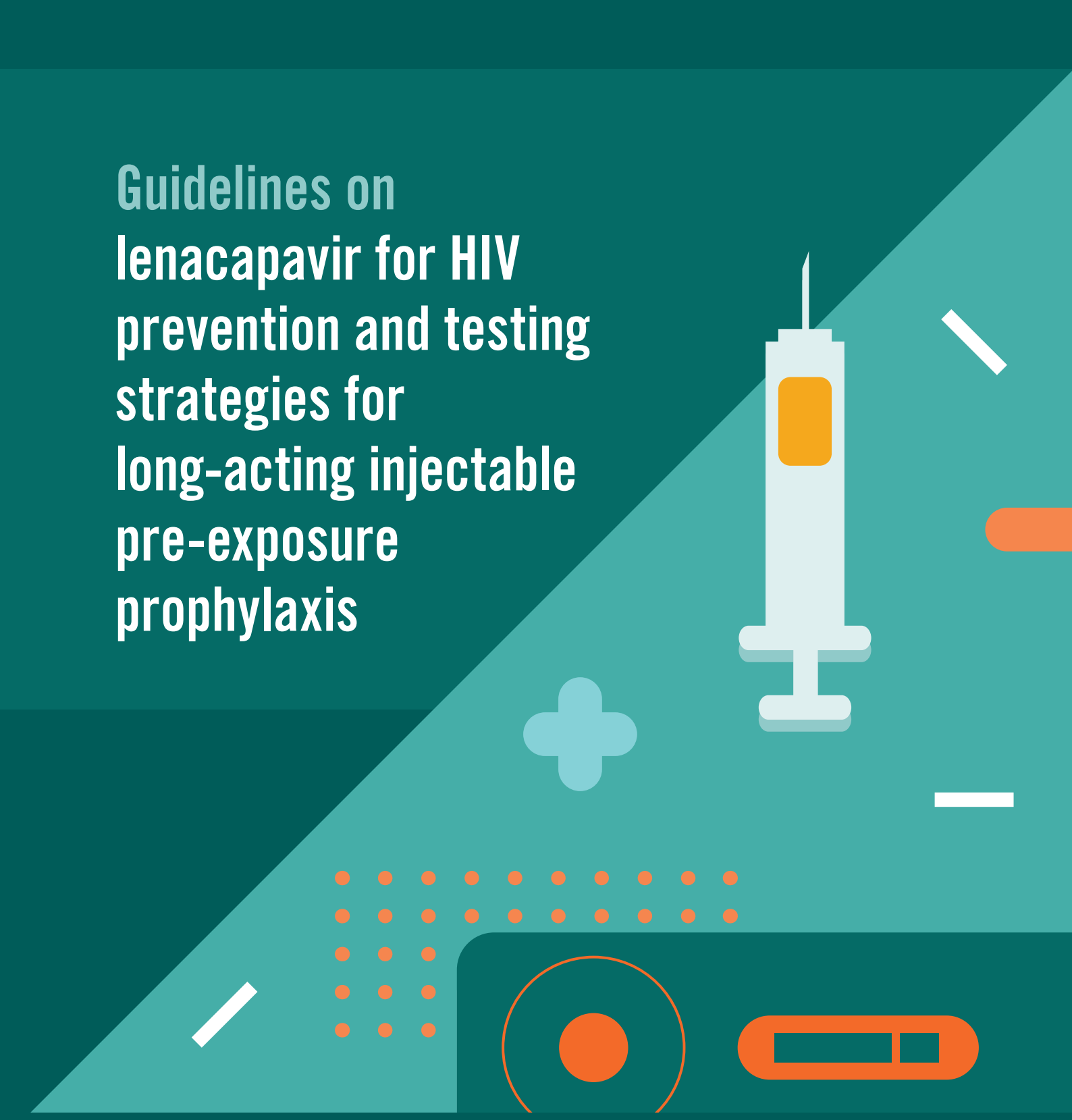
Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis



Web Annex B. Safety and efficacy of long-acting injectable lenacapavir as pre-exposure prophylaxis to reduce the risk of HIV acquisition: a systematic review

