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Oral pre-exposure prophylaxis (PrEP) continuation, measurement, and reporting: a systematic review and meta-analysis

Running head: PrEP continuation systematic review

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Abstract

Objective:

To appropriately plan for rollout and monitor impact of oral pre-exposure prophylaxis (PrEP) it is important to understand PrEP continuation and come to a consensus on how best to measure PrEP continuation. This study reviews data on PrEP continuation to document how it is reported, and to compare continuation over time and across populations.

Design

Systematic review and meta-analysis.

Methods

We searched MEDLINE, Embase, and Global Health and reviewed abstracts from HIV conferences from 2017-2018 for studies reporting primary data on PrEP continuation. Findings were summarized along a PrEP cascade and continuation was presented by population at months 1, 6, and 12, with random-effects meta-analysis.

Results

Of 2,578 articles and 596 abstracts identified, 41 studies were eligible covering 22,034 individuals. Continuation data were measured and reported inconsistently. Results showed high discontinuation at month 1 and persistent discontinuation at later time points in many studies. Pooled continuation estimates were 66% at month 1 (n=5,348; 95% CI: 48%-82%), 63% at month 6 (n=13,629; 95% CI: 48%-77%), and 71% at month 12 (n=14,933; 95% CI: 60%-81%; higher estimate than previous timepoints due to inclusion of different studies). Adequate data were not available to reliably compare estimates across populations.

Conclusions

This review found that discontinuation at 1 was high, suggesting PrEP initiations may be a poor measure of effectiveness. Continuation declined further over time in many studies, indicating existing cross-sectional indicators may not be adequate to understand PrEP use patterns. Studies do not measure continuation consistently, and consensus is needed.

Key words: Oral Pre-Exposure Prophylaxis (PrEP), HIV/AIDS, HIV prevention, PrEP continuation

Introduction

The effectiveness of oral pre-exposure prophylaxis (PrEP) is contingent upon continued use during periods of risk for HIV, which evidence shows is difficult for many clients.[1–3] Continual engagement in care via follow-up visits is important not only for refills, but for ongoing continuation support, risk reduction counseling, screening for sexually transmitted infections (STIs), and management of side effects. [4–6] The World Health Organization (WHO) and national PrEP guidelines recommend that PrEP clients are tested for HIV at one and three months after initiation and every three months thereafter. [7,8] Despite increasing adoption of PrEP, [9] there have been challenges in achieving continued engagement in follow-up visits.

As countries approve PrEP for HIV prevention and prepare for widespread provision, monitoring of continued follow-up and refill – or continuation - is essential to estimate the potential impact of the intervention and eventually measure the success of PrEP programs. Continuation data can inform costing of PrEP implementation by providing evidence of the likelihood that PrEP clients will return at each follow-up visit, helping to adequately project the cost of PrEP provision over time. Continuation data can also provide insight into whether some population groups are more or less likely to continue on PrEP and help ensure that strategies to promote PrEP continuation are designed to meet the requirements of specific populations.

Despite the importance of consistent measurement of PrEP continuation, there is little consensus on how to do so. Conversations about the appropriate indicators to measure PrEP program success are ongoing, and approaches are rapidly evolving. Consensus is building that the word "retention" is not appropriate for prevention, because unlike antiretroviral therapy (ART), PrEP is not taken for life; at times clients may safely cycle on and off of PrEP, in consultation with their providers. However, in the literature terms like retention, adherence, and continuation are

often used interchangeably. Further complication arises with different dosing for different populations. WHO guidance supports intermittent, event-driven, or "on demand" dosing for men who have sex with men (MSM) and provision of time-limited PrEP to HIV-negative people in serodiscordant relationships. [7] Existing PrEP indicators, including those endorsed by the WHO[7] and PEPFAR, [10] do not account for differences in dosing schedules or safe cycling.

This systematic review and meta-analysis will document reporting of continuation in published literature and compare continuation across diverse populations. The analysis will inform the ongoing conversation about how to measure PrEP program success, support future modelling and costing studies, and highlight how PrEP continuation vary among target populations.

Methods

Search strategy and selection criteria

The purpose of this systematic review and meta-analysis was to identify data from clinical trials, demonstration projects, and real-world settings on participant continuation on oral PrEP Due to the limited evidence base currently available on this topic, the search was intended to cover programs run among any of the target groups considered to be at risk of HIV infection and in any setting. Only those studies reporting on primary data were deemed eligible, with modelling studies and simulations excluded. Studies on programs utilizing methods other than oral PrEP delivery (e.g., topical gels, vaginal rings) were also excluded. Where trials or studies included two modes of delivery (i.e., one oral PrEP and one other, or one oral PrEP and one placebo), only data from the oral PrEP arm were included. Studies reporting on eligibility and enrolment figures only, and not continuation data, were excluded. Grey literature was not included.

