Discontinuation, suboptimal adherence, and reinitiation of oral HIV pre-exposure prophylaxis: a global systematic review and meta-analysis

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Summary

Background Poor adherence to oral HIV pre-exposure prophylaxis (PrEP) diminishes its clinical and public health benefits. This study synthesises evidence regarding discontinuation, adherence, and reinitiation of PrEP among geographically diverse PrEP users.

Methods We did a systematic review and meta-analysis evaluating studies published in MEDLINE, Embase, and Cochrane Central Register of Controlled Trials from inception to Dec 18, 2020. We included longitudinal studies that presented data for PrEP discontinuation, defined as investigator-reported loss to follow-up or participant self-reported PrEP stoppage. Data were extracted from published reports and assessed for risk of bias. We used a random-effects meta-analysis to pool estimates of discontinuation and I^2 and τ^2 to evaluate heterogeneity. This study is registered with PROSPERO, CRD42020155675.

Findings We identified 4129 records, of which 59 articles were included (n=43 917 participants). 41·0% (95% CI 18·8–63·5) of participants discontinued PrEP within 6 months, with the highest rates in observational studies. The discontinuation rate in sub-Saharan Africa (47·5%, 95% CI: 29·4–66·4%) was higher than in other regions (p<0·001). Discontinuation rates were lower in studies with adherence interventions than in those without (24·7% *vs* 36·7%, p=0·015). Gay or bisexual men who have sex with men and transgender women offered daily or non-daily dosing options had lower discontinuation rates than those offered daily dosing alone (21·6% *vs* 31·5%; p<0·001). The pooled suboptimal adherence within 6 months was 37·7% (95% CI 8·4–66·9). Among people who discontinued PrEP, 47·3% (95% CI 31·5–63·2) reinitiated PrEP within 1 year of PrEP initiation. The included studies had poor quality in terms of study design, with a moderate risk of bias.

Interpretation Strategies to encourage reinitiating PrEP for new or persistent risk should be a focus of future PrEP implementation strategies.

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Introduction

Oral pre-exposure prophylaxis (PrEP) for HIV, using tenofovir disoproxil fumarate or tenofovir alafenamide in combination with emtricitabine, has shown high effectiveness in preventing HIV infection when the drug is used with high adherence.[1–5] In 2016, WHO recommended that people at substantial risk of HIV infection should be offered PrEP as part of comprehensive HIV prevention.[6] By the end of 2020, 928 750 individuals were receiving PrEP in 76 countries and regions,[7,8] and 54 countries have included PrEP as part of national HIV-prevention strategies alongside clinical guidelines for PrEP implementation.[9–14]

However, high rates of premature PrEP discontinuation have hindered this prevention strategy. The rate of discontinuation within 1 year of PrEP initiation varies enormously across populations, ranging from 2% to 80% among gay, bisexual, and other men who have sex with men (GBMSM) and transgender women,[15–18] serodiscordant couples,[19–21] female sex workers,[22,23] and people who inject drugs.[24] Importantly, HIV seroconversion frequently occurs shortly after the discontinuation of PrEP,[25–27] and HIV incidence rebounds from 0·0–0·1/100 person-years among PrEP users to 2·1–3·6/100 person-years among people who stop PrEP.[18,28]

Data summarising PrEP discontinuation are scarce. Gaps in knowledge regarding stopping and restarting PrEP could compromise maximising the benefit of this prevention strategy.[29] When defined as the proportion of enrolled or initiated study participants who returned for a follow-up visit, 63% of people continued on PrEP at 6 months and 71% of people continued at 12 months;[30] however, this definition included people retained in a study but who had stopped using PrEP.[24,31–33] Given increasingly recognised dynamic patterns of PrEP use, it is crucial to appreciate the full scope of PrEP use, including the correlates of continuation, reasons for discontinuation, and reinitiation among people who discontinued use. A comprehensive

Research in context

Evidence before this study

We searched MEDLINE, Embase, and Cochrane Central Register of Controlled Trials with the search terms "oral pre-exposure prophylaxis", "stop", "discontinuation", "drop out", "retention", or "adherence" (see appendix p 10 for full search terms) for studies published in English presenting data on discontinuation of oral pre-exposure prophylaxis (PrEP) from inception to Dec 18, 2020. One previous meta-analysis of PrEP continuation included studies published up to 2018, and results suggested that PrEP retention was 63% at 6-month follow-up. However, the definition of continuation had clinically significant gaps as it did not account for people retained in studies but who had stopped PrEP, nor those who transferred care; furthermore, since 2018, crucial new evidence surrounding PrEP persistence has emerged. An updated, comprehensive summary of the evidence surrounding PrEP discontinuation, suboptimal adherence, and reinitiation among geographically diverse populations at elevated risk of HIV (ie, key populations) is crucial.

Added value of this study

We did a global systematic review and meta-analysis to update and extend previous work by quantifying PrEP discontinuation, suboptimal adherence among those who continued PrEP, and reinitiation among those who stopped PrEP during the observed period of follow-up. Our results support previous studies, showing that PrEP discontinuation in the first 6 months following initiation is common worldwide. By accounting for suboptimal adherence (ie, adherence that would not be expected to result in HIV-protective drug levels), we estimate that less than 30% of PrEP initiators received the HIV-protective benefit of PrEP within 6 months of initiation. Demonstration projects (ie, so-called real-world settings), studies conducted in sub-Saharan Africa, and studies that did not include an adherence intervention had higher PrEP discontinuation than did randomised controlled trials, studies conducted in other regions, and studies that included an adherence intervention.

Implications of all the available evidence

Our analysis suggests that PrEP discontinuation was common within 6 months of PrEP initiation in a wide range of geographical locations and HIV risk populations. Poor PrEP persistence, with premature discontinuation, suboptimal adherence, and infrequent restarts despite persistent or recurrent risk, fundamentally undermines efforts to maximise the prevention potential of PrEP. Efforts to prevent premature discontinuation and support reinitiation of PrEP for new or persistent risk need to be strengthened and should be a focus of future PrEP implementation strategies.

review of evidence on oral PrEP adherence, discontinuation, and reinitiation is urgently needed. Although alternative forms of PrEP (eg, long-acting injectable PrEP and topical microbicide) are now approved and others (eg, long-acting implants and subdermal patches) are in development, evidence synthesised from studies of oral PrEP will inform and improve the implementation of PrEP in the future.

In this Article, we synthesise estimated rates of oral PrEP discontinuation, suboptimal adherence among people who continued using PrEP, and reinitiation among those who discontinued across key populations from diverse geographical locations. We summarise the potential reasons and correlates related to PrEP discontinuation.