World Health Organization

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Safety and efficacy of long-acting injectable lenacapavir as pre-exposure prophylaxis to reduce the risk of HIV acquisition: a systematic review

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Background: HIV remains a significant health threat, despite the increasing availability of effective HIV prevention tools such as oral pre-exposure prophylaxis (PrEP). Injectable lenacapavir (LEN), a capsid inhibitor, is one potential new PrEP option. Results from several efficacy studies of LEN have recently become available. The purpose of this review was to synthesize the evidence to determine the overall safety and efficacy, safety of LEN as PrEP in order to inform global guidelines as to whether LEN should be recommended as an additional prevention option for people at risk of HIV.

Methods: A comprehensive search strategy reviewed multiple electronic databases and conference abstracts for relevant citations between January 2010 and January 2025. Outcomes of interest included: HIV acquisition; adverse events; drug resistance; any adverse maternal, pregnancy or birth outcomes; effect on hormonal contraception, gender-affirming hormones or opioid substitution therapy; and outcomes relevant to sexual behaviour, including condom use, number of sexual partners and incidence of sexually transmitted infections (STIs). Results were summarized narratively due to the limited number of studies conducted among diverse populations. Data were summarized and evaluated using the GRADE methodology, with particular attention to certainty of evidence.

Results: Two studies were included – PURPOSE 1 and PURPOSE 2. Both studies were phase 3 multicentred, double-blind, randomized, active-controlled trials. The two studies assessed the efficacy of LEN compared with a background HIV incidence cohort, as well as with daily oral PrEP (tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)). The study population of PURPOSE 1 included cisgender adolescent girls and young women ages 16–25 years. The study population of PURPOSE 2 included cisgender gay, bisexual and other men who have sex with men; transgender women; transgender men and gender-nonbinary persons. Overall, 8660 individuals underwent randomization across the two trials, with 4333 individuals randomized to receive active LEN. Compared with background HIV incidence rates, LEN was 100% effective in preventing HIV acquisition in PURPOSE 1 and 96% in PURPOSE 2. Compared with TDF/FTC, LEN was 100% in preventing HIV acquisition in PURPOSE 1 and 89% effective in PURPOSE 2. Only two HIV acquisitions were identified among participants randomized to LEN in PURPOSE 2. A mutation responsible for resistance to capsid inhibitors was identified in both cases. No safety concerns were identified. Rates of any adverse events (AEs) were similar across groups in PURPOSE 1 and 2. Rates of any GRADE 3 or 4 AEs were similar in PURPOSE 1, while PURPOSE 2 found fewer grade 3+ AEs in the LEN arm than in the TDF/FTC arm. In both studies injection site reactions were more common in the LEN groups than among those in the TDF/FTC groups who received placebo injections. No drug-related adverse events related to maternal, pregnancy or birth outcomes were identified. Regarding sexual behaviour, STI incidence was similar across arms in PURPOSE 1, whereas in PURPOSE 2 more incident STIs were identified in the LEN group than in the TDF-FTC group.

Conclusion: LEN is an effective means of HIV prevention and appears to have few safety risks beyond injection site reactions. LEN may lead to an increased risk of resistance to capsid inhibitors among those who experience a breakthrough infection. Notably, this review included only two controlled studies; more research is needed to understand implementation of LEN outside research settings.

GRADE tables for review of lenacapavir as PrEP

Authors: Virginia Fonner, Kyria Louis Charles and Mu-Tien Lee

Question: Should injectable lenacapavir (LEN), compared with oral PrEP containing tenofovir disoproxil (TDF) (or no use of PrEP), be offered as an additional prevention choice for people at risk of HIV as part of combination prevention approaches?