A literature search was run on three databases (MEDLINE, Embase, and Global Health) to identify articles written in English and published in 2010 or later. Search terms used were ("pre-exposure prophylaxis" OR "PrEP") AND ("HIV" OR "HIV/AIDS") AND ("implementation" OR "demonstration" OR "observation" OR "trial" OR "open label extension"). The search was completed on November 6, 2018. Titles and abstracts were screened initially, followed by review of full text articles deemed potentially eligible for inclusion. In addition to the database searches, abstracts from the Conference on Retroviruses and Opportunistic Infections (CROI) in 2017 and 2018, the 22nd International AIDS Conference (AIDS 2018), and the 2017 International AIDS Society (IAS) Conference were also screened on the basis of their titles, and full abstracts were reviewed when they were deemed potentially eligible for inclusion.

Study screening and extraction

The primary outcome for this review is continuation in PrEP services at various time points, which are represented along a simplified PrEP cascade in Figure 1 [11]. Continuation data were extracted from the literature and mapped to the timepoints in this cascade. It is important to note that studies reporting on continuation in PrEP services cover PrEP programs of varying structures, with study visits occurring and continuation reported at different intervals. The cascade is not an accurate reflection of each study visit in every study included but affords the benefit of allowing for comparison between studies. When continuation was reported between time points, the continuation value was presented for the closest preceding timepoint. Note that many

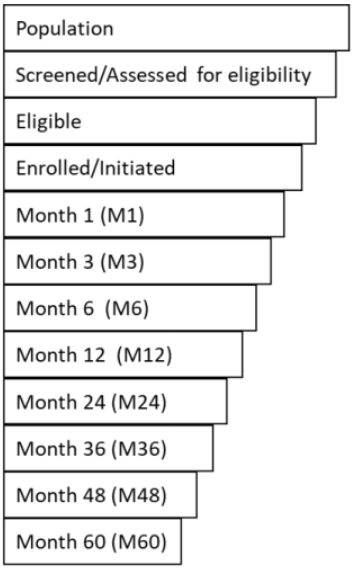

Figure 1: PrEP services cascade

proposed PrEP services cascades also include adherence, or effective use[11–13]; however, this important indicator of PrEP program success is beyond the scope of this review.

For the purpose of this analysis, continuation at each point in the PrEP cascade is defined as the number or proportion of enrolled or initiated study participants who returned for a follow-up visit at the relevant time point. This definition does not account for true duration of use among clients who discontinue as these data are not available– instead, clients who do not return to the study visit are considered to have discontinued use at the time of the visit. We also do not account for use of PrEP during periods of risk and discontinuation when no longer at risk, which is sometimes referred to as prevention-effective use or prevention-effective adherence. [14–16] Limiting our interpretation of effective continuation to only continual use over time could underestimate the impact of PrEP, ignoring the risk averted by those with other use patterns. However, none of the studies in this review tracked prevention-effective use, so we report on PrEP continuation only as continual use time.

Data were extracted and entered into Excel. Four weeks were considered one month for continuation reported at weekly intervals. If no specific population group was targeted in the study, the population was deemed "All at risk". When continuation at different points in the cascade was reported separately by study population or study site, the continuation data were extracted separately for each population or site to allow for comparison.

Two independent reviewers (JL and KS) completed the full review process to determine studies for inclusion. Both reviewers then screened the full text of each study and extracted data, and discrepancies were discussed and resolved.

Data analysis

Study quality was assessed using the Joanna Briggs Institute Checklist for Prevalence Studies. [17] This tool allows assessment of studies based on study design, implementation, and analysis. No papers were excluded, as all were deemed to be of sufficient quality (score of 5 or more).

All statistical and meta-analyses were completed using Stata 15. [18] We summarized reporting of continuation by calculating the percentage of studies reporting on each aspect of the cascade. We calculated percent discontinuation between time periods by taking the difference in continuation between the time periods. PrEP continuation cascades were developed presenting continuation from studies reporting continuation from at least three of the four time points from month 1 to month 12. We created forest plots of continuation at month 1, month 6, and month 12, grouped by population, using random-effects meta-analysis with Freeman-Tukey double arcsine transformation. The analysis was done using Metaprop, a program specifically designed for binomial data that calculates confidence intervals within the admissible values of 0-1. [19] We estimated pooled continuation and 95% confidence intervals (CIs) overall, and not by population, because of high heterogeneity (I^2 statistic) within groups.