Methods

Search strategy and selection criteria

We did this systematic review and meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (figure 1).[34] We searched MEDLINE, Embase, and Cochrane Central Register of Controlled Trials for studies reporting on adherence and persistence of oral PrEP with the following terms: "oral pre-exposure prophylaxis", "stop", "discontinuation", "drop out", "retention", or "adherence" (full search terms are in the appendix p 10). We also searched trial registries from ClinicalTrials.gov and abstracts from previous International AIDS Conferences and Conference on Retroviruses and Opportunistic Infections meetings to include published literature and ongoing PrEP studies. We searched for studies published in English from database inception to Dec 18, 2020. Only longitudinal studies (ie, randomised controlled trials and longitudinal

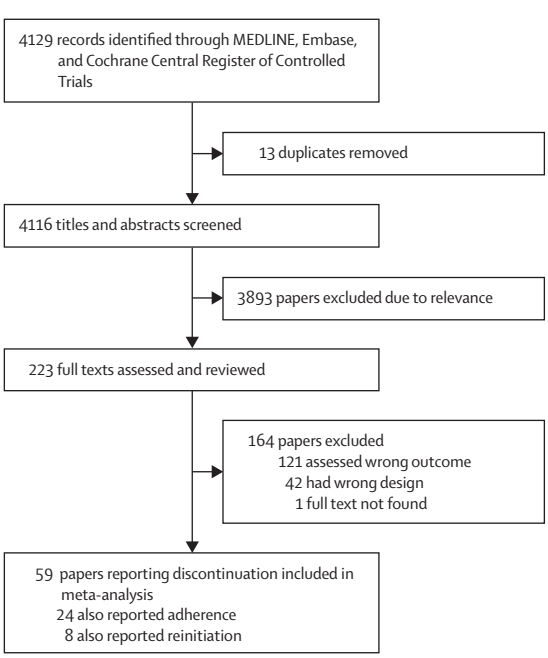

Figure 1: **Study selection**

observational studies) were included in the systematic review and meta-analysis. Two investigators (CL and ZH) independently screened the titles and abstracts, and discrepancies were resolved by a third investigator (JZ). Full texts for the screened studies were read to extract data for the proportions of PrEP users who discontinued PrEP. In the event of multiple publications from one study population, we included the publication with the largest sample size that also had key PrEP discontinuation or adherence outcomes. Among the included discontinuation studies, we investigated the proportion of participants with suboptimal adherence among those who continued PrEP and reinitiation among those who discontinued. For further details of the methods, see the protocol.

For **protocol** see https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=155675

Definitions and measurements

Discontinuation was defined as participants who self-reported stopping PrEP, study team or medical staff who reported having stopped PrEP refills, or participants who were lost to follow-up (LTFU) without reaching a predefined study endpoint and with no evidence of transferring care. The definition of LTFU included participants who did not return for scheduled follow-up visits, who could not be reached by study team or medical staff, or those without possession of tenofovir disoproxil fumarate or emtricitabine (calculated by retrospective chart review and pharmacy refill data) despite assumed ongoing HIV risk. This definition excluded participants who had evidence of transferring care but included participants who discontinued but then reinitiated PrEP (appendix pp 15–20).

We defined suboptimal adherence as having taken fewer doses than required to reach a protective drug concentration, according to reported HIV risk (ie, penile–anal or penile–vaginal exposure). Although daily PrEP dosing is recommended for any individual who has a substantial risk of HIV infection, non-daily PrEP dosing can be appropriate for GBMSM and transgender women with only penile–anal exposure to HIV and infrequent intercourse. PrEP regimens were classified as daily and non-daily dosing. Daily dosing was one pill of oral PrEP every 24 h. The approved non-daily dosing was the 2-1-1 dosing for GBMSM and transgender women (also known as on demand, event driven, or sex driven), which is two PrEP pills at least 2–24 h before sex, one pill 24 h after the first dose, and another pill 48 h after the first dose. The adherence measurements included self-report, pill counting, pharmacy or study refill records, or tenofovir diphosphate concentration testing in blood. If there was more than one adherence measurement, we prioritised tenofovir diphosphate concentration over pill count and self-report. We used different thresholds of adherence for daily versus non-daily dosing. For daily dosing, adherence was defined as at least four doses per week (by self-report), an intracellular tenofovir diphosphate concentration of 16 fmol per million peripheral blood mononuclear cells,[2] tenofovir diphosphate concentration of at least 700–19 fmol/punch in dry blood spots samples,[35] tenofovir concentration of 0·023 ng/mg in hair sample,[36] tenofovir diphosphate concentration of 1000 ng/mL in urine sample,[37] tenofovir reported as being taken for more than 90% of the days in follow-up,[38] or a medication possession ratio higher than 80% (ie, the number of tablets dispensed at the previous visit divided by days).[25] For non-daily dosing for GBMSM and transgender women, pill counts were adjusted to account for missing pills from the expected 2-1-1 regimen.[39] Suboptimal adherence was further classified if tenofovir was not detected in plasma, indicating a gap of drug intake greater than 1 week.[40] There are no clearly defined protective tenofovir diphosphate concentration thresholds for PrEP adherence among cisgender women, although observational data suggesting tenofovir concentrations of 35–40 ng/mL in plasma indicate daily dosing for cisgender women, which is the recommended dosing frequency for this group.[41,42] Furthermore, the PrEP drug concentration threshold during pregnancy and post-partum periods are highly variable, complicating the use of drug concentrations to establish PrEP adherence during these periods,[43] with differences in median steady-state tenofovir diphosphate in pregnancy (965 fmol/punch, IQR 691–1166) and post partum (1406 fmol/punch, 1053–1859; p=0·0064). We did not distinguish between whether cisgender women were pregnant or immediately post partum.

We categorised the study population into GBMSM and transgender women, cisgender girls and women, heterosexual men and women, serodiscordant couples, female sex workers, and people who inject drugs. Given the scarcity of transgender women in each study and the fact that the data among transgender women were not distinguished from the data of GBMSM in most studies, we included them in a subgroup comprising GBMSM and transgender women. Mean or median lengths were used to categorise follow-ups according to how they were reported in the primary data source. We used the exact number of discontinuation cases from the reported follow-up visit if this information was unavailable. Study designs were categorised as randomised controlled trials (RCTs) focusing on the efficacy of PrEP, demonstration projects focusing on the effectiveness of PrEP, and real-world implementation focusing on the routine clinical dissemination of PrEP. We further categorised studies by their geographical regions of enrolment according to UNAIDS' definition (ie, North America, South America, sub-Saharan Africa, Middle East and North Africa, Europe, Asia and the Pacific, and the Caribbean).[44] If the study was done in more than one region, we categorised according to the country with the largest sample size. Youth was defined as people aged 15–24 years.[45] High HIV incidence was defined as greater than 0·5/100 person-years.