Setting: Global

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	injectable LEN	Background incidence (no PrEP use)	Relative (95% CI)	Absolute (95% CI)		
HIV acquisition: PURPOSE 1– Comparison with background HIV incidence												
1 *(1)*	Non-randomized study[a]	Very serious[b]	Not serious[c]	Not serious[d,e]	Not serious[f]	Very strong association[g]	0/2134[h]	92/8094[i]	Rate ratio 0.00 (0.00 to 0.04)	11 fewer cases per 1000 patients per year (from 8 fewer to 0)[j]	⨁⨁⨁⨁ High[b,c,d,e,f,g]	CRITICAL

a Although this comparison was conducted within the context of a randomized controlled trial, the comparison itself is based on non-randomized comparative retrospective-controlled cohort study; thus, the study design was non-randomized.

b Risk of bias was assessed using the ROBINS-I tool. Areas of bias identified included: serious bias due to confounding (analysis did not control for potential confounding variables), moderate bias due to classification of the intervention (intervention classification influenced by knowledge of HIV status), moderate selection bias (intervention and follow-up did not coincide across groups) and serious bias in measurement of the outcome (for the background incidence comparator, recent HIV acquisition was determined through using a recent infection testing algorithm with a limiting antigen antibody avidity assay, which could have misclassified individuals; in contrast, in the LEN arm HIV acquisition was measured through use of standard HIV tests). The overall risk of bias assessed using ROBIN-I was "serious". Because some risk of bias was identified in multiple domains, the outcome was downgraded two levels to "very serious".

c Results based on one study. However, two trials were conducted overall (PURPOSE 1 and PURPOSE 2). Results from both trials were relatively consistent. Results were not pooled, as the trials were conducted among different populations. PURPOSE 1 was conducted among cisgender women, and PURPOSE 2 was conducted among gay, bisexual and other men who have sex with men; transgender women; transgender men and gender-nonbinary persons at risk for HIV.

d The study could not directly compare those randomized to LEN with no PrEP (a placebo) because this would be unethical. Instead, the study provided a somewhat indirect comparison by estimating the background HIV incidence among the screened population and comparing this with HIV incidence assessed in the group randomized to LEN. This comparison introduced some bias, which has been accounted for in the assessment of risk of bias. Given that these limitations have already been accounted for in the risk of bias assessment, and given that the investigators provide a strong justification for using this design and methods in the published manuscript reporting trial results (for example, design recommended in consensus statement on how to conduct next-generation HIV prevention trials, substantial drawbacks to alternative designs). For these reasons, the outcome was not downgraded for indirectness.

e The evidence from PURPOSE 1 and PURPOSE 2 is directly relevant to many populations of interest that could be at risk of HIV, including cisgender women; gay, bisexual and other men who have sex with men; transgender women; transgender men and gender-nonbinary persons. There are some populations not included that can be at risk of HIV, such as people who inject drugs.

f Although the number of events is small, the evidence was not downgraded for imprecision, as the sample size was deemed sufficiently large, and the study was adequately powered.

g The incidence rate ratio was 0.0 as no HIV infections occurred among the group randomized to LEN; Thus, the outcome was upgraded two levels as the effect was very large (defined as the rate ratio being <0.20).

h Sample size reflects modified intent-to-treat analysis; four participants from the LEN arm were subsequently determined to have had HIV infection at the time of randomization and were excluded from the analysis

i The denominator reflects the total number of individuals screened, including those diagnosed with recent and chronic HIV infection during screening.

j Absolute numbers at less or greater risk of the outcome were calculated using relative risk (RR). The calculated RR was 0.02 (95% CI: 0.00, 0.33). In the intervention arm, there were no events and 2134 participants randomized to LEN (a modified intent-to-treat analysis was used; four people randomized to LEN were found to have had HIV at baseline and were excluded). In the control arm, there were 92 events (92 people were identified with recent infection during screening) and 8094 people in total in the screened population (including those with recent and chronic HIV infection).

