WRCResearch

EBM WORKSHOP SERIES

Systematic Reviews

Andrew Costa, PhD

Schlegel Chair in Clinical Epidemiology & Aging | Assistant Professor | Dept. of Clinical Epidemiology & Biostatistics | | Dept. of Medicine |Michael G. DeGroote School of Medicine
McMaster University | acosta@mcmaster.ca | @andrew.p.costa

WRCResearch

What we will cover today

- **Topic:** Cochrane systematic review - Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals

- **Our EBM lessons will be**:
  - How to read systematic reviews,
  - Cochrane reviews,
  - GRADE, and
  - much more.

WRCResearch

Our case scenario

A 28 year old man comes in to your family practice to talk about PrEP. He has sex with other men and occasionally uses intravenous drugs.
Although he typically uses condoms during intercourse and does not share needles, sometimes he does not use STI protection and may share needles.
He has heard that PrEP may reduce his risk of contracting HIV from his partners and wants to start on the drug.

WRCResearch

Paper

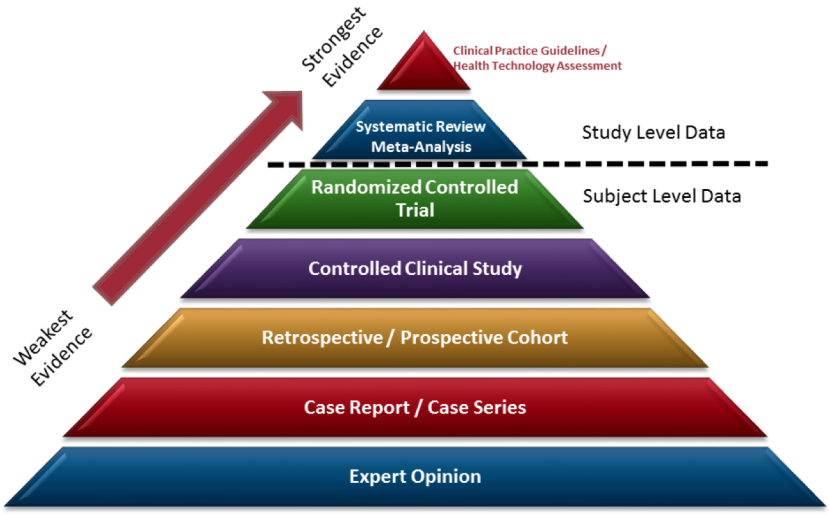
Cochrane Library

Cochrane Database of Systematic Reviews

Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals (Review)

Okwundu CI, Uthman OA, Okoromah CAN

WRCResearch



WRCResearch

Literature Reviews

- Literature Syntheses
  - Broad-based questions used to understand the nature of the clinical issue and who and how others have approached it before.
- Systematic Reviews
  - Narrow review of a specific clinical topic with explicit a-priori criteria for whether to include research in review.
- Meta Analyses
  - Very narrow perspective seeking to examine a specific clinical question, usually by collating randomized controlled trials

WRCResearch

"Meta analyses are predicated on the assumption (or it may be more a belief and hope) that objectivity regarding the criteria used for conducting literature searchers, selecting the articles in include or exclude, and abstracting and summarizing the findings would results in unbiased and unequivocal answers."

David Streiner, PhD

WRCResearch

Many steps..

1. Study question (PICOT)
2. Identification of studies (studies design, source, search strategy)
3. Eligibility criteria (study, patient, and disease characteristics, treatments, outcomes)
4. Data extraction (definition of outcomes, quality assessment)
5. Data summary and analysis (outcomes used, intention to treat, heterogeneity models)

WRCResearch

How certain are you of the evidence?

- Do the results directly relate to my question/patient/practice?
  - **Directness**

- Are the studies well done?
  - **Risk of bias**
- Are these all of the studies?
  - **Publication bias**
- Are the results consistent across studies?
  - **Consistency**

- Is the study well done?
  - **Risk of bias**
- Is the effect size precise?
  - **Precision**
- Is the effect size large?
  - **Magnitude**
- Does the effect depend on dose?
  - **Dose response**
- Can something else plausibly explain the effect?
  - **Confounding**

WRCResearch

GRADE

- GRADE (*G*rades of *r*ecommendation, *a*ssessment, *d*evelopment and *e*valuation)

- Two components:
  1. Confidence in the evidence

  2. Strength of Recommendation

strong or weak

WRCResearch

Confidence in the evidence

- Bias
  - study design and implementation
    - concealment, blinding, loss to follow-up
  - publication bias
- Imprecision
  - wide confidence intervals
  - variation in size of effect
- Indirectness
  - patients, interventions
  - outcomes
  - indirect comparisons
  - statistical significance of heterogeneity

WRCResearch

Background

More than 30 years into the global HIV/AIDS epidemic, infection rates remain alarmingly high, with over 2.7 million people becoming infected every year. There is a need for HIV prevention strategies that are more effective. Oral antiretroviral pre-exposure prophylaxis (PrEP) in high-risk individuals may be a reliable tool in preventing the transmission of HIV.