	Number of studies	Number of participants	Pooled estimate on rate of discontinuation, % (95% CI)	Heterogeneity (I^2), %	Heterogeneity (τ^2)	p value
Overall						
Summary details	59	43 917	..	..	..	..
Study follow-up length	..	..	..	..	..	0·61
≤6 months	16	7321	41·0% (18·8–63·5)	99·8%	2·0	..
>6 months to 12 months	31	28 541	35·6% (28·9–42·2)	99·3%	0·5	..
>12 months	12	8055	34·8% (13·9–55·6)	99·8%	2·2	..
Study design	..	..	..	..	..	0·017
Randomised controlled trial	4	3748	16·3% (8·0–30·5)	98·6%	0·7	..
Observational (demonstration)	22	17 590	34·0% (22·7–47·5)	99·5%	1·8	..
Observational (real-world implementation)	33	22 579	39·5% (34·4–44·9)	98·1%	0·4	..
Region	..	..	..	..	..	<0·0001
North America	32	20 068	37·8% (32·9–43·0)	97·7%	0·3	..
Sub-Saharan Africa	13	12 889	47·5% (29·4–66·4)	99·6%	2·0	..
Asia and Pacific	6	7118	33·4% (19·5–50·9)	99·4%	0·8	..
Europe	6	2167	17·4% (13·0–22·9)	85·6%	0·1	..
South America	2	1675	8·9% (2·4–28·4)	98·3%	1·0	..
Definition of discontinuation	..	..	..	..	..	0·43
Stopped refills or LTFU reported by study team	30	25 723	39·5% (32·3–47·3)	99·0%	0·7	..
Participants self-reported stopping PrEP	14	7044	29·4% (15·1–49·3)	99·4%	2·6	..
Both	15	11 150	33·1% (24·7–42·8)	98·9%	0·6	..
Age (median or mean) of study participants	..	..	..	..	..	0·59
Mainly adults (aged ≥25 years)	49	38 689	36·3% (30·5–42·5)	99·2%	0·8	..
Mainly youth (aged ≤24 years)	10	5228	31·0% (16·6–50·4)	99·1%	1·7	..
HIV incidence of the study	..	..	..	..	..	0·081
>0·5/100 person-years	15	13 290	31·6% (21·7–43·4)	99·3%	1·0	..
≤0·5/100 person-years	24	16 424	30·6% (22·0–40·9)	99·3%	1·2	..
Not reported	20	14 203	44·8% (35·4–54·6)	98·5%	0·8	..
Adherence interventions other than standardised follow-up service	..	..	..	..	..	0·015
Yes	6	1234	24·7% (18·2–32·5)	87·0%	0·2	..
No	53	42 683	36·7% (31·0–42·9)	99·2%	0·9	..
GBMSM or transgender women						
Summary details	39	20 461	..	..	..	..
Study follow-up length	..	..	..	..	..	0·86
≤6 months	10	2277	31·5% (19·2–47·0)	97·4%	1·1	..
>6 months to 12 months	19	13 835	30·4% (23·1–38·7)	98·9%	0·6	..
>12 months	10	4349	26·7% (15·9–41·1)	98·5%	1·1	..
Study design	..	..	..	..	..	0·0008
Randomised controlled trial	2	519	14·9% (8·6–24·5)	74·9%	0·2	..
Observational (demonstration)	12	9440	21·0% (13·6–31·0)	98·9%	0·8	..
Observational (real-world implementation)	25	10 502	36·3% (29·5–43·8)	97·9%	0·6	..
Region	..	..	..	..	..	<0·0001
North America	26	10 299	36·0% (29·7–42·8)	97·5%	0·5	..
Sub-Saharan Africa	0	0	..	..	..	..
Asia and Pacific	5	6320	28·3% (15·5–45·9)	99·3%	0·7	..
Europe	6	2167	17·4% (13·0–22·9)	85·6%	0·1	..
South America	2	1675	8·9% (2·4–28·4)	98·3%	1·0	..

(Table 1 continues on next page)

	Number of studies	Number of participants	Pooled estimate on rate of discontinuation, % (95% CI)	Heterogeneity (I^2), %	Heterogeneity (τ^2)	p value
(Continued from previous page)						
Definition of discontinuation	..	..	..	..	..	0·79
Stopped refills or LTFU reported by study team	16	7976	32·1% (24·0–41·4)	98·2%	0·7	..
Participants self-reported stopping PrEP	10	3118	26·5% (14·9–42·5)	98·0%	1·3	..
Both	13	9367	29·3% (20·3–40·3)	98·9%	0·8	..
Regimen of PrEP provided in the study	..	..	..	..	..	0·0009
Daily	33	16 792	31·5% (25·4–38·3)	98·5%	0·7	..
Non-daily	1	361	17·5% (13·9–21·7)	0·0%	0·0	..
Both	5	3308	21·6% (7·9–46·8)	99·3%	1·7	..
Age (median or mean) of participants	..	..	..	..	..	0·44
Mainly adults (aged ≥25 years)	33	19 699	30·3% (24·2–37·2)	98·8%	0·8	..
Mainly youths (aged ≤24 years)	6	762	26·1% (18·9–35·0)	83·1%	0·2	..
HIV incidence in the study	..	..	..	..	..	0·096
>0·5/100 person years	10	8644	32·6% (20·9–47·0)	99·2%	0·9	..
≤0·5/100 person years	17	9365	23·8% (17·5–31·5)	98·1%	0·6	..
Did not provide	12	2452	36·8% (27·5–47·0)	95·5%	0·5	..
Provided interventions for adherence other than standardised follow-up service	..	..	..	..	..	0·24
Yes	6	1234	24·7% (18·2–32·5)	87·0%	0·2	..
No	33	19 227	30·6% (24·5–37·6)	98·8%	0·8	..
Cisgender girls and women						
Summary details	4	4390	..	..	..	..
Study follow-up length	..	..	..	..	..	<0·0001
≤6 months	3	2380	43·3% (27·5–60·6)	95·6%	0·3	..
>6 months to 12 months	1	2010	10·1% (8·9–11·5)	0·0%	0·0	..
>12 months	0	0	..	..	..	..
Heterosexual men and women						
Summary details	3	3903	72·4% (12·4–98·0)	99·8%	6·6	..
Serodiscordant couples						
Summary details	4	3875	42·0% (10·9–81·1)	99·7%	3·2	..
Clinical and pharmacy records without population specified						
Summary details	5	9748	45·7% (34·0–57·9)	98·6%	0·3	..
Female sex workers						
Summary details	3	742	50·7% (25·7–75·4)	98·0%	1·0	..
People who inject drugs						
Summary details	1	798	62·0% (58·6–65·3)	0·0%	0·0	..

