PrEP effectiveness and cost effectiveness

Review of the literature

No. 2018/06Ae, The Hague, March 27, 2018

Backgrounddocument to:

Preventive use of HIV medication

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Health Council of the Netherlands

contents

01 summary tables of PrEP studies

This background document expands on some of the scientific literature used during the preparation of the advisory report: *PrEP (Pre Exposure Prophylaxis for prevention of HIV)* This includes a summary of the results of the PrEP trials (Table 1), a more detailed description of the most relevant trials (Table 2), and an overview of the cost-effectiveness studies with specific reference to high-risk MSM in affluent countries (Table 3).

Table 1

Table 1 gives an overview of published reviews on the effectiveness of PrEP supplemented by recent publications on new RCTs and cohort studies. Five systematic reviews were used (from the period 2012-2016), which summarised the results of RCTs and follow-up studies, and five studies with supplementary information: European studies on men who have sex with men (MSM), and as-yet unfinished implementation studies.

Reviews of PrEP studies:

1. Cochrane 2012 (review of 6 RCTs)[1];
2. CDC PrEP guidelines 2014 (description of 2 RCTs in MSM, 5 in heterosexuals, 1 in injecting drug users) [2];
3. NHS report 2015 (Evidence review with descriptions of the main RCTs up to October 2014)[3];
4. Fonner 2016 (Review and meta-analysis for WHO PrEP guideline[4] with 15 RCTs and 3 observational studies)[5];
5. Hanscom 2016 (meta-analysis 5 trials in women)[6]

PrEP studies with supplementary information:

- MSM in Europe (completed): PROUD[7], IPERGAY[8]
- Recent/current trials: AMPrEP (Amsterdam)[9] and Be-PrEP-ared (Antwerp),[10] VicPrEP Australia.[11]

Effectiveness was calculated by comparing the incidence of HIV in the group not using PrEP with that of the group using PrEP. In this way, risk reduction can be determined (% of the reduction of the risk of HIV). The quality of the studies reflects the quality of what was reported in the reviews on the quality of individual RCTs and follow-up studies. The table gives the findings on MSM separately. Adherence to therapy, safety and side effects are also reproduced in brief in the table.

Table 2

Table 2 gives an overview of the most important individual PrEP trials[7-24] and describes the characteristics and results of these trials (name and reference in the first column), in which the effectiveness of TDF/FTC as PrEP was investigated.

Table 3

Table 3 summarises the most important studies concerning cost effectiveness in men who have sex with men (MSM) in affluent countries.[25-36] The costs of PrEP and HIV treatment have a big effect on cost effectiveness (the incremental cost-effectiveness ratio, ICER), which

is usually expressed as the price per quality adjusted life year in good health (QALY). Costs vary enormously in time and between countries.
The outcomes (ICER or price per prevented infection) and important scientific hypotheses in the base case of every study are reported on. The hypotheses concern the effectiveness, risk behaviour, prevalence or incidence of HIV in the PrEP target group (sometimes also indicated as the number needed to treat [NNT]). Not every study examines all hypotheses. In conclusion, in each study a number of striking additional hypotheses or findings are reported.
The table is ordered from the newest publication to the oldest. The most recent publications are the most relevant as more scientific data are included. Nichols et al[32] is the only publication that specifically concerns the Netherlands.