Objectives

To evaluate the effects of oral antiretroviral chemoprophylaxis in preventing HIV infection in HIV-uninfected high-risk individuals.

Search methods

We revised the search strategy from the previous version of the review and conducted an updated search of MEDLINE, the Cochrane Central Register of Controlled Trials and EMBASE in April 2012. We also searched the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov for ongoing trials.

Selection criteria

Randomised controlled trials that evaluated the effects of any antiretroviral agent or combination of antiretroviral agents in preventing HIV infection in high-risk individuals

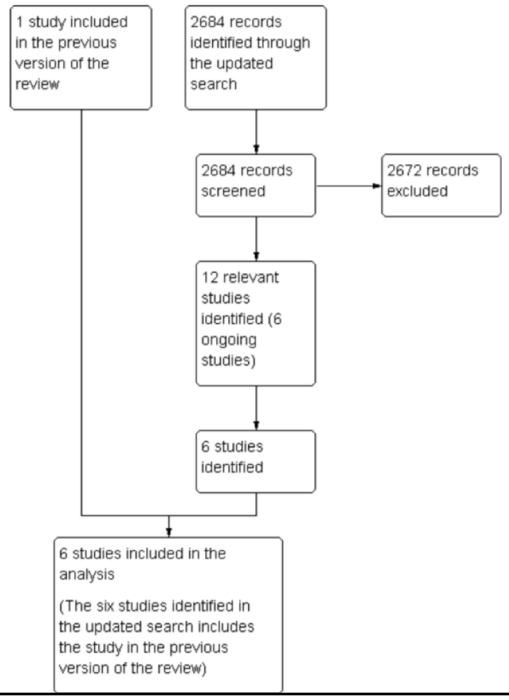
Data collection and analysis

Data concerning outcomes, details of the interventions, and other study characteristics were extracted by two independent authors using a standardized data extraction form. Relative risk with a 95% confidence interval (CI) was used as the measure of effect.

Main results

We identified 12 randomised controlled trials that meet the criteria for the review. Six were ongoing trials, four had been completed and two had been terminated early. Six studies with a total of 9849 participants provided data for this review. The trials evaluated the following: daily oral tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) versus placebo; TDF versus placebo and daily TDF-FTC versus intermittent TDF-FTC. One of the trials had three study arms: TDF, TDF-FTC and placebo arm. The studies were carried out amongst different risk groups, including HIV-uninfected men who have sex with men, serodiscordant couples and other high risk men and women.

Figure 1. Study flow diagram.



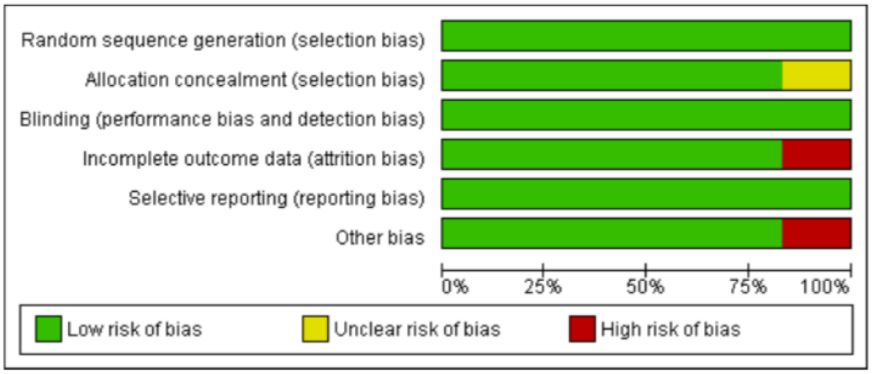
Overall results from the four trials that compared TDF-FTC versus placebo showed a reduction in the risk of acquiring HIV infection (RR 0.49; 95% CI 0.28 to 0.85; 8918 participants). Similarly, the overall results of the studies that compared TDF only versus placebo showed a significant reduction in the risk of acquiring HIV infection (RR 0.33; 95% CI 0.20 to 0.55, 4027 participants). There were no significant differences in the risk of adverse events across all the studies that reported on adverse events. Also, adherence and sexual behaviours were similar in both the intervention and control groups.