Role of the funding source

This work was funded by the US Agency for International Development and led by the OPTIONS Consortium. The funders did not play any role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Results

Search Results

The search yielded 2,578 articles and 596 abstracts, of which 249 were retained for full text review (As depicted in Appendix S1; see Supplemental Digital Content, http://links.lww.com/QAD/B770). Fifty records met the inclusion criteria for this review, covering 41 individual trials, demonstration projects, or routine implementation/clinical programs.

Study Characteristics

Key features of the studies, including type of study, site, and study population are included in Appendix 2 (see Supplemental Digital Content, http://links.lww.com/QAD/B770). Although some trials published multiple papers, they all contributed to a single record if they reported on the same data. On the other hand, a single paper is considered to contribute to multiple studies if it reported data along the cascade separately by population or location. The 41 programs covered by the studies in this review included 24 open-label or demonstration projects, nine routine implementation/clinical programs, and eight randomized controlled trials (RCTs). Studies were most commonly conducted in Africa (16, 39%) and North America (12, 29%). Populations most commonly reported were MSM and transgender women (TGW) (18, 44%), all people at risk (9, 22%), and women (6, 15%).

Reporting of PrEP cascade components

Table 1 presents the number of clients screened, eligible, and enrolled/initiated for each study, along with the percentage of those enrolled/initiated still retained in care (continuation) at each time point of the PrEP services cascade. No studies reported prevention-effective use and none discussed a continuation definition that suggested continued need for PrEP was considered in the statistics presented. Reported components of the PrEP services cascade varied by study, as shown in Figure 2.

Figure 2: Components of the PrEP services cascade reported in literature review

Just under half of studies reported the numbers of clients screened and the number of clients determined eligible for PrEP. All studies reported number of clients enrolled/initiated (a requirement for inclusion) but reported this information in different ways. Some studies reported the number enrolled, while others also reported those who were prescribed PrEP or those who

started taking PrEP, and sometimes these numbers differed from those enrolled. [21] We reported the number who started taking PrEP as enrolled/initiated when such information was provided.

Continuation was most commonly reported at month 6, followed by months 3 and 12, and then month 1. Continuation past one year was rarely reported and was not reported in any of the routine implementation studies included in this review. Other time points at which continuation was reported were months 4, 9, 15, 16, 18, and 20, [31,35,43] and weeks 6, 10, 14, 18, 22, 26, 30, 34. [55,58]

Some studies only reported continuation as total or average length of follow-up (in days, months, or years). Since it was not possible to fit these data into the PrEP cascade, those studies were excluded. Other methods for reporting continuation included using the number who "opted out" at certain time points[24] or the percentage retained among those still remaining in the study at the previous time point. [48]

Continuation up to one year

All studies reported continuation at a minimum of one time point within one year of initiation. Continuation at each time point varied greatly across studies, with some studies maintaining relatively high continuation over time and others with an immediate drop-off. To compare continuation within studies over time we looked at continuation among studies reporting three or more of the four timepoints up to month 12 in Figure 3. Average continuation among these studies was: 65% (M1), 62% (M3), 51% (M6), and 43% (M12). Percent discontinuation between time periods varied by study, with discontinuation ranging from 2% to 18% from months 1-3, 1% to 25% from months 3-6, and 7%-35% from months 6-12.