LTFU=lost to follow-up. PrEP=pre-exposure prophylaxis. GBMSM=gay, bisexual, and other men who have sex with men.

Table 1: **Meta-analysis for discontinuation among PrEP users by subgroup**

Data analysis

Two investigators (CL and ZH) independently extracted data from the final list of selected studies, including study characteristics (eg, study year, design, region, regimen, mean and median follow-up time), patient characteristics (eg, age, population, gender at birth), and the number of people categorised as discontinued, suboptimal adherence, and reinitiation.

The primary outcomes included discontinuation and suboptimal adherence. The preplanned secondary measures included PrEP reinitiation after discontinuation. We pooled independent study estimates and calculated the 95% CI by use of random-effects models due to the high heterogeneity of included studies. Heterogeneity across assessments was assessed by use of I^2, τ^2, and visual inspection for overlapping of 95% CI. We considered the level of heterogeneity significant if I^2 was higher than 75%. We evaluated whether study estimates varied by the study population, study design, country regions, PrEP regimen provided in the study, and the follow-up period. We did not assess the variability within studies. Leave-one-out sensitivity analyses were done to explore how sensitive associations were between study characteristics and PrEP discontinuation.

We further assessed the quality of evidence by study characteristics based on the Quality Assessment Tool for Quantitative Studies, including selection bias, study design, confounders, blinding, data collection methods, withdrawals, and drop-outs (appendix pp 13–14).[46] We also assessed publication bias using funnel plots for

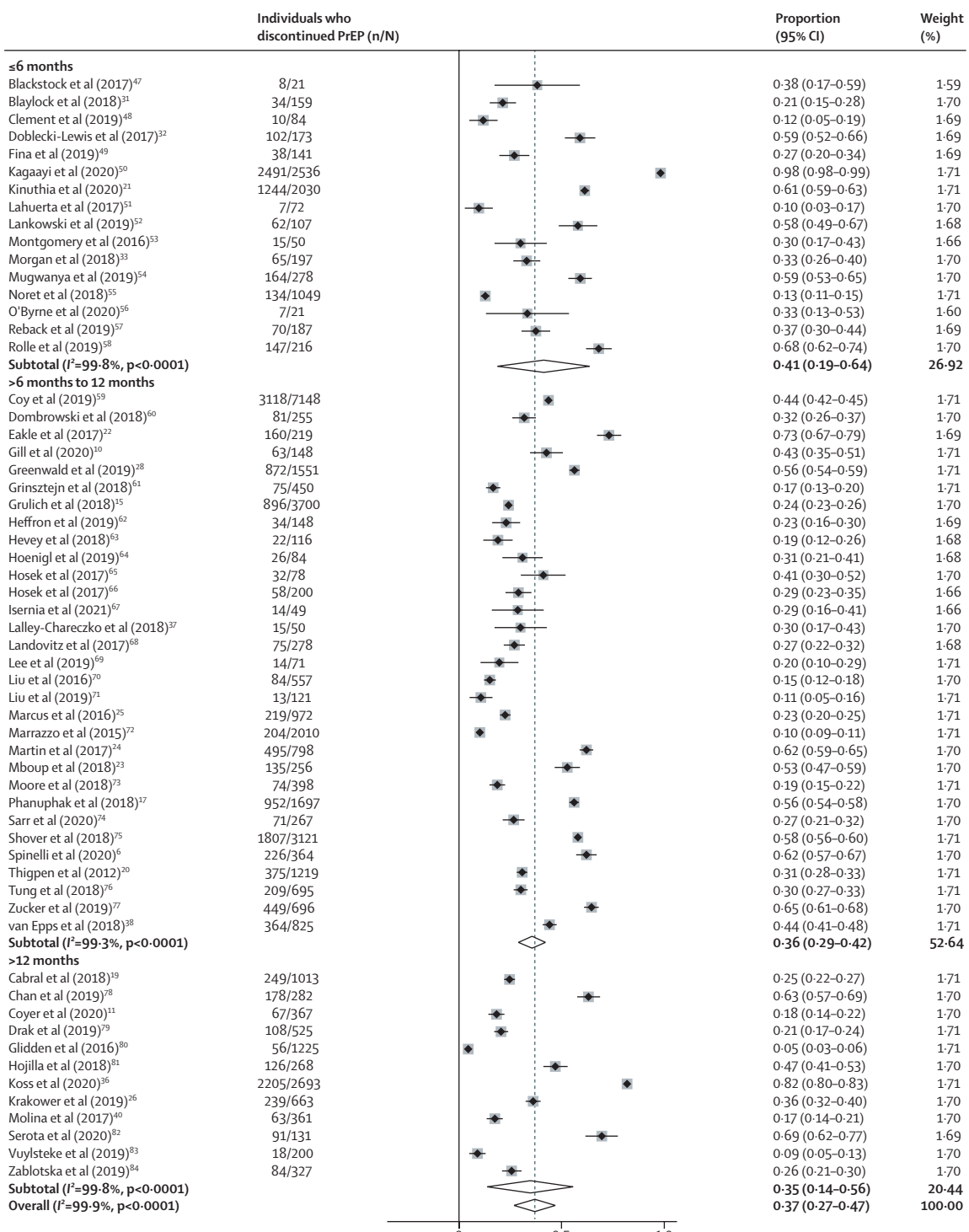

Figure 2: **Forest plots for the proportion of participants who discontinued PrEP by time period**
Weights are from random-effects analysis. n/N represents individuals who discontinued PrEP/individuals receiving PrEP. PrEP=pre-exposure prophylaxis.