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	injectable LEN	Background incidence (no PrEP use)	Relative (95% CI)	Absolute (95% CI)		
HIV acquisition: PURPOSE 2 – Comparison with background incidence												
1*(2)*	Non-randomized study[a]	Very serious[b]	Not serious[c]	Not serious[d,e]	Not serious[f]	Very strong association[k]	2/2179[h]	45/4634[i,l]	Rate ratio 0.04 (0.01 to 0.18)	9 fewer cases per 1000 patients per year (from 10 fewer to 6 fewer)[m]	⨁⨁⨁⨁ High[b,c,d,e,f,k]	CRITICAL

a Although this comparison was conducted within the context of a randomized controlled trial, the comparison itself is based on non-randomized comparative retrospective-controlled cohort study; thus, the study design was non-randomized.

b Risk of bias was assessed using the ROBINS-I tool. Areas of bias identified included: serious bias due to confounding (analysis did not control for potential confounding variables), moderate bias due to classification of the intervention (intervention classification influenced by knowledge of HIV status), moderate selection bias (intervention and follow-up did not coincide across groups) and serious bias in measurement of the outcome (for the background incidence comparator, recent HIV acquisition was determined through using a recent infection testing algorithm with a limiting antigen antibody avidity assay, which could have misclassified individuals; in contrast, in the LEN arm HIV acquisition was measured through use of standard HIV tests). The overall risk of bias assessed using ROBIN-I was "serious". Because some risk of bias was identified in multiple domains, the outcome was downgraded two levels to "very serious".

c Results based on one study. However, two trials were conducted overall (PURPOSE 1 and PURPOSE 2). Results from both trials were relatively consistent. Results were not pooled, as the trials were conducted among different populations. PURPOSE 1 was conducted among cisgender women, and PURPOSE 2 was conducted among gay, bisexual and other men who have sex with men; transgender women; transgender men and gender-nonbinary persons at risk for HIV.

d The study could not directly compare those randomized to LEN with no PrEP (a placebo) because this would be unethical. Instead, the study provided a somewhat indirect comparison by estimating the background HIV incidence among the screened population and comparing this with HIV incidence assessed in the group randomized to LEN. This comparison introduced some bias, which has been accounted for in the assessment of risk of bias. Given that these limitations have already been accounted for in the risk of bias assessment, and given that the investigators provide a strong justification for using this design and methods in the published manuscript reporting trial results (for example, design recommended in consensus statement on how to conduct next-generation HIV prevention trials, substantial drawbacks to alternative designs). For these reasons, the outcome was not downgraded for indirectness.

e The evidence from PURPOSE 1 and PURPOSE 2 is directly relevant to many populations of interest that could be at risk of HIV, including cisgender women; gay, bisexual and other men who have sex with men; transgender women; transgender men and gender-nonbinary persons. There are some populations not included that can be at risk of HIV, such as people who inject drugs.

f Although the number of events is small, the evidence was not downgraded for imprecision, as the sample size was deemed sufficiently large, and the study was adequately powered.

h Sample size reflects modified intent-to-treat analysis; four participants from the LEN arm were subsequently determined to have had HIV infection at the time of randomization and were excluded from the analysis.

i Sample size reflects modified intent-to-treat analysis; four participants from the LEN arm were subsequently determined to have had HIV infection at the time of randomization and were excluded from the analysis.

k The incidence rate ratio was 0.04; thus, the outcome was upgraded two levels as the effect was very large (defined as the rate ratio being <0.20).

l The numerator reflects the number of recent HIV acquisitions identified among the screened populations.

m Absolute numbers at less or greater risk of the outcome were calculated using RR. The calculated RR was 0.09 (95% CI: 0.02, 0.39). In the intervention arm, there were two events and 2179 participants randomized to LEN. In the control arm, there were 45 events (45 people were identified with recent infection during screening) and 4634 people in total in the screened population (including those with recent and chronic HIV infection).