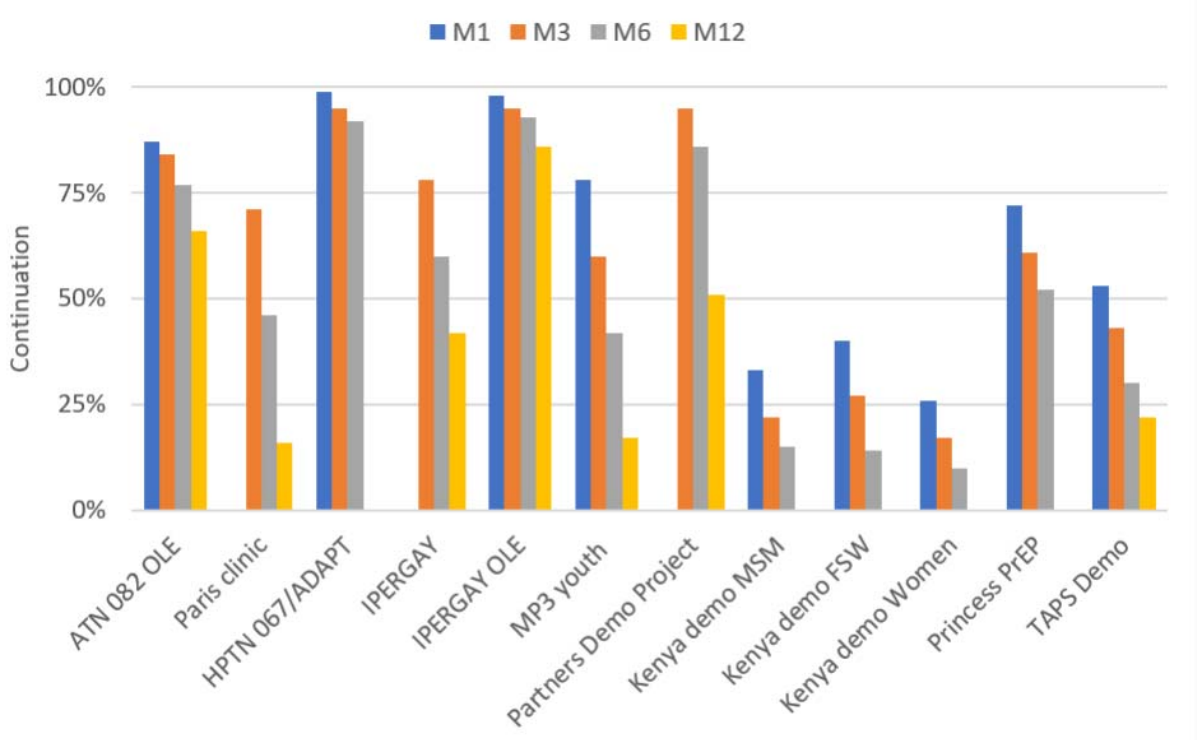

Figure 3: PrEP continuation cascade among studies reporting on three or more time periods up to month 12.

Continuation after one year

Few studies reported continuation after month 12. Six of the studies reported continuation at month 24, which ranged from 22% to 82%. At 36 months, continuation ranged from 33% to 77%, as reported by three studies. The only study providing continuation data past 36 months, the Bangkok Tenofovir Study (BTS), reported continuation on PrEP among injection drugs users (IDU) as 71% at 48 months and 63% at 60 months. [32]

Continuation by population

We examined continuation by population visually over time using forest plots. Data from 3,107 MSM, 897 women, 597 all at risk, and 747 female sex workers (FSW) were available for the meta-analysis of continuation at month 1 (Figure 4a).