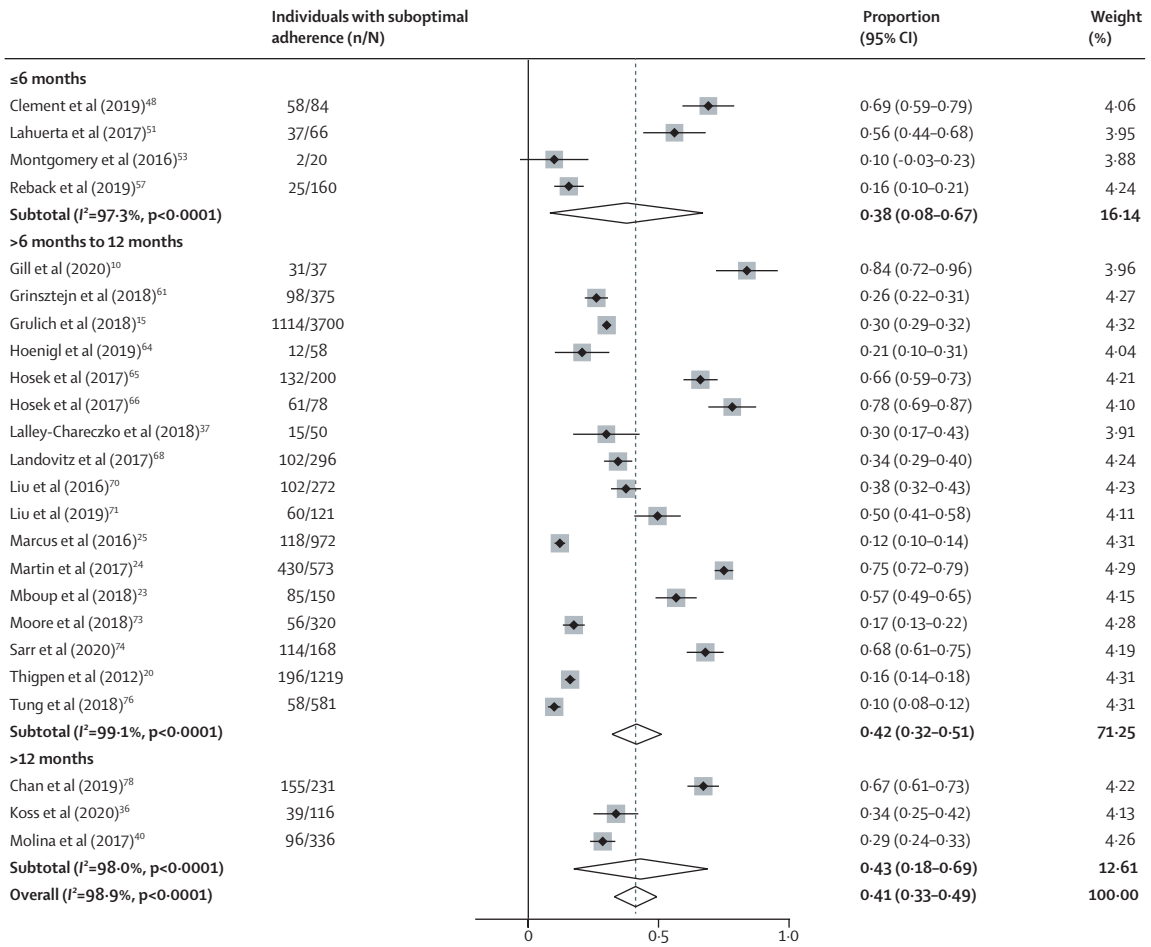

Figure 3: **Forest plot for the proportion of participants with suboptimal adherence by time period**
Weights are from random-effects analysis. n/N represents individuals with suboptimal adherence/individuals who continued PrEP. PrEP=pre-exposure prophylaxis.

asymmetry. All analyses were done with Comprehensive Meta-Analysis software (version 3.3.070). This study is registed with PROSPERO, CRD42020155675.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

4129 records were identified, 223 full-text articles were assessed, and 59 articles were included in the systematic review and meta-analysis (figure 1). 55 observational studies and four RCTs were included, providing estimates for 43 917 individuals from 20 countries or regions (appendix p 22). 54·2% of studies were conducted in North America, 22·0% in Africa, 10·2% in Asia and the Pacific, 10·2% in Europe, and 3·4% in South America. Nearly half (46·6%) of participants were GBMSM or transgender women. 9·9% of participants were cisgender girls and women, 8·9% were heterosexual men and women, and 8·8% were partners who were HIV-negative in serodiscordant relationships (table 1).

The included studies had poor quality in terms of study design, with a moderate risk of bias (appendix pp 13–14). Discontinuation was commonly self-reported or defined by LTFU. Adherence estimates relied only on self-report in five of 24 studies. Among the 55 observational studies, 22 were demonstration projects and 33 were real-world setting implementation experiences. Most studies used convenient samples (ie, convenience sampling or snowball sampling), which might be subject to selection bias. The measurements of discontinuation and adherence were inconsistent across studies, which might have introduced heterogeneity. The sensitivity analysis result is stable (appendix pp 21–22). No publication bias was observed by the symmetry of the funnel plot (appendix p 23).

The pooled proportion of PrEP discontinuation within 6 months after PrEP initiation was 41·0% (table 1; figure 2). There was significant difference between pooled PrEP discontinuation when comparing study designs and regional variation in PrEP discontinuation. Studies that

	Number of studies	Number of participants	Pooled estimate of suboptimal adherence, % (95% CI)	Heterogeneity (I^2), %	Heterogeneity (τ^2)	p value
Overall						
Summary details	24	10183	..	..	..	..
Study follow-up length	..	..	..	..	..	0·93
≤6 months	4	330	37·7% (8·4–66·9)	97·3%	1·8	..
>6 months to 12 months	17	9170	41·6% (32·1–51·1)	99·1%	0·9	..
>12 months	3	683	43·1% (17·5–68·7)	98·0%	0·9	..
Study design	..	..	..	..	..	0·16
Randomised controlled trial	4	1697	38·1% (19·0–61·9)	97·4%	0·9	..
Observational (demonstration)	12	6330	49·0% (37·4–60·8)	98·1%	0·7	..
Observational (real-world implementation)	8	2156	25·7% (11·6–47·5)	98·2%	1·8	..
Region	..	..	..	..	..	0·18
North America	14	3443	34·2% (22·0–49·1)	98·0%	1·3	..
Sub-Saharan Africa	6	1756	51·7% (27·3–75·2)	98·3%	1·6	..
Asia and Pacific	2	4273	53·2% (14·5–88·4)	99·7%	1·9	..
Europe	1	336	28·6% (24·0–33·6)	0·0%	0·0	..
South America	1	375	26·1% (21·9–30·8)	0·0%	0·0	..
Age (median or mean) of study participants	..	..	..	..	..	0·0038
Mainly adults (aged ≥25 years)	19	9697	33·7% (25·1–43·6)	98·4%	0·8	..
Mainly youths (aged ≤24 years)	5	486	62·5% (45·6–76·7)	90·6%	0·5	..
Measurement of adherence	..	..	..	..	..	0·017
Pill count and refill records	3	5891	18·4% (9·8–32·0)	98·9%	0·4	..
Self-report	5	1629	43·7% (15·6–76·5)	99·2%	0·6	..
Drug concentrations	16	2663	43·1% (33·6–53·1)	95·3%	2·7	..
HIV incidence in the study	..	..	..	..	..	0·65
>0·5/100 person-years	6	1704	51·1% (23·2–78·3)	98·6%	2·3	..
≤0·5/100 person-years	12	7299	35·5% (25·4–47·0)	98·4%	0·7	..
Did not provide	6	1180	35·9% (14·3–65·4)	98·3%	2·3	..
Provided intervention for adherence	..	..	..	..	..	0·75
Yes	5	729	36·1% (17·1–60·7)	96·6%	1·3	..
No	19	9454	40·2% (30·3–51·0)	98·5%	0·9	..
GBMSM or transgender women						
Summary details	16	6882	..	..	..	..
Study follow-up length	..	..	..	..	..	0·76
≤6 months	3	264	27·5% (5·0–73·3)	96·9%	2·9	..
>6 months to 12 months	11	6051	34·3% (25·6–44·2)	96·8%	0·5	..
>12 months	2	567	47·4% (15·5–81·7)	98·7%	1·3	..
Study design	..	..	..	..	..	0·56
Randomised controlled trial	2	441	31·3% (9·2–67·2)	97·7%	1·1	..
Observational (demonstration)	7	5257	41·8% (32·2–52·0)	96·3%	0·3	..
Observational (real-world implementation)	7	1184	28·3% (11·2–55·1)	97·9%	2·2	..
Regimen of PrEP provided in the study						0·17
Daily	15	6546	35·8% (26·9–45·7)	97·2%	0·6	..
Non-daily	1	336	28·6% (24·0–33·6)	0·0%	0·0	..
Both	0	0	..	..	..	..
Region	..	..	..	..	..	0·28
North America	13	2471	36·8% (24·1–51·6)	97·4%	1·2	..
Sub-Saharan Africa	0	0	..	..	..	..
Asia and Pacific	1	3700	30·1% (28·7–31·6)	0·0%	0·0	..
Europe	1	336	28·6% (24·0–33·6)	0·0%	0·0	..
South America	1	375	26·1% (21·9–30·8)	0·0%	0·0	..