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Injectable LEN	Oral PrEP containing TDF	Relative (95% CI)	Absolute (95% CI)		
HIV acquisition: PURPOSE 1 – Comparison with TDF/FTC												
1 *(1)*	Randomized trial	Not serious	Not serious[c]	Not serious[e]	Not serious[f]	None	0/2134[n]	16/1068[n]	Rate ratio 0.0 (0.0 to 0.1)	15 fewer cases per 1000 patients per year (from 11 fewer to –)	⨁⨁⨁⨁ High[c,e,f]	CRITICAL
HIV acquisition: PURPOSE 2 – Comparison with TDF/FTC												
1 *(1)*	Randomized trial	Not serious	Not serious[c]	Not serious[e]	Not serious[f]	None	2/2179[p]	9/1086[p]	Rate ratio 0.11 (0.02 to 0.51)	7 fewer cases per 1000 patients per year (from 8 fewer to 4 fewer)[q]	⨁⨁⨁⨁ High[c,e,f]	CRITICAL
Any AE: PURPOSE 1 – Comparison with F/TDF												
1 *(1)*	Randomized trial	Not serious	Not serious[c]	Not serious[e]	Not serious	None	1631/2138 (76.3%)[r]	830/1070 (77.6%)[r]	RR 0.98 (0.94 to 1.02)	16 fewer per 1000 (from 47 fewer to 16 more)	⨁⨁⨁⨁ High[c,e]	CRITICAL
Any AE: PURPOSE 2 – Comparison with F/TDF												
1 *(2)*	Randomized trial	Not serious	Not serious[c]	Not serious[e]	Not serious	None	1607/2183 (73.6%)[r]	803/1088 (73.8%)[r]	RR 1.00 (0.96 to 1.04)	0 fewer per 1000 (from 30 fewer to 30 more)	⨁⨁⨁⨁ High[c,e]	CRITICAL

c Results based on one study. However, two trials were conducted overall (PURPOSE 1 and PURPOSE 2). Results from both trials were relatively consistent. Results were not pooled, as the trials were conducted among different populations. PURPOSE 1 was conducted among cisgender women, and PURPOSE 2 was conducted among gay, bisexual and other men who have sex with men; transgender women; transgender men and gender-nonbinary persons at risk for HIV

e The evidence from PURPOSE 1 and PURPOSE 2 is directly relevant to many populations of interest that could be at risk of HIV, including cisgender women; gay, bisexual and other men who have sex with men; transgender women; transgender men and gender-nonbinary persons. There are some populations not included that can be at risk of HIV, such as people who inject drugs.

f Although the number of events is small, the evidence was not downgraded for imprecision, as the sample size was deemed sufficiently large, and the study was adequately powered.

n Sample size reflects modified intent-to-treat analysis; seven participants were subsequently determined to have had HIV infection at the time of randomization and were excluded from the total (four in the LEN arm and three in the TDF arm).

p Sample size reflects modified intente-to-treat analysis; six participants were subsequently determined to have had HIV infection at the time of randomization and were excluded from the total (four in the LEN arm and two in the TDF arm).

q Absolute numbers at less or greater risk of the outcome were calculated using RR. The calculated RR was 0.11 (95% CI: 0.02, 0.51). In the intervention arm, there were two events and 2179 participants randomized to LEN. In the TDF arm, there were nine events and 1086 participants.

r Sample includes all individuals who underwent randomization and received at least one dose of study drug.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Injectable LEN	Oral PrEP containing TDF	Relative (95% CI)	Absolute (95% CI)		
Any grade 3 or 4 AE: PURPOSE 1												
1 *(1)*	Randomized trial	Not serious	Serious[s]	Not serious[e]	Not serious	None	88/2138 (4.1%)[r]	50/1070 (4.7%)[r]	RR 0.88 (0.63 to 1.24)	6 fewer per 1000 (from 17 fewer to 11 more)	⨁⨁⨁◯ Moderate[e,s]	CRITICAL
Any grade 3 or 4 AE: PURPOSE 2												
1 *(2)*	Randomized trial	Not serious	Serious[s]	Not serious[e]	Not serious	None	91/2183 (4.2%)[r]	65/1088 (6.0%)[r]	RR 0.70 (0.51 to 0.95)	18 fewer per 1000 (from 29 fewer to 3 fewer)	⨁⨁⨁◯ Moderate[e,s]	CRITICAL
Injection site reactions: PURPOSE 1												
1 *(1)*	Randomized trial	Not serious	Not serious[c]	Not serious[e]	Not serious	None	1470/2138 (68.8%)[r]	363/1070 (33.9%) [r]	RR 2.03 (1.86 to 2.21)	349 more per 1000 (from 292 more to 410 more)	⨁⨁⨁⨁ High[c,e]	CRITICAL
Injection site reactions: PURPOSE 2												
1 *(2)*	Randomized trial	Not serious	Not serious[c]	Not serious[e]	Not serious	None	1816/2183 (83.2%) [r]	756/1088 (69.5%) [r]	RR 1.20 (1.15 to 1.25)	139 more per 1000 (from 104 more to 174 more)	⨁⨁⨁⨁ High[c,e]	CRITICAL
Drug resistance among those diagnosed with HIV: PURPOSE 1 – not reported												
–	–	–	–	–	–	–	No HIV infections were identified among participants randomized to LEN. Thus, no drug resistance occurred.				–	CRITICAL