Table 1. Summary of most relevant outcomes of PrEP-trials worldwide

Outcome variable	Effectivity		Risk reduction *(per personyear)*	Number of participants (number of trials)	Quality of trial	Other remarks
	Control group	PrEP group				
Effect on hiv incidence	All groups: 0.7-9.0% incidence	All groups: 0.0-4.7% incidence	All groups: 51% (95%CI: 27-67%)[a]	~20.000 16 trials (+ 4 ongoing)	Low-high	2 trials of low quality (on women and serodiscordant couples). MSM trials in the US and Europe high quality
	MSM: 3.0-9.0% incidence	MSM: 0-2.9% incidence	Men: 62% (95%CI: 40-75%)[a] MSM: 66% (95%CI: 20-85%)[a]	Men: 8.700 (7 trials) MSM: 3.166 (4 trials + 4 ongoing)	Medium-high	
Adherence to therapy	All groups: 30-94%			11 trials	Different methods used to assess adherence: by drug levels in blood or prescription/self-report/pill-count	
	MSM: 51-94%			MSM: 5 trials	Intermittent PrEP: proportion of sex acts adequately covered low, but drug detection rates in blood high (IPERGAY)	
Side effects						
Mild	Nausea, gastro-intestinal symptoms, headache		In RCTs no/little difference compared to placebo	16 trials	High quality	TDF-FTC is used for HIV-treatment and found to be safe; difference with HIV-negative population not reported.
Severe	Renal function and bone mineral density; depression		Effect on kidney or bone is subclinical and reversible; depression reported in 1 trial only, no clear difference with control group after correction			Note that trials were in adults; not enough data in adolescents or younger persons
Resistance	17% (8/46) of HIV-inf before start PrEP (7/26 in PrEP arm; 1/20 placebo arm) 0.5% (1/286) of HIV-inf after start in placebogroup[5]	2.0% (5/247) of HIV-inf on PrEP after start, of which 5 on TDF/FTC (of 157), 0 on TDF[5]	Small numbers. Resistance levels before start higher in PrEP group (RR[b] 3.3[1.1-10]), difference not significant post-randomisation (RR 3.1[0.5-19]). Resistance is more frequently against FTC than TDF	6 trials (review Fonner 2016)[5]	Medium quality	Not investigated (properly) in all studies, resistance may occur more commonly
STI incidence	STI incidence remains high and does not decrease and may increase slightly with PrEP; no difference between PrEP/placebo					In general, trials have a relative short follow-up period
Risk behaviour	Outcomes vary: some studies reported a decrease in risk, most found no difference (condom-use, number of partners, anal sex acts), some reported an increase in unprotected anal sex acts or more partners					Behavior reported in an RCT/cohort-study without placebo is probably not equal to that under non-observed, routine PrEP use

[a] 95%CI: confidence interval, measure of variance around mean; [b] RR relative risk

Table 2. List of individual PrEP trials

	Trial	Target group, risk population	N	Intervention/control (PrEP = TDF-FTC)	Hiv incidence (per 100 personyears) PrEP versus control group	Risk reduction	Adherence
MSM	IPrex[7]	MSM/TG[a] (US, S-America, Thailand, S-Africa)	2.499	PrEP/placebo	48/1.251 vs 83/1.248 pers.	44%	90% by pill count; 51% based on blood level
	IPrex OLE[14]	MSM/TG[a] (US)	1.603	PrEP/placebo (IPrex +OLE; 1225 op PrEP)	1.8 vs 2.6	51%	71% blood level
	PROUD[20]	MSM (UK)	544	PrEP immediate vs deferred	1.3 vs 8.9	86%	88% prescription; 100% blood level in sample of participants
	IPERGAY[8]	MSM (France, Canada)	414	Event-driven PrEP vs placebo	0.94 vs 6.7	86%	43% sex acts covered; 86% blood level (71% in open label extension)
	CDC Safety trial[15]	MSM (US)	400	PrEP immediate vs deferred	0.0 vs 7.0	100%	93% pill count; 79% bottle openings
	Project PrEPare[17]	Young MSM 18-22 yrs (US)	58	PrEP/placebo/ prevention intervention	Not reported		63% in week 4 declining to 20% in week 24
IDU[b]	Bangkok Tenofovir study[13] (+ OLE)	Injecting Drug Users	2.413 (787)	PrEP/placebo	0.35 vs 0.68	49%	67%
Hetero M/F[5]	Partners PrEP[12]	Serodiscordant couples (Kenya, Uganda)	4.747	PrEP and TDF vs placebo	0.5 and 0.65 vs 1.99	75% and 67%	81%
	TDF2[23]	Heterosexual M/F[c] (Botswana)	1.219	PrEP/placebo	1.2 vs 3.1	62%	80%
	FEM-PREP[24]	Women[c] (Kenya, Tanzania, S-Africa)	2.120	PrEP/placebo	4.7 vs 5.0	6%	37%
	VOICE[19]	Women[c] (Uganda, S-Africa, Zimbabwe)	5.029	PrEP/placebo and TDF/placebo	4.7 vs 4.6 and 6.3 vs 4.2	-4% and -49%	30%
	Phase 2 TDF study[22]	Women[c] (Cameroon, Ghana, Nigeria)	936	TDF/placebo	0.86 vs 2.48	65%	Not reported
	IAVI[18,21]	MSM, SW[d], discordant couples (Kenya, Uganda)	114	PrEP/placebo	Not reported		80-90% daily users 55-90% intermittent users
MSM/ new trials	ADAPT[16]	MSM (young, coloured; US)	179	PrEP (daily or on demand)	US	Ongoing	
	AMPREP[9]	MSM (Netherlands)	376	PrEP (daily or on demand)	Amsterdam 2 seroconversions, 1 despite good adherence	Ongoing	100% for daily users; high for intermittent PrEP use
	Be-PREP-ared[10]	MSM (Belgium)	200	PrEP (daily or on demand)	Antwerpen 0 seroconversions	Ongoing	High
	VicPrEP[11]	MSM (Australia)	114	PrEP (daily)	2 seroconversions at start PrEP	Interim analyses	90% blood levels equivalent to 4 or more tablets per week