(Table 2 continues on next page)

	Number of studies	Number of participants	Pooled estimate of suboptimal adherence, % (95% CI)	Heterogeneity (I^2), %	Heterogeneity (τ^2)	p value
(Continued from previous page)						
Age (median or mean) of subjects	..	..	..	..	..	0·0050
Mainly adults (aged ≥25 years)	12	6433	29·1% (21·8–37·7)	96·6%	0·4	..
Mainly youths (aged ≤24 years)	4	449	57·0% (39·3–73·1)	91·4%	0·5	..
Measurement of suboptimal adherence	..	..	..	..	..	0·51
Self-report	4	1056	35·6% (9·6–74·1)	98·9%	2·8	..
Pill counts	1	3700	30·1% (28·7–31·6)	0·0%	0·0	..
Drug concentrations	11	2126	35·9% (26·3–46·8)	95·1%	0·5	..
HIV incidence of the study	..	..	..	..	..	0·19
>0·5/100 person-years	3	298	55·5% (29·6–78·7)	89·8%	0·8	..
≤0·5/100 person-years	8	5470	30·9% (26·3–35·9)	87·6%	0·1	..
Did not provide	5	1114	32·3% (10·5–66·0)	98·6%	2·5	..
Provided intervention for adherence	..	..	..	..	..	0·95
Yes	5	729	36·1% (17·1–60·7)	96·6%	1·3	..
No	11	6153	35·2% (25·8–45·9)	97·4%	0·5	..
Cisgender girls and women						
Summary details	1	66	56·1% (44·0–67·5)	0·0%	0·0	..
Heterosexual men and women (follow-up length >6 months to 12 months)						
Summary details	2	1256	49·1% (3·7–96·1)	98·1%	5·3	..
Serodiscordant couples (follow-up length 1–6 months)						
Summary details	1	116	33·6% (25·6–42·7)	0·0%	0·0	..
Clinical and pharmacy records without population specified (follow-up length >6 months to 12 months)						
Summary details	1	972	12·1% (10·2–14·3)	0·0%	0·0	..
Female sex workers (follow-up length >6 months to 12 months)						
Summary details	2	318	62·4% (51·5–72·7)	76·3%	0·1	..
People who inject drugs (follow-up length >6 months to 12 months)						
Summary details	2	573	75·0% (71·3–78·4)	0·0%	0·0	..

GBMSM=gay, bisexual, and other men who have sex with men. PrEP=pre-exposure prophylaxis.

Table 2: **Meta-analysis for the suboptimal adherence among PrEP users who continued treatment by subgroup**

included adherence interventions besides standard follow-up services reported significantly lower discontinuation than those studies that did not include adherence. Multiple definitions of discontinuation were deployed across studies. There was no evidence of publication bias for the proportion of PrEP users who discontinued (appendix p 23).

Regarding study populations, the pooled PrEP discontinuation in the 6 months following PrEP initiation was 43·3% (95% CI 27·5–60·6) among cisgender girls and women and 31·5% (19·2–47·0) among GBMSM and transgender women. Among all the studies conducted among GBMSM and transgender women, the PrEP discontinuation was significantly higher in observational studies compared with RCTs. Studies based in North America pooled significantly higher discontinuation than did other regions. In terms of dosing frequency, six studies offered a non-daily regimen of PrEP for GBMSM and transgender women, among which two studies were demonstration studies[40,83] and four were real-world implementation.[4,28,49,55,67] PrEP discontinuation was significantly higher in daily PrEP studies compared with studies offering non-daily options or studies offering both strategies. We observed marginally higher PrEP discontinuation in studies with a high HIV incidence compared with studies with low incidence.

24 studies reported PrEP adherence among participants who continued PrEP. Pooled suboptimal adherence within 6 months was 37·7% (95% CI 8·4–66·9; figure 3; table 2). Studies of participants with a median age of 24 years or younger had significantly higher suboptimal adherence than did those with a median age of older than 24 years. Suboptimal adherence also varied significantly across different measurements of adherence.

Eight studies collected data on PrEP reinitiation among those who discontinued PrEP. Pooled reinitiation was 47·3% (95% CI 31·5–63·2; n=2658; I^2=96·9%; figure 4) at more than 12 months after discontinuation. We did not observe any significant difference between reinitiation rates according to study design or HIV incidence rate, with statistical testing limited due to small sample size (table 3).