s Results based on one study. However, two trials were conducted overall (PURPOSE 1 and PURPOSE 2). Results from the two trials showed different effects. In PURPOSE 1 there was no difference in grade 3 or 4 AEs between the LEN group and the TDF group. In PURPOSE 2 there were more grade 3 and 4 AEs in the TDF group than in the LEN group. However, other categories of AEs, including any AE, any grade 2+ AE and serious AEs, were similar across groups in PURPOSE 2. Results were not pooled, as the trials were conducted among different populations. However, because the two trials differed with respect to the relative effect size, the outcome was downgraded one level for inconsistency.

c Results based on one study. However, two trials were conducted overall (PURPOSE 1 and PURPOSE 2). Results from both trials were relatively consistent. Results were not pooled, as the trials were conducted among different populations. PURPOSE 1 was conducted among cisgender women, and PURPOSE 2 was conducted among gay, bisexual and other men who have sex with men; transgender women; transgender men and gender-nonbinary persons at risk for HIV.

e The evidence from PURPOSE 1 and PURPOSE 2 is directly relevant to many populations of interest that could be at risk of HIV, including cisgender women; gay, bisexual and other men who have sex with men; transgender women; transgender men and gender-nonbinary persons. There are some populations not included that can be at risk of HIV, such as people who inject drugs.

r Sample includes all individuals who underwent randomization and received at least one dose of study drug.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Injectable LEN	Oral PrEP containing TDF	Relative (95% CI)	Absolute (95% CI)		
Drug resistance among those diagnosed with HIV: PURPOSE 2												
1 *(2)*	Randomized trial	Not serious	Not serious[u]	Not serious[e]	Very serious[v]	None	Only two HIV infections were identified among participants randomized to LEN; both patients had the N74D capsid resistance mutation. Of the nine HIV infections identified among participants randomized to F/TDF, eight had blood samples available for drug resistance testing, and one was found to have an emtricitabine resistance mutation (M184V).				⨁⨁◯◯ Low[e,u,v]	CRITICAL
Effectiveness of hormonal contraception: PURPOSE 1 – not reported												
–	–	–	–	–	–	–	Being on contraception was not required for study participation (but was provided if pregnancy was not desired). Effectiveness of contraception was not measured in the study.				–	CRITICAL
Effectiveness of hormonal contraception: PURPOSE 2 – not reported												
–	–	–	–	–	–	–	No pregnancies were reported in PURPOSE 2.				–	CRITICAL
Effectiveness of gender affirming hormones- PURPOSE 2 – not reported												
–	–	–	–	–	–	–	PURPOSE 2 included transgender and non-binary populations. Among study participants 11.6% (n=253) of those randomized to LEN and 12.0% (n=131) of those randomized to F/TDF reported taking gender-affirming hormones at baseline. The effectiveness of gender-affirming hormones was not assessed in the study.				–	CRITICAL
Effectiveness of opioid substitution therapy (OST): PURPOSE 1 – not reported												
–	–	–	–	–	–	–	Effectiveness of OST was not assessed in the study.				–	CRITICAL
Effectiveness of OST: PURPOSE 2 – not reported												
–	–	–	–	–	–	–	Effectiveness of OST was not assessed in the study.				–	CRITICAL

e The evidence from PURPOSE 1 and PURPOSE 2 is directly relevant to many populations of interest that could be at risk of HIV, including cisgender women; gay, bisexual and other men who have sex with men; transgender women; transgender men and gender-nonbinary persons. There are some populations not included that can be at risk of HIV, such as people who inject drugs.