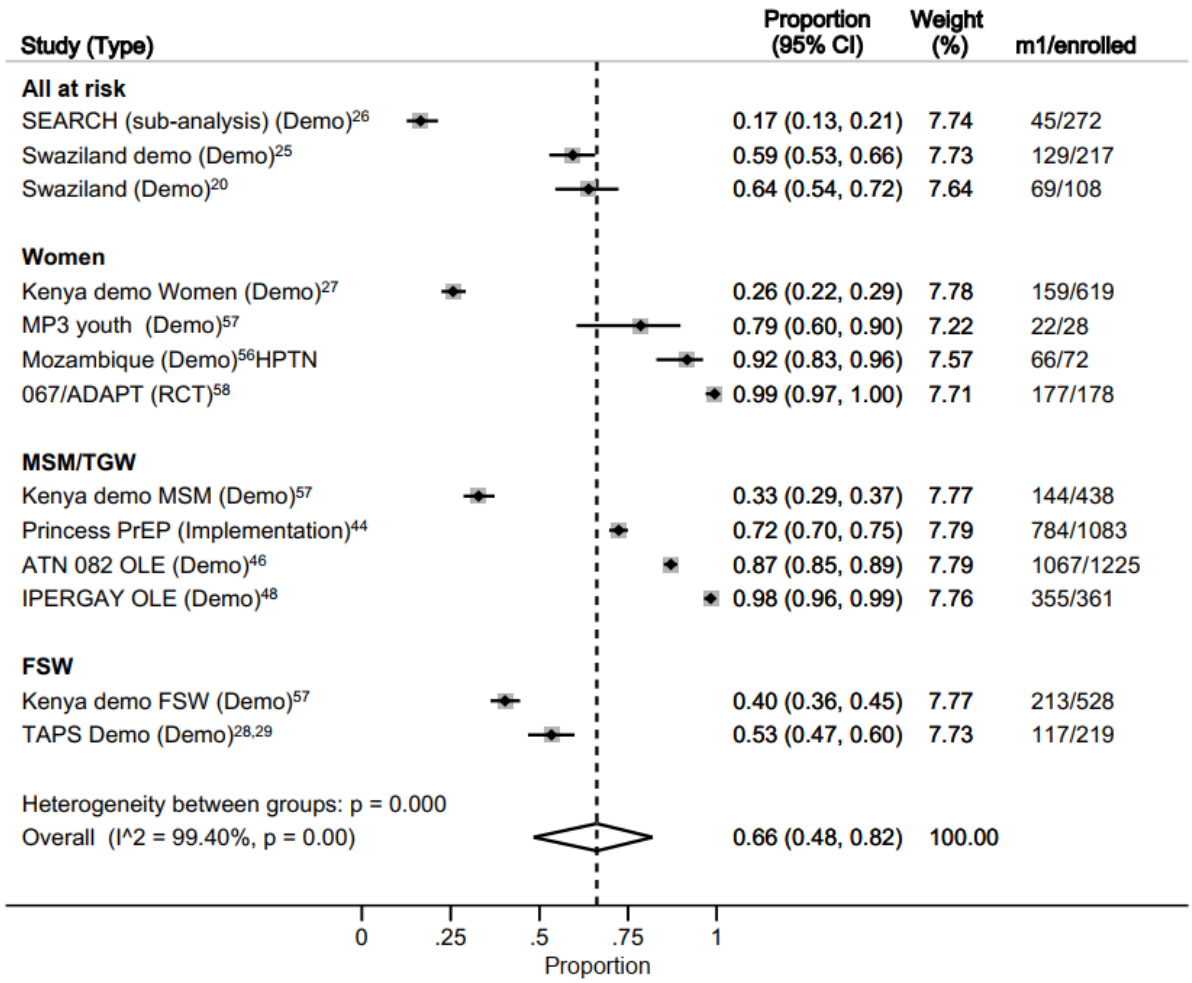

Figure 4a: Forest plot of continuation by subpopulation at 1 month after initiation

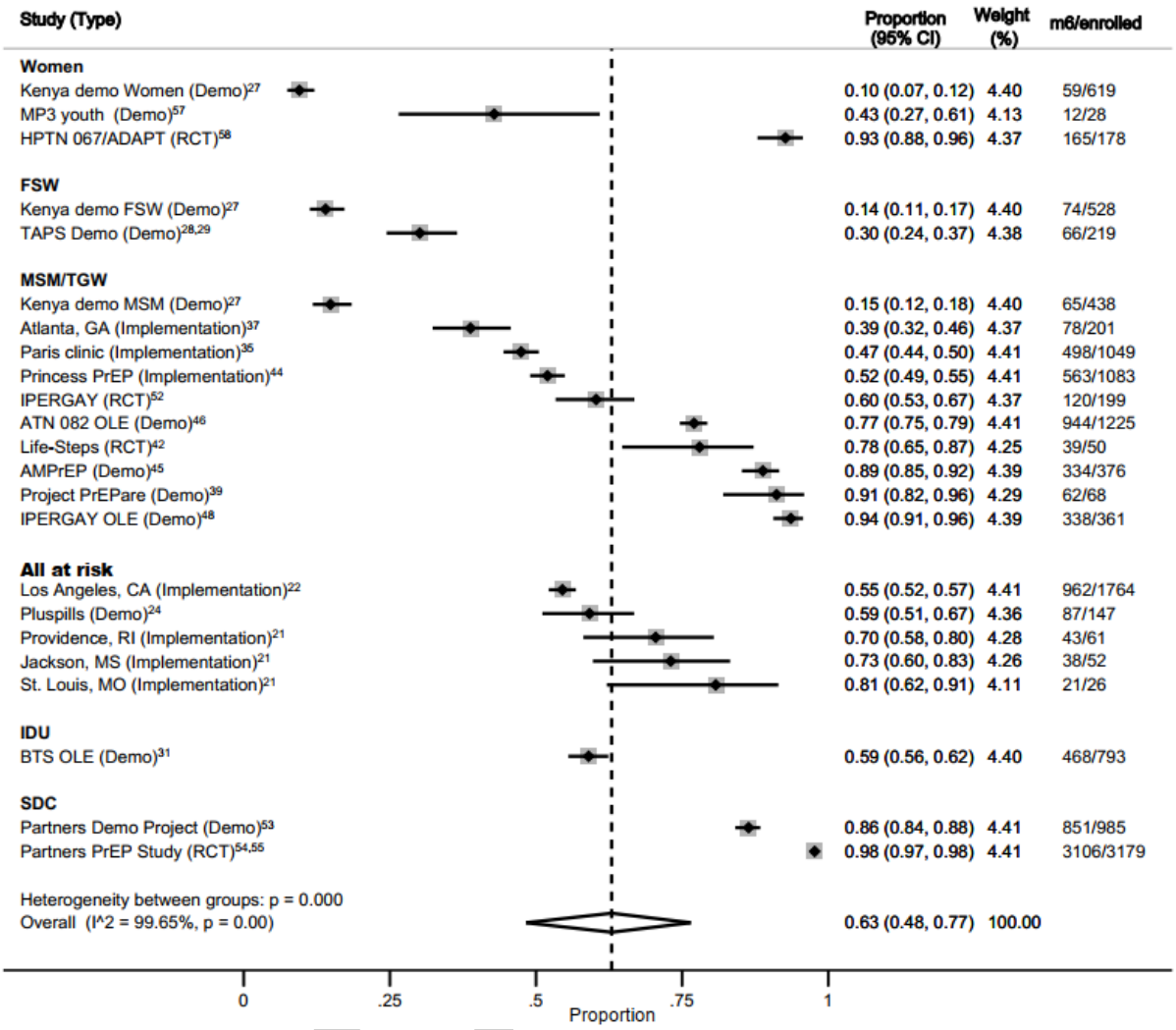

Figure 4b: Forest plot of continuation by subpopulation at 6 months after initiation