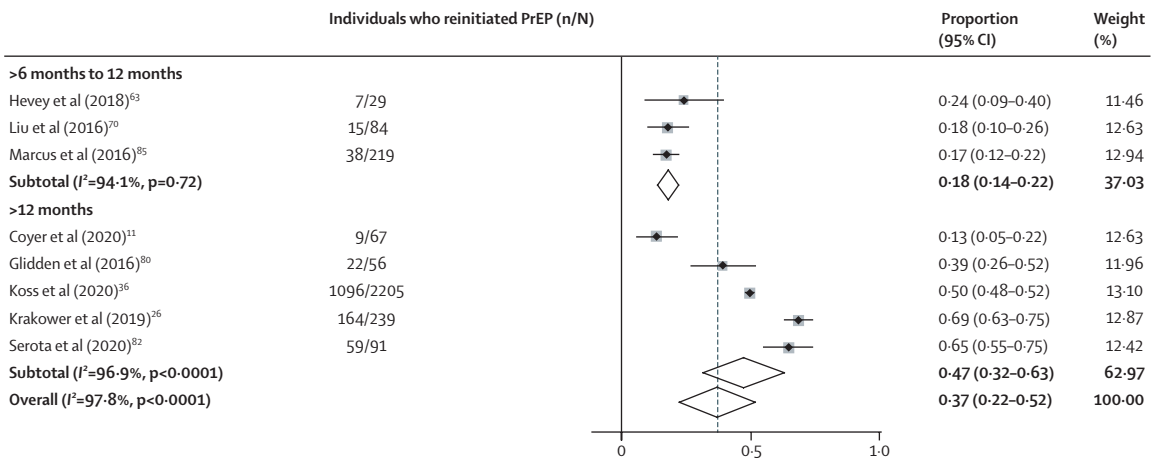

Figure 4: **Forest plot for the proportion of participants who reinitiated PrEP by time period**
Weights are from random-effects analysis. n/N represents individuals who reinitiated PrEP/individuals who discontinued PrEP. PrEP=pre-exposure prophylaxis.

	Number of studies (n=8)	Number of participants (n=2990)	Pooled estimate of suboptimal adherence, % (95% CI)	Heterogeneity (I^2), %	Heterogeneity (τ^2)	p value
Study follow-up length	..	..	..	..	..	<0·0001
≤6 months	0	0	..	..	..	..
>6 months to 12 months	3	332	18·0 (13·8–22·1)	94·1	0·4	..
>12 months	5	2658	47·3 (31·5–63·2)	96·9	0·0	..
Study design	..	..	..	..	..	0·45
Randomised controlled trial	0	0	..	..	..	..
Observational (demonstration)	4	2412	28·4 (13·7–49·8)	94·5	0·8	..
Observational (real-world implementation)	4	578	42·3 (16·7–72·8)	97·6	1·7	..
Region	..	..	..	..	..	<0·0001
North America	5	662	36·5 (15·3–64·7)	97·3	1·7	..
Sub-Saharan Africa	1	2205	49·7 (47·6–51·8)	00·0	0·0	..
Asia and Pacific	0	0	..	..	..	..
Europe	1	67	13·4 (7·1–23·8)	00·0	0·0	..
South America	1	56	39·3 (27·5–52·5)	00·0	0·0	..
Age (median or mean) of study participants	..	..	..	..	..	0·26
Mainly adults (aged ≥25 years)	7	2961	36·9 (23·6–52·5)	96·5	0·7	..
Mainly youths (aged ≤24 years)	1	29	24·1 (12·0–42·7)	00·0	0·0	..
HIV incidence in the study	..	..	..	..	..	0·19
>0·5/100 person-years	2	295	54·9 (27·0–80·0)	93·6	0·7	..
≤0·5/100 person-years	5	2666	30·1 (15·1–50·9)	96·9	1·0	..
Did not provide	1	29	24·1 (12·0–42·7)	00·0	0·0	..
Provided intervention for adherence	..	..	..	..	..	1·00
Yes	0	0	..	..	..	..
No	8	2990	35·4 (23·1–49·9)	96·1	0·7	..

PrEP=pre-exposure prophylaxis.

Table 3: **Meta-analysis for the reinitiation among all PrEP users who discontinued**

We included and reviewed 30 studies reporting reasons for and correlates of PrEP discontinuation. We categorised these reasons into three levels: individual, interpersonal, and structural. The most common reasons for stopping PrEP were low perceived risk of HIV infection (21 studies), experiencing side-effects (25 studies), concerns for the long-term side-effects of PrEP (five studies), challenges with medication adherence or pill burden (seven studies), choosing prevention methods other than PrEP (three studies), and relocation (seven studies). Inter-

personal reasons included absence of family support (one study), whereas structural reasons were primarily related to cost or absence of health insurance (ten studies) and inaccessibility to care (nine studies; appendix p 30). We synthesised correlates of discontinuation from 16 longitudinal studies. The most-reported factors positively associated with discontinuation were individual-level factors, such as young age (six studies), being a woman (one study), and being transgender (three studies; appendix p 23).

Discussion

This systematic review and meta-analysis updates and synthesises the rates and correlates of PrEP discontinuation in global literature, extending previous work by quantifying adherence among people who continued PrEP and describing reinitiation among those who discontinued PrEP. Our meta-analysis showed that two-fifths of participants discontinued PrEP within 6 months of initiation. Among the remainder of people who continued PrEP, more than a third were using it with a frequency that was not expected to be adequate to prevent HIV acquisition. Taken together, these results suggest that less than a third of PrEP initiators used PrEP properly within 6 months of initiation. Among people who discontinued PrEP, about half restarted it within the year after the first initiation, further showing the fluidity and dynamic patterns of oral PrEP use.

In this systematic review and meta-analysis, we attempted to classify PrEP discontinuation in two ways: by study-team reporting and by participants' self-reporting. There was no significant difference in PrEP discontinuation between LTFU or stopped refills reported by the study team and self-reported stoppage. Our discontinuation definition excluded cases with evidence of transferring care, and five studies reported data for transferring care among LTFU.[55,60,76,79,81] The LTFU designation is probably an overestimate, as the results were influenced by the study follow-up frequency and study design. This overestimation was especially true among retrospective chart reviews that relied heavily on refill records and clinician notes to calculate drug possession and possible discontinuation dates. Although LTFU can be considered as termination of PrEP access (and thus a reliable estimate of discontinuation), participants might discontinue the study but continue to access PrEP via other channels, particularly as PrEP becomes easily accessible globally. This shift to non-study access to PrEP enforces the importance of documenting or verifying care transfers to improve estimation of retention on PrEP and clinical outcomes after recorded PrEP discontinuation.

Definitions of PrEP discontinuation vary substantially in the scientific literature and among the studies included in this systematic review. The complexity of discontinuation rests in the fundamental difference between antiretroviral therapy and PrEP. Antiretroviral therapy requires lifelong use for effectiveness, whereas PrEP is needed only during periods of substantial risk for HIV acquisition. Unfortunately, the capacity of study investigators, and indeed participants to some extent, to accurately assess and report a need for PrEP on the basis of objective HIV risk continues to complicate our ability to define and distinguish clinically meaningful premature PrEP discontinuation from appropriate stoppage. One strategy is to examine the reasons for participants discontinuing PrEP and describe correlates of discontinuation. Exploring these discontinuation reasons can help to distinguish appropriate discontinuation and inform possible strategy to improve persistence among people at ongoing elevated risk of HIV infection.

