonorrhoea or chlamydia or infectious syphilis at baseline assessment. HIV incidence was higher in those who reported using crystal methamphetamine at baseline (3·02 per 1000 person-years, 1·71–5·31) than in those who did not (1·23 per 1000 person-years, 0·77–1·95; p=0·016). HIV incidence increased as the number of baseline risk criteria increased (p_{trend}<0·0001), from 1·05 per 1000 person-years (95% CI 0·61–1·81) in those reporting one risk criterion to 7·58 per 1000 person-years (1·07–53·84) in those who reported four or five risk criteria (p_{trend}<0·0001).

HIV incidence was lowest in the first year after participants were dispensed PrEP (1·09 per 1000 person-years, 95% CI 0·58–2·02) before increasing slightly to 2·10 per 1000 person-years (95% CI 1·24–3·55) in the second year of follow-up and 2·18 per 1000 person-years (0·98–4·86) in the third (p_{trend}=0·086; table 4). HIV incidence increased from 0·38 per 1000 person-years (0·05–2·71) in the first calendar year of the study to 2·24 per 1000 person-years (1·46–3·44) in the final calendar year (p_{trend}=0·018). HIV incidence was higher in those with a mean MPR during follow-up of less than 0·6 (4·76 per 1000 person-years, 2·96–7·66) than in those with a mean MPR of 0·6–1·0 (0·39 per 1000 person-years, 0·16–0·93; p<0·0001). In 2264 participants whose MPR during follow-up was 1·0, the incidence of HIV infection was 0 over 4802 person-years, and the upper

	Number of HIV seroconversions	Incidence per 1000 person-years	Incidence rate ratio (95% CI)	p value
Age				
18–24	5	4·13	1 (ref)	0·029*
25–34	12	1·78	0·43 (0·15–1·22)	..
35–44	9	1·61	0·39 (0·13–1·17)	..
≥45	4	0·78	0·19 (0·05–0·71)	..
Place of birth				
Australia	16	1·59	1 (ref)	0·85†
English-speaking high-income country‡	3	1·41	0·88 (0·26–3·03)	..
Asia	5	2·18	1·37 (0·50–3·73)	..
Other	2	1·01	0·64 (0·15–2·76)	..
Proportion of adult male population of postcode who were gay				
≥5%	9	0·91	1 (ref)	0·019
<5%	20	2·32	2·57 (1·17–5·63)	..
Risk criteria reported				
Receptive condomless anal intercourse with casual partner				
No	3	2·12	1 (ref)	..
Yes	27	1·57	0·74 (0·22–2·44)	0·62
Infectious syphilis or anal gonorrhoea or chlamydia				
No	18	1·17	1 (ref)	..
Yes	12	3·69	3·16 (1·52–6·55)	0·0020
Use of crystal methamphetamine				
No	18	1·23	1 (ref)	..
Yes	12	3·02	2·45 (1·18–5·09)	0·016
Condomless anal intercourse with HIV-positive regular partner with detectable viral load				
No	27	1·55	1 (ref)	..
Yes	3	2·42	1·56 (0·47–5·14)	0·47
Number of risk criteria reported				
1	13	1·05	1 (ref)	0·0006*
2	11	2·16	2·06 (0·92–4·60)	..
3	5	4·96	4·73 (1·69–13·26)	..
≥4	1	7·58	7·23 (0·94–55·41)	..
Recruiting site				
Public sexual health clinic	20	2·08	1 (ref)	0·11†
Hospital	1	1·28	0·62 (0·08–4·60)	..
Private general practice	9	1·10	0·53 (0·24–1·16)	..

PrEP=pre-exposure prophylaxis. *p_{trend}. †$p_{heterogeneity}$. ‡Canada, Ireland, New Zealand, the UK, the USA.

Table 3: **Association between baseline variables and incident HIV in the EPIC-NSW study in 9566 participants dispensed PrEP who had at least one follow-up HIV test**

	Number of HIV seroconversions	Incidence per 1000 person-years	Incidence rate ratio (95% CI)	p value
Years since first PrEP dispensed				
<1	10	1·09	1 (ref)	0·086*
1–2	14	2·10	1·93 (0·86–4·35)	..
2–3	6	2·18	2·01 (0·73–5·53)	..
Calendar period of follow-up				
Year 1 (March, 2016–February, 2017)	1	0·38	1 (ref)	0·018*
Year 2 (March, 2017–February, 2018)	8	1·20	3·15 (0·39–25·21)	..
Year 3 (March, 2018–March, 2019)	21	2·24	5·88 (0·79–43·69)	..
Mean MPR†				
<0·6	17	4·76	1 (ref)	<0·0001
0·6–1·0	5	0·39	0·08 (0·03–0·22)	..

MPR=medication possession ratio. PrEP=pre-exposure prophylaxis. *p_{trend}. †Mean MPR during follow-up was calculated for participants with at least 6 months of adherence data available.