[a] TG: transgender; [b] IDU: intravenous drug user; [c] M/F: male/female; [d] SW: sexworkers

Tabel 3. Cost effectiveness studies on PrEP for MSM in developed countries

Study	Population	Scenarios/assumptions	Results (ICER)	Remarkable
Cambiano 2017[25]	MSM in the UK	Effectivity 86% Incidence 2.0% per year in target group. Intermittent PrEP £360 per month	Cost-effective after 30 years Cost saving after 40 years	25% of HIV-infections prevented (after 80 years). Effect of price reduction of ARV on cost effectiveness
Koh Jun Ong 2017[33]	MSM in the UK	Effectivity: 64% Risk behaviour: 20% increase Incidence: 16.9% for highrisk	+£23,500 (€31,900)	PrEP for 1 year, effects over longer period No population group effect
Nichols 2016[32]	MSM in the Netherlands	Effectivity 80% No change in risk behaviour Following the Dutch HIV epidemic (two scenarios)	€11,000	Stable or decreasing HIV epidemic Population group effect PrEP for 10% of the most active group (2-5% of MSM; >5 partners per year)
MacFAdden 2016[31]	MSM Canada	Effectivity 44%-99% No change in risk behaviour Following the epidemiological parameters for Toronto	500,000-800,00CAD$ 35,000-70,000CAD$	PrEP for all MSM vs PrEP for highest risk group 10%
Ouellet 2015[34]	MSM Canada	Effectivity 86% No change in risk behaviour NNT 51.78 (as indicator for prevalence)	Cost saving when discounted at 0 or 3%; CAD$60,311 to CAD$47,407 at 5% discounting	Intermittent use
Kessler 2014[29]	MSM NY (USA)	Effectivity 44% No change in risk behaviour Comparison between risk groups	Results in costs per infection prevented: $11 million	Uptake of 50% in target population Comparison of risk groups: PrEP most cost effective with target group of high risk MSM (based on risk behaviour)
Chen 2014[26]	MSM USA	Effectivity 44% No change in risk behaviour Prevalence 19%	$160,000	Multivariable analyses: best scenario: high adherence and high prevalence
Schneider 2014[36]	MSM Australia	Effectivity varying (75% good adherence and effectivity 95%) No change in risk behaviour	Aus $400,000 Aus $110,000	10-30% MSM as base-case 15-30% MSM with 10-50 partners per 6 months
Juusola 2012[28]	MSM USA	Effectivity 44% Prevalence 12,3% No change in risk behaviour	$172,091 $216,480	20% uptake 100% uptake
Koppenhaver 2011[30]	MSM USA	Effectivity 44% Prevalence 17.5% No information on risk behaviour	$570,273	100% uptake
Paltiel 2009[35]	MSM USA	Effectivity 50% Hiv incidence 1.6% per year No change in risk behaviour	$298,000	All MSM (not limited to high risk group)
Desai 2008[27]	MSM USA	Effectivity 50/70% Prevalence 14.6% No information on risk behaviour	$31,970	25% high risk MSM

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