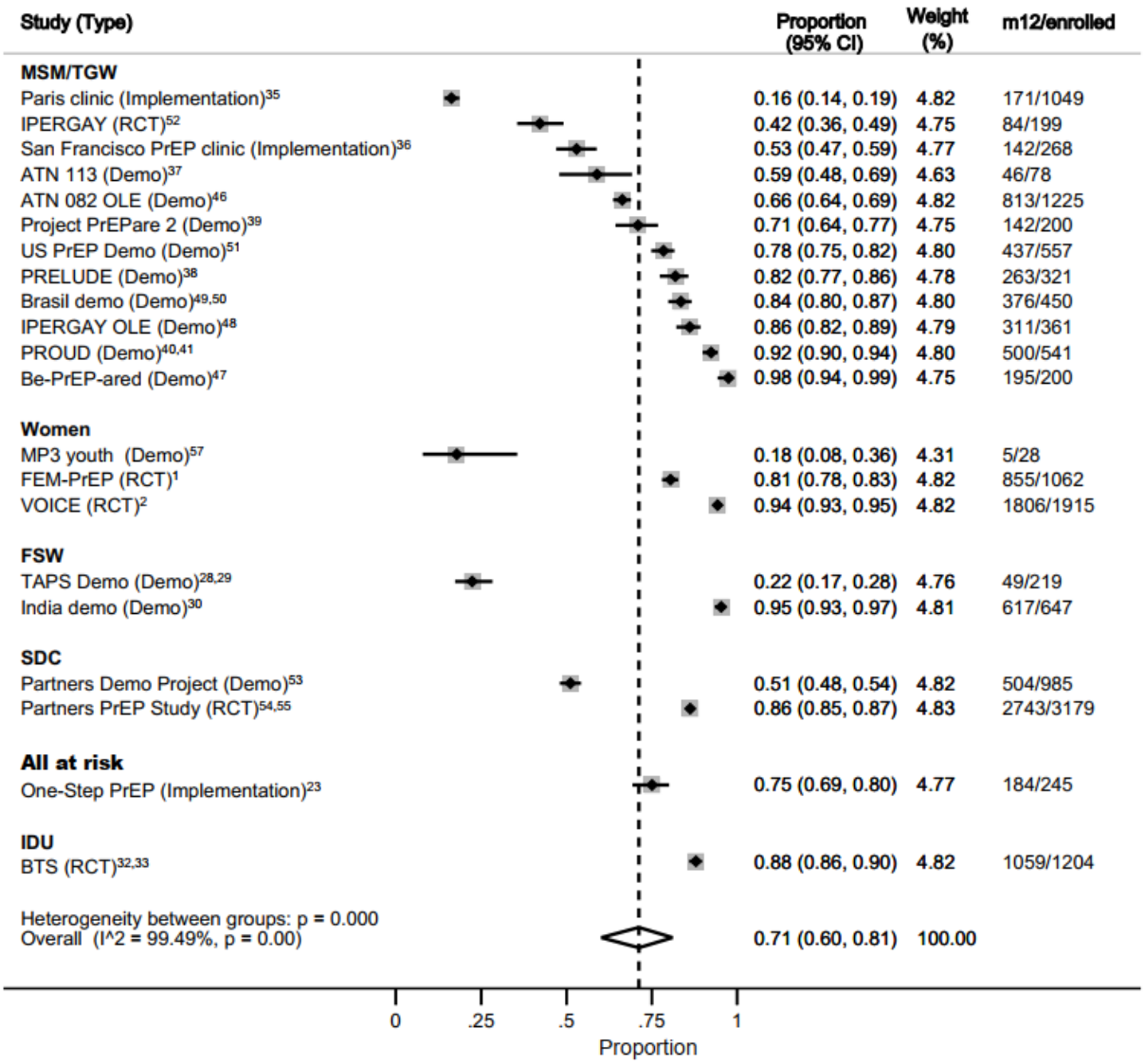

Figure 4c: Forest plot of continuation by subpopulation at 12 months after initiation

Considerable variation was observed across studies and populations. Significant inter-group heterogeneity was observed ($p<0.001$ and high I^2 statistic in each group), so pooled estimates by population were omitted. Heterogeneity among groups was also significant, suggesting the pooling of all studies may not be appropriate.