Table 4: **Years since first dispensed PrEP, calendar period of follow-up, and mean MPR during follow-up and risk of HIV infection**

limit of the 95% CI of the incidence was 0·77 per 1000 person-years. There were only three HIV seroconversions in 4925 men who had a mean MPR greater than 0·8, and all of these were documented to be related to non-adherence to daily PrEP at the time of the exposure.

Discussion

In this cohort of almost 10 000 mostly gay and bisexual men who were dispensed PrEP and followed up for up to 3 years, there were only 30 new HIV infections, with a very low HIV incidence of 1·61 per 1000 person-years. This incidence was 92% less than the expected incidence of at least 20 per 1000 person-years in the absence of PrEP.[4] Among men who started PrEP, younger age, living in a postcode with fewer than 5% of men who were gay, and reporting more eligibility risk behaviours at baseline were all associated with increased HIV incidence. There was no significant increase in HIV incidence after the first year of follow-up and incidence remained at about 2 per 1000 person-years in the third year of follow-up. 3 years after the commencement of PrEP roll-out, in the year of transition from study-provided PrEP to subsidised PrEP, HIV incidence in the cohort had increased only slightly, and remained low, at 2·24 per 1000 person-years. Those who had a mean MPR of less than 0·6 during follow-up had a significantly higher incidence of 4·76 per 1000 person-years, compared with those with a higher MPR. In participants with a mean MPR during follow-up of 1, the incidence was 0 over almost 5000 person-years of follow-up. All 30 HIV seroconversions were observed when PrEP was not taken daily at the time of infection.

Those who were at higher HIV risk at baseline, as reflected in reporting a higher number of behavioural risk criteria, had higher HIV incidence. The association of younger age and residence outside of postcodes with more than 5% of men who were gay with higher HIV incidence is consistent with population-wide trends in NSW showing little if any decline in HIV diagnoses in men who have sex with men in these population subgroups.[4] Overseas-born men did not have higher HIV incidence in the cohort. These data suggest that, once linked to PrEP, overseas-born men are no more likely to acquire HIV than are Australian-born men. A combination of inadequate PrEP access and issues with PrEP adherence might underlie the lower levels of success in HIV prevention in the young and in those from outside of those Sydney postcodes where more than 5% of the male population is gay.[4]

The high rates of PrEP adherence that have been documented in short-term implementation projects are often not replicated in routine clinical settings, and might be associated with higher incidence of HIV seroconversion.[5,8–11] In our cohort, in the context of free or highly subsidised health care, the mean MPR had declined to 0·64 by the ninth quarter of follow-up, the last quarter for which we had complete data on drug dispensing. At the individual level, low MPR was associated with increased HIV incidence, indicating some inappropriate cessation of PrEP. However, despite the low mean MPR in the third year after first receipt of study PrEP, the HIV incidence remained low, at 2·24 per 1000 person-years. The continuing low HIV incidence might be illustrative of the fact that people do not need to take daily PrEP for long-term protection. Rather, they need to be adherent to PrEP during periods in which they are at risk, a concept that has been termed prevention-effective adherence.[15] The declining MPR that we documented could reflect an increasing frequency of participants periodically going on and off PrEP depending on risk behaviour, as opposed to inadequate adherence. Previous studies have shown that gay men have high levels of interest in taking short courses of PrEP during periods of increased risk.[16] The very low incidence of HIV we have documented, despite a low MPR, suggests that in our setting many of the men who had stopped taking PrEP were no longer at risk of HIV. This might not be the case in other settings in which PrEP and associated care is costly to individuals. Another contributing factor towards the continuing low incidence we documented might be the high coverage of PrEP in gay men who have casual partners, which had reached 50% in Australian behavioural surveillance in 2018,[17] creating partial herd protection, and levels of HIV testing and treatment that exceed the UNAIDS 90-90-90 targets in this population.[18]

The occurrence of 30 HIV infections in EPIC-NSW participants who had been dispensed PrEP but who had ceased PrEP or not taken PrEP at the time of HIV infection highlights that some gay and bisexual men who stop PrEP might not appropriately restart PrEP when they re-enter periods of risk.[19] Providing complete long-term protection from HIV infection remains a substantial

challenge. Ultimately, forms of biomedical prevention that do not require years of daily adherence, such as long-term injectable or implantable PrEP,[20] or ideally an HIV vaccine, will probably be required for elimination of HIV transmission.

In the USA, Centers for Disease Control and Prevention guidance states that PrEP, if taken consistently, reduces the risk of acquiring HIV sexually by about 99%.[21] Globally, there have been at least six case reports of HIV infection in people who have been documented to be adherent to daily PrEP, and the majority have been in cases where the transmitted HIV has been resistant to emtricitabine.[22] In our cohort, among men who had a mean MPR of 1, we documented no new HIV infections in close to 5000 person-years of follow-up. This provides reassuring real-life data that the efficacy of daily oral PrEP is close to 100% in adherent gay and bisexual men.

