World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach - second edition, WHO; 2016

Evidence profile for systematic review on pre-exposure prophylaxis effectiveness, safety and sexual and reproductive health outcomes

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Question: Should oral PrEP (containing tenofovir) be used for preventing HIV infection among people at substantial risk of HIV infection?

Setting: Global

Bibliography: 15 randomized controlled trials and 3 observational studies

Quality assessment							No of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral PrEP (containing tenofovir)	Control	Relative (95% CI)	Absolute		
HIV infection – PrEP versus placebo – adherence >70%												
3[1]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	39/3866 (1%)	79/2284 (3.5%)	RR 0.30 (0.21 to 0.45)	24 fewer per 1000 (from 19 fewer to 27 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
HIV infection – PrEP versus placebo – adherence 40–70%												
2[3]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	53/2455 (2.2%)	97/2457 (3.9%)	RR 0.55 (0.39 to 0.76)	18 fewer per 1000 (from 9 fewer to 24 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
HIV infection – PrEP versus placebo – adherence <40%												
2[4]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	146/3002 (4.9%)	95/2031 (4.7%)	RR 0.95 (0.74 to 1.23)	2 fewer per 1000 (from 12 fewer to 11 more)	⊕⊕⊕⊕ HIGH	CRITICAL
HIV infection – PrEP versus no PrEP												
2[5]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/367 (0.82%)	22/353 (6.2%)	RR 0.15 (0.05 to 0.46)	53 fewer per 1000 (from 34 fewer to 59 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Any adverse event												
10[6]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	7670/9922 (77.3%)	5718/7308 (78.2%)	RR 1.01 (0.99 to 1.03)	8 more per 1000 (from 8 fewer to 23 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Any grade 3 or 4 adverse event												

11[7]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1289/9680 (13.3%)	839/7058 (11.9%)	RR 1.02 (0.92 to 1.13)	2 more per 1000 (from 10 fewer to 15 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Drug resistance (drug-resistant HIV infection among participants with acute infection at enrolment)												
4[8]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	7/25 (28%)	1/17 (5.9%)	RR 3.34 (1.11 to 10.06)	138 more per 1000 (from 6 more to 533 more) Per seroconversion	⊕⊕⊕O MODERATE	CRITICAL
Drug resistance (drug-resistant HIV infection among participants who became infected post-randomization (incident infections))												
3[10]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	5/155 (3.2%)	2/119 (1.7%)	RR 2.27 (0.48 to 10.6)	21 more per 1000 (from 9 fewer to 161 more) Per seroconversion	⊕⊕⊕O MODERATE	CRITICAL
Drug resistance – overall risk (relative risk of acquiring or developing drug-resistant HIV infection among everyone at risk)												
3[10]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	5/3612 (0.14%)	2/2637 (0.08%)	RR 1.74 (0.36 to 8.38)	1 more per 1000 (from 0 fewer to 6 more)	⊕⊕⊕O MODERATE	CRITICAL
Contraception effectiveness – FEM-PrEP (assessed with: women using contraceptives comparing PrEP to placebo arms)												
1[11]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[12]	none	69/602 (11.5%)	48/614 (7.8%)	aHR 1.20 (0.9 to 1.8)	15 more per 1000 (from 8 fewer to 58 more)	⊕⊕⊕O MODERATE	CRITICAL
Contraception effectiveness – Partners PrEP COCs (assessed with: comparing pregnancy rates among women using oral contraception to women not using contraception in the PrEP arm[13])												
1[14]	randomized trials	no serious risk of bias	no serious inconsistency[15]	no serious indirectness	serious[12]	none	37/209 (17.7%)	11/108 (10.2%)	aHR 0.96 (0.58-1.58)	-- [13]	⊕⊕⊕O MODERATE	CRITICAL
Contraception effectiveness – Partners PrEP Injectables (assessed with: comparing pregnancy rates among women using injectable contraception to women not using contraception in the PrEP arm[13])												
1[14]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[12]	none	29/564 (5.1%)	17/319 (5.3%)	aHR 0.26 (0.16-0.41)	--[13]	⊕⊕⊕O MODERATE	CRITICAL
Adverse pregnancy event												

2[16]	randomized trials	no serious risk of bias	no serious inconsistency[17]	no serious indirectness	serious[12]	none	99/266 (37.2%)	48/147 (32.7%)	RR 1.25 (0.64 to 2.45)	82 more per 1000 (from 118 fewer to 473 more)	⊕⊕⊕O MODERATE	CRITICAL
Condom use[18]												
9[19]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
Number of sexual partners[18]												
11[20]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] Partners PrEP (Baeten et al., 2012), TDF2 (Thigpen et al., 2012) and CDC Safety Study (Groshkopf et al., 2013).