At six months, a total of 5,050 MSM, 4,164 serodiscordant couples (SDC), 2,050 all at risk, 825 women, 793 IDUs (from one study), and 747 FSW available for the meta-analysis (Figure 4b). Again, heterogeneity was high among studies and across population groups.

At month 12, data on 5,449 MSM, 4,164 SDC, 3,005 women, 1,204 IDU (from one study), 866 FSW, and 245 members of the general population (from one study) were available for the meta-analysis (Figure 4c). Again, inter-studies and inter-group heterogeneity were high.

Discussion

This systematic review synthesizes the growing body of literature on PrEP continuation. The results show that the metric by which oral PrEP continuation is measured and reported are not consistent. Continuation varies widely across studies and target populations, and continues to decline over time.

Collation of data along the PrEP cascade revealed that the time points at which continuation is reported vary widely. This is not surprising, given the abundance of proposed PrEP cascades in published literature and the lack of consensus on which components are most important to track.[11–13] In studies that reported multiple time points, we found that discontinuation often persisted over time, with discontinuation as high as 25% and 35% from months 3 to 6 and from months 6 to 12, respectively.

These results have implications for existing monitoring and evaluation guidelines, which focus heavily on cross-sectional indicators over client-level longitudinal indicators. The WHO PrEP

M&E guidelines suggest a core indicator of "Continuation on PrEP," defined as the "Percentage of PrEP users who continued on oral PrEP for three consecutive months after having initiated PrEP in the last 12 months." [7] The decision to limit this indicator to three months was justified based on early data from demonstration projects suggesting that many users who discontinue oral PrEP do so during the first few months. This review contradicts those early results, given it has shown that discontinuation in the studies currently under review was common even after month 3.

The PEPFAR oral PrEP indicators also do not promote longitudinal monitoring, rather they parallel existing treatment indicators, which give a snapshot of changes in the total number in care over time, rather than allowing for an understanding of duration of continuation. [10] While M&E indicators of client-level continuation may not be feasible, organizations should promote evaluation studies to understand this important dimension of PrEP rollout, without which impact and cost-effectiveness cannot be assessed.

Just under a third of studies reported continuation at month 1; among those, discontinuation was high, averaging 37·3%. High discontinuation at month 1 indicates a large percentage of PrEP clients are not returning for the first follow-up visit and has important implications for PrEP effectiveness. While discontinuation at subsequent time points could be due to periods of low risk, discontinuation at one month likely indicates other reasons for stopping. These findings suggest that when assessing whether a client should initiate PrEP, attention should be paid to not only PrEP eligibility, but also the client's readiness to take PrEP consistently over time. Initiations are costly[59], and no prevention impact can be assumed without at least one return visit. This finding suggests that the number of PrEP initiations may not be a very useful indicator in estimating PrEP effectiveness.

Recent studies show that side effects, stigma, influence of partners, difficulty accessing services, and reduced HIV-risk perception have contributed to discontinuation in some PrEP users[27, 60, 61]. Discontinuation due to lack of risk is an important concept for continuation measurement, as discussed previously, that we were unable to account for in our analysis due to lack of data. More research is needed to determine the reasons for high early and ongoing discontinuation.

In designing this review, we felt it was important to make the distinction between continuation of all clients who initiated and continuation among just those still at risk or indicated for PrEP, known as prevention-effective use.[16] No studies in this review reported prevention-effective use or stopping and restarting of clients on PrEP. Some studies reported planned cycling or dosing schedules, such as studies among serodiscordant couples that promoted PrEP as a bridge to ART and the Gaza miners study, which offered PrEP during periods of high risk. [53,56,62] Future research is needed to examine cycling among PrEP users and how to appropriately monitor prevention-effective use.

This review found that continuation varied by population and across time. Pooled estimates at 12 months were actually higher than previous timepoints. This is likely due to different studies reporting at the different timepoints, and some studies with particularly low continuation reporting at only months 1 and 6[27]. Continuation also varied within populations. Some of this variation can likely be attributed to differences in study types, intervention models, and mechanisms for client support.

This systematic review has limitations. Studies had various designs, populations and geographic locations. Given the paucity of data on combinations of population, study type, and geography, it is not currently possible to examine pooled continuation by just one population, study type, and region. As PrEP delivery progresses, programs should be encouraged to publish data on

continuation across time so that these analyses can be completed and shed further light on this important topic. To better understand PrEP continuation, researchers should consider longitudinal studies that account for prevention effective adherence (time at-risk) and explore probabilities of continuation via survival analysis or other more robust methods.