In our context, an important issue was whether the very low incidence of HIV we initially found[4] could be maintained after PrEP provision was integrated into the Australian health-care system. We continued to follow up the cohort for 12 months after the transition from study provision of free PrEP to subsidised PrEP. It was very encouraging that the HIV incidence we documented in the final year of study follow-up remained low, at 2·24 per 1000 person-years. In our setting, transition to PrEP associated with a modest copayment of about $40 was not associated with an increase in HIV incidence. Other treatment-related costs, including clinic visits and pathology testing, are free of any charge at public sexual health clinics, and highly subsidised at private general practice clinics.

State-wide surveillance data in NSW showed continuing declines in HIV diagnoses in men who have sex with men between 2015, the last full year before PrEP roll-out, and 2019. State-wide, there was a 25% decrease in HIV notifications (from 285 to 215) and there was a larger decline, of 40%, in early-stage HIV notifications, reflecting HIV infections acquired in the past 12 months (from 141 to 84).[23,24] Decreases in early infections occurred in both Australian-born (40% decline) and overseas-born (42% decline) individuals.[23,24] Decreases in early infections were of a much greater magnitude in men residing in postcodes with more than 20% of men who were gay (70% decline) than in postcodes where 5–19% of men were gay (48% decline) or postcodes in which fewer than 5% of men were gay (14% decline; appendix p 2).[24] Although decreases occurred in all age groups, the smallest decline (6%) was in men younger than 25 years.[24] HIV notifications in heterosexual people and injecting drug users were stable over this period.[25] Taken overall, we interpret these surveillance data as being consistent with rapid declines in HIV incidence in men who have sex with men in NSW that were greatest in inner city areas of Sydney with large populations of gay men. The smaller declines in incidence in parts of NSW with smaller populations of resident gay men, and in the young, highlight future HIV prevention challenges.

EPIC-NSW is one of the largest studies of PrEP implementation, with close to 10 000 participants and more than 18 000 person-years of follow-up. However, the study had several limitations. Although complete data on drug dispensing were available for study-provided PrEP, adherence data were not available after transition to subsidised PrEP. However, the fact that HIV incidence remained at about 2 per 1000 person-years suggests that the transition occurred successfully, without a clinically important drop off in prevention-effective PrEP adherence among individuals at high risk of infection. In the overall EPIC-NSW study, our data on adherence were limited to estimation based on dispensing records allowing calculation of MPR. We did not have measures comparing behaviour and adherence over specific time periods, so-called prevention-effective adherence, in the whole cohort, but this was measured in a substudy.[26] Our follow-up of up to 3 years was longer than most studies, but is still a short period of a person's lifetime experience of HIV prevention. Studies with longer-term follow-up will be required to examine the sustainability of long-term daily PrEP, and to measure the complexity of how gay men start and stop PrEP in relation to both episodic and periodic HIV risk. The predictors of HIV infection that we have identified were relatively few, and given the small number of infections, we did not do a multivariate analysis of risk. Our finding of continuing low incidence might not be generalisable to settings without universal health care.

The final follow-up of the EPIC-NSW study provides reassuring data that extended provision of PrEP for a period of up to 3 years, associated with a transition to off-study PrEP provision with a moderate drug copayment, was associated with a continuing very low HIV incidence and a population-wide reduction in recently acquired HIV infections of about 40%. PrEP failures in our large cohort only occurred in association with non-adherence, suggesting a real-world efficacy in adherent individuals that is close to 100%.

Contributors

AEG, FJ, BRB, BY, MAH, JA, SV, TV, NJD, DJS, CS, IZ, and RG made substantial contributions to the conception or design of the work, and the analysis and interpretation of data for the work. GC, SC, EO, DAB, KB, MB, CJC, AC, DC, RF, DAL, JL, SM, AM, CO, KP, CP, PR, DS, CTMS, DJT, and EV made substantial contributions to the acquisition and interpretation of data for the work. AEG drafted the work. FJ, BRB, BY, MAH, JA, SV, TV, NJD, IZ, DAB, KB, MB, CJC, AC, DC, RF, DAL, JL, SM, AM, CO, KP, CP, PR, DS, CTMS, DJT, and EV revised drafts critically for important intellectual content. FJ and SV accessed and verified the data for the study. ND and NR made substantial contributions to the acquisition and interpretation of data and critically revised drafts for important intellectual content. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had full access to all the data in the study.

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Declaration of interests

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Data sharing

Deidentified data, a data dictionary, and the study protocol will be available to be shared with outside researchers upon approval of submitted proposals. A team of EPIC-NSW investigators will review proposals to ensure they do not overlap with previously approved proposals or analyses in progress. Investigators can submit proposals to the corresponding author.

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