[2] Data are only for participants aged 18 years and older. This footnote applies to all outcomes, since trials only included participants aged 18 years and older.

[3] iPrEx (Grant et al., 2010) and Bangkok Tenofovir Study (Choopanya et al., 2013).

[4] FEM-PrEP (Van Damme et al., 2012) and VOICE (Marrazzo et al., 2015).

[5] PROUD (Molina et al., 2015) and CDC Safety Study (Groshkopf et al., 2013).

[6] Bangkok TDF Study (Choopanya et al., 2013), FEM-PrEP (Van Damme et al., 2012), IAVI Kenya Study (Mutua et al., 2012), IAVI Uganda Study (Kibengo et al., 2013), Ipergay (Molina et al., 2015), iPrEx (Grant et al., 2010), Partners PrEP (Baeten et al., 2012), TDF2 (Thigpen et al., 2012), West Africa Study (Peterson et al., 2007) and VOICE (Marrazzo et al., 2015).

[7] Bangkok Tenofovir Study (Choopanya et al., 2013), CDC Safety Study (Groshkopf et al., 2013), FEM-PrEP (Van Damme et al., 2012), IAVI Kenya Study (Mutua et al., 2012), IAVI Uganda Study (Kibengo et al., 2013), Ipergay (Molina et al., 2015), iPrEx (Grant et al., 2010), Partners PrEP (Baeten et al., 2012), TDF2 (Thigpen et al., 2012), West Africa Study (Peterson et al., 2007) and VOICE (Marrazzo et al., 2015),

[8] iPrEx (Grant et al., 2010), Partners PrEP (Baeten et al., 2012), TDF2 (Thigpen et al., 2012) and VOICE (Marrazzo et al., 2015).

[9] The total number of events was less than 50; therefore, evidence was downgraded for serious imprecision. Evidence was not further downgraded for imprecision because the outcome (drug-resistant HIV infection) was an extremely rare event among a relatively large sample size (*n*=6249) involving four methodologically sound randomized controlled trials.

[10] FEM-PrEP (Van Damme et al., 2012), TDF2 (Thigpen et al., 2012) and VOICE (Marrazzo et al., 2015).

[11] FEM-PrEP (Callahan et al., 2015).

[12] Total number of events was less than 300; therefore, evidence was downgraded for imprecision.

[13] Adjusted hazard ratios compare pregnancy events among women using contraception to women not using contraception in the PrEP arm. The results comparing PrEP and placebo arms show no statistical difference for COCs (*P*=0.26) and Injectables (*P*=0.19). Adjusted hazard ratios for women in the placebo arm are not shown.

[14] Partners PrEP (Murnane et al., 2014).

[15] Raw data show trends toward higher rates of pregnancy among women using hormonal contraception receiving PrEP. Rates become nonsignificant once controlled for confounders.

[16] FEM-PrEP (Van Damme et al., 2012) and Partners PrEP (Baeten et al., 2012).

[17] For the FEM-PrEP study, authors note the higher pregnancy-related adverse event rate in the FTC + TDF group (*P* = 0.04) but also note that there were more pregnancies in this group than in the placebo group (IR=11.2 per 100 person-years versus 7.5 per 100 person-years, respectively).

[18] Data could not be pooled due to differences in outcome measurements. The results are presented narratively in report and presentation.

[19] 9 randomized controlled trials: FEM-PrEP (Van Damme et al., 2012), iPrEx (Grant et al., 2010), Partners PrEP randomized controlled trial (Baeten et al., 2012), Partners PrEP OLE (Baeten et al., 2014), TDF2 (Thigpen et al., 2012), West Africa Study (Peterson et al., 2007), CDC Safety Study (Liu et al, 2013), Project PrEPare (Hosek et al., 2013), and PROUD (McCormick et al., 2015). 1 Observational study: iPrEx OLE (Grant et al., 2014)

[20] 11 randomized controlled trials: Bangkok Tenofovir Study (Martin et al., 2014), FEM-PrEP (Van Damme et al., 2012), iPrEx (Grant et al., 2010), IAVI Kenya Study (Mutua et al., 2012), IAVI Uganda Study (Kibengo et al., 2013), Partners PrEP randomized controlled trial (Baeten et al., 2012), Partners PrEP OLE (Baeten et al., 2014), TDF2 (Thigpen et al., 2012), West Africa Study (Peterson et al., 2007), CDC Safety Study (Liu et al., 2013), and PROUD (McCormick et al., 2015). 2 Observational Study: Bangkok Tenofovir Study OLE (Martin et al., 2015) and iPrEx OLE (Grant et al., 2014).