Some studies had to be excluded because the reported continuation data did not align with the cascade used in the study design. We could not distinguish in this review participants who were lost to follow-up versus those who went off the product and stayed in the study. Finally, this study did not assess the influence of potential confounders. Further research is needed to examine the predictors of PrEP continuation and discontinuation to more fully understand this important component of PrEP program effectiveness and efficiency.

Despite these limitations, the findings have implications for the evolving discussion on how to monitor PrEP programs and provide valuable information for decision makers. Our analysis of continuation suggests that PrEP initiations may not be a good measure of effectiveness and that longitudinal monitoring of continuation may be important for understanding long-term use patterns. Research should examine methods of ensuring PrEP-readiness prior to initiation and reasons for early and later discontinuation. Guidance is needed on how best to measure prevention-effective use, which was not reported by any studies in this review.

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Author Contributions

KS conducted the systematic review, data validation, data analysis, data interpretation, and led writing. HG contributed to study design, data interpretation and review. JL conducted the systematic review and supported study design, data analysis, data interpretation, and writing. GG contributed to study design, data analysis, data interpretation, and review. KK contributed to study design, data interpretation, and review. KT contributed to study design, data interpretation, and review. JO contributed to study design, data validation, data interpretation, and review. FTP contributed to study design, data interpretation, and review.

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Table 1: Percentage of participants/clients who continued on PrEP over time

Study Code	Priority populations	Screened/ assessed for eligibility	Eligible	Enrolled/ Initiated	Percent who continued PrEP (%)							
					M1	M3	M6	M12	M24	M36	M48	M60
Swaziland[20]	All at risk	438	333	108	63							
Providence, RI[21]	All at risk		80	61		90	70					
Jackson, MS[21]	All at risk		61	52		82	73					
St. Louis, MO[21]	All at risk		30	26		100	80					
Los Angeles, CA[22]	All at risk			1,764		67	54					
One-Step PrEP[23]	All at risk	251		245				75				
Pluspills[24]	All at risk	244		147		82	58					
Swaziland demo[1]	All at risk			217	59							
SEARCH (sub-analysis) [26]	All at risk		701	272	16							
Kenya demo FSW[27]	FSW			528	40	27	14					
TAPS demo[28,29]	FSW	241	224	219	53	43	30	22				
India demo[30]	FSW	707	652	647				95				
BTS OLE[31]	IDU	1,348	1,315	793		72	59					
BTS[32,33]	IDU			1204				88	81	77	71	63
Atlanta, GA[34]	MSM		184	63			39					
Paris clinic[35]	MSM		1,069	1049		71	46	16				
San Francisco PrEP clinic[36]	MSM	344		268				53				
ATN 113[37]	MSM	2,864	260	78				60				
PRELUDE[38]	MSM			321				81	81			
Kenya demo MSM[27]	MSM			438	33	22	15					
Project PrEPare[39]	MSM	753	241	68			91					
Project PrEPare 2[39]	MSM	2186	400	200				71	71			
PROUD[40,41]	MSM		544	541				92	82	76		
Life–Steps[42]	MSM	58		50		82	78					
Intermittent PrEP in Africa[43]	MSM, FSW	107		48		91						
Princess PrEP[44]	MSM, TGW			1,083	72	61	52					

Study Code	*Priority populations*	*Screened/ assessed for eligibility*	*Eligible*	*Enrolled/ Initiated*	*Percent who continued PrEP (%)*							
					M1	*M3*	*M6*	*M12*	*M24*	*M36*	*M48*	*M60*
AMPrEP[45]	MSM, TGW			376			89					
ATN 082 OLE[46]	MSM, TGW	2,846	1,603	1,225	87	84	77	66				
Be-PrEP-ared[47]	MSM, TGW	219		200				97				
IPERGAY OLE[48]	MSM, TGW		369	361	98	95	93	86				
Brasil demo[49,50]	MSM, TGW	1,270	753	450				83				
US PrEP demo[51]	MSM, TGW	1,069		557		88		78				
IPERGAY[52]	MSM, TGW	445	414	199		78	60	42	22			
Partners demo project[53]	SDC	1,694		985		95	86	51				
Partners PrEP Study[53,55]	SDC	7,856	4758	3,179			98	86	47	33		
Mozambique[56]	Women	97	74	72	91							
MP3 youth[57]	Women	40		28	78	60	42	17				
Kenya demo women[27]	Women			619	26	17	10					
FEM–PrEP[1]	Women			1,062				80				
HPTN 067/ADAPT[58]	Women	294		178	99	95	92					
VOICE[2]	Women		2010	1,915				94				

*FSW = Female sex workers, IDU = Injection drug users, MSM = Men who have sex with men, TGW = Transgender women, SDC = Serodiscordant couple