u Results based on one study, and so inconsistency cannot be determined.

v In PURPOSE 2 only two HIV infections were identified among those randomized to LEN. Both had N74D capsid resistance mutation identified at the visit in which they were diagnosed with HIV. The outcome was downgraded due to the small absolute number of events.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Injectable LEN	Oral PrEP containing TDF	Relative (95% CI)	Absolute (95% CI)		
Any adverse maternal, pregnancy or birth outcome (defined as pregnancy, puerperium and perinatal conditions grade 3 or higher): PURPOSE 1												
1 *(1)*	Randomized trial	Not serious	Not serious[u]	Not serious[e]	Serious[w]	None	24/2138 (1.1%)	16/1070 (1.5%)	RR 0.75 (0.40 to 1.41)	4 fewer per 1000 (from 9 fewer to 6 more)	⨁⨁⨁◯ Moderate[e,u,w]	CRITICAL
Any adverse maternal, pregnancy or birth outcome (defined as pregnancy, puerperium and perinatal conditions grade 3 or higher): PURPOSE 2 – not reported												
–	–	–	–	–	–	–	No pregnancies were reported in PURPOSE 2.				–	CRITICAL
Sexual behavior – STI incidence (gonorrhea, chlamydia, and Trichomonas vaginalis): PURPOSE 1												
1 *(1)*	Randomized trial	Not serious	Serious[d]	Not serious[e]	Not serious	None	930/2008	452/989	Rate ratio 1.01 (0.90 to 1.13)	5 more per 1000 patients per year (from 32 fewer to 46 more)[y]	⨁⨁⨁◯ Moderate[e,x]	IMPORTANT
Sexual behavior – STI incidence (gonorrhea and chlamydia): PURPOSE 2												
1 *(2)*	Randomized trial	Not serious	Serious[x]	Not serious[e]	Not serious	None	1504/2096	668/1036	Rate ratio 1.12 (1.02 to 1.23)	71 more per 1000 patients per year (from 39 more to 110 more)[z]	⨁⨁⨁◯ Moderate[e,x]	IMPORTANT

CI = confidence interval; RR = risk ratio

e The evidence from PURPOSE 1 and PURPOSE 2 is directly relevant to many populations of interest that could be at risk of HIV, including cisgender women; gay, bisexual and other men who have sex with men; transgender women; transgender men and gender-nonbinary persons. There are some populations not included that can be at risk of HIV, such as people who inject drugs.

u Results based on one study, and so inconsistency cannot be determined.

w Downgraded due to few events and a wide confidence interval that spans appreciable benefit and harm.

x Risk of bias based on one study, although two studies (with different populations) measured this outcome. Results were not pooled due to differences in study populations. Outcomes differed between these two studies. In PURPOSE 1, conducted among cisgender women, no association between LEN and TDF and STI incidence was found. In PURPOSE 2 STI incidence was lower for one STI (urethral chlamydia) in the TDF/FTC group, but not others. The incidence of STIs, using a composite measure that combined incidence of gonorrhea (all types) and chlamydia (all types), was higher in the LEN group compared to the TDF/FTC group in PURPOSE 2 but not in PURPOSE 1. (The composite measure combined incidence of gonorrhea (all types), chlamydia (all types) and Trichomonas vaginalis. For this reason the outcome was downgraded one level for inconsistency.

y Absolute numbers of people at less or greater risk of the outcome were calculated using RR. The calculated RR was 1.01 (95% CI: 0.93, 1.10).

z Absolute numbers of people at less or greater risk of the outcome were calculated using RR. The calculated RR was 1.11 (95% CI: 1.06, 1.17).

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