We observed a marginal correlation between higher discontinuation and HIV incidence among GBMSM and transgender women, further supporting the effectiveness of PrEP in reducing HIV acquisition. In some cases, study design helped to identify examples of appropriate discontinuation. For example, in the Partners Demonstration Project,[86] PrEP was a bridge for HIV prevention among serodiscordant couples until the partner living with HIV had reached viral suppression. In a study by Kinuthia and colleagues, PrEP was co-dispensed with HIV self-test kits for secondary distribution to male partners.[21] Some participants discontinued PrEP after confirming their partner's HIV-negative status via the HIV self-tests. Hence, pooled PrEP discontinuation included both inappropriate and appropriate discontinuations, emphasising the importance of differentiating these categories to reach prevention-effective PrEP use in future studies,[87] instead of calls for near-perfect adherence regardless of risk exposure.

High heterogeneity existed in PrEP adherence assessments. This systematic review prioritised adherence data measured by drug concentration when several measurements were used in a single study. However, tenofovir concentration was measured in only two-thirds of studies. Given that we observed higher suboptimal adherence when adherence was measured by tenofovir-diphosphate concentrations than by pill counting or refill record review, our estimates are probably an underestimate. Interestingly, the difference between suboptimal adherence when assessed with patient self-report versus tenofovir concentration was not substantial. Considering the already resource-strained health-care systems in which PrEP is being provided, patients' self-reported history of PrEP use might be a more convenient and affordable approximation to PrEP adherence than is tenofovir. Digital health tools for measuring PrEP adherence can reduce reporting bias when recalling pill-taking history and are a compelling advance in PrEP monitoring and clinical care.[88,89]

We observed highly variable proportions of discontinuation between different key populations. Within 6 months of PrEP initiation, more than 40% of cisgender girls and women discontinued PrEP. This subgroup was drawn from the general population in settings with high HIV burden, including adolescent girls and young

women (ie, aged ≤25 years) from studies conducted in sub-Saharan Africa. Importantly, rates of discontinuation were highest in sub-Saharan Africa. Data were scarce regarding PrEP continuation during pregnancy and the post-partum periods as only two studies allowed enrolment of pregnant or breastfeeding participants. Barriers to PrEP persistence are likely to vary by gender, age, pregnancy status, and cultural context. Strategies to improve engagement and PrEP persistence for cisgender girls and women are urgently needed.

Our results suggest that a third of GBMSM and transgender women discontinued PrEP within 6 months of initiation. Studies that offered daily and non-daily regimen options reported significantly lower discontinuation than did studies that offered only daily PrEP. This correlation suggests that providing choices of PrEP regimen and dosing frequency can improve how GBMSM and transgender women cope with fluctuations in risk (ie, using PrEP as needed rather than a complete cessation of PrEP). Providing options in PrEP dosing frequency for GBMSM and transgender women is probably superior to limiting to daily dosing,[11,40,83] but there are no data to support this strategy for cisgender women or people who inject drugs.

In real-world settings, the full potential of oral PrEP for HIV prevention has been undermined by poor persistence. Results from the HIV Prevention and Trials Network 083 and 084 efficacy trials of long-acting injectable PrEP[90,91] suggest that this form of PrEP is a compelling alternative to oral formulations, particularly for people who struggle with adherence. In contrast to once daily or event-driven PrEP regimens, long-acting PrEP reduces dosing frequency to once every 2 months. However, the successful implementation of long-acting PrEP will depend highly on the capacity of local HIV-care systems and effective public messaging. Unlike oral regimens that can be distributed for up to 3 months at a time, injectable PrEP could require more frequent clinic visits and higher costs. Long-acting PrEP provides crucial new choices for biomedical HIV prevention but is unlikely to replace oral PrEP entirely, and the effect of long-acting PrEP on premature discontinuation should be studied in future research.

Our study has several implications. From a policy perspective, high discontinuation within the first 6 months of PrEP suggests that additional attention is needed on providing comprehensive HIV prevention in the era of PrEP, strengthening counselling provided before initiation of PrEP and during PrEP. Although increased incidences after stopping PrEP in many studies suggest inappropriate discontinuation, the identification of strategies to counsel patients appropriately on when it might be appropriate to pause PrEP and to ensure they have adequate resources to re-engage in PrEP is crucial. These strategies will require objective assessment of HIV infection risk and prediction tools for discontinuation that are tailored to different key populations. Our findings emphasise the importance of designing interventions that encourage PrEP reinitiation, messaging that might be different from those for people considering starting PrEP for the first time. Cost-effectiveness analyses and mathematical models should include the rate of discontinuation as an essential indicator to assess the economic and epidemiological effects of PrEP implementation.[92,93]

Our study has several limitations. First, there was substantial heterogeneity across studies. The low quality of included studies and the inconsistent outcome measurement probably introduced additional heterogeneity in our pooled results. Although PrEP research evolved rapidly from RCT, to demonstration, to real-world implementation, we observed the expected finding of poorer retention outside of controlled study settings. Our inclusion of various key populations, PrEP regimens, and diverse geographical settings to evaluate our research outcome globally also contributed to heterogenicity. Second, most studies did not provide evidence on transferring care among people who were LTFU but might continue or reinitiate PrEP outside of the study, resulting in an overestimation of discontinuation. Third, most of the included studies were done in North America, and the target populations were mainly GBMSM and individuals aged 25 years or older. Our subanalyses might lead to a bias that underestimates PrEP persistence, including suboptimal adherence, globally. Fourth, some studies did not report disaggregated data for cisgender men and women. In these studies, we used four pills per week as a level of adherence for cisgender women, and tenofovir concentrations were not detected in GBMSM using the 2-1-1 regimen, which systematically underestimates what is expected to result in a protective drug concentration. Fifth, we did not include grey literature or literature in languages other than English. However, several studies suggest exclusion of non-English studies does not impact systematic reviews.[94,95] Finally, there are few data that represent or reflect PrEP use among people who inject drugs, and additional research is needed for this population.

70% of PrEP users either stopped or had suboptimal PrEP adherence within 6 months of initiation. Among people who discontinued, nearly half restarted PrEP 1 year after the first initiation. Strategies to encourage reinitiating PrEP for new or persistent risk should be a focus of future PrEP implementation and are crucial considerations even in the era of long-acting PrEP.

Contributors

WT and JZ conceived the idea for the study and designed the protocol. STW contributed to developing the literature search strategy. JZ, CL, and ZH did the study selection and data extraction. JZ and CL wrote the manuscript. JZ did the statistical analysis. JZ and CL accessed and verified the data. WT, JX, SER, JDT, JJO, YJ, MSC, WG, and HS critically revised the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

All data will be made available on request directed to the corresponding author. Proposals will be reviewed and approved by the sponsor, investigator, and collaborators on the basis of scientific merit. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement.

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