Authors' conclusions

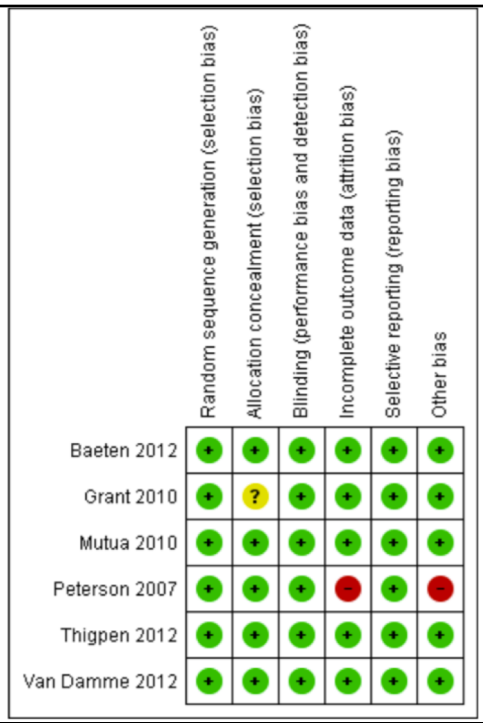
Finding from this review suggests that pre-exposure prophylaxis with TDF alone or TDF-FTC reduces the risk of acquiring HIV in high-risk individuals including people in serodiscordant relationships, men who have sex with men and other high risk men and women.

WRCResearch

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

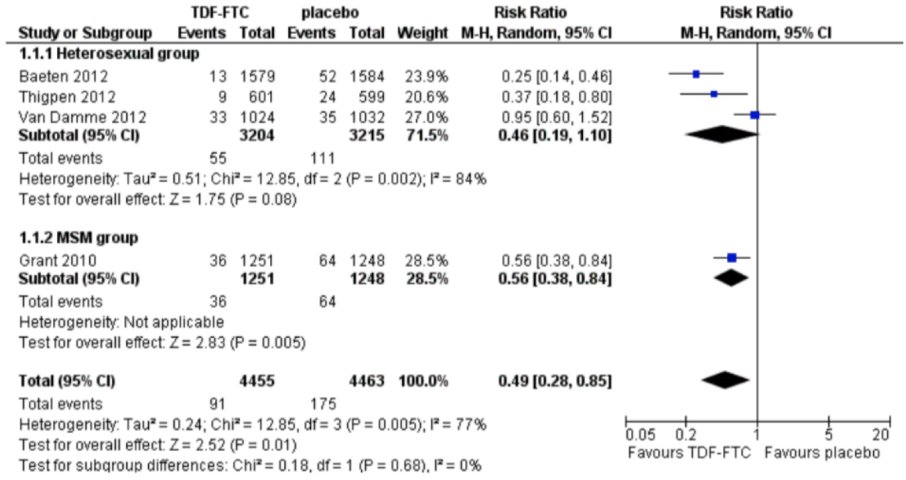


WRCResearch



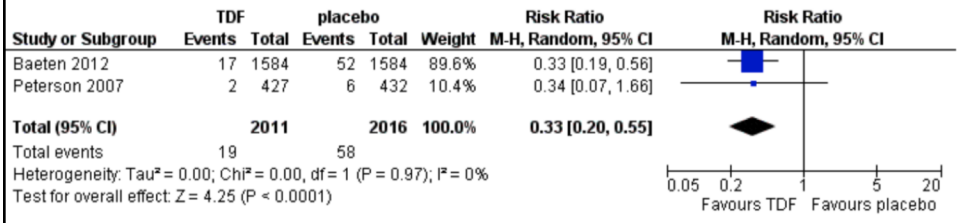
WRCResearch

Figure 4. Forest plot of comparison: 1 TDF+ FTC vs placebo, outcome: 1.1 HIV infection (by risk group).



WRCResearch

Figure 5. Forest plot of comparison: 2 TDF vs placebo, outcome: 2.1 HIV infection.



WRCResearch

Tenofovir + Emtricitabine compared to placebo for preventing HIV in high-risk individuals

Patient or population: High-risk HIV-uninfected individuals (including serodiscordant couples, men who have sex with men and sex workers)
Settings: High, middle and low income settings
Intervention: Oral Tenofovir + Emtricitabine
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	TDF+ FTC				
HIV infection	Study population		RR 0.49 (0.28 to 0.85)	8813 (4 studies)	⊕⊕⊕○ Moderate[1]	
	39 per 1000	19 per 1000 (11 to 33)				
Serious adverse events	Study population		RR 1 (0.83 to 1.19)	6862 (3)	⊕⊕⊕○ Moderate[1]	
	65 per 1000	65 per 1000 (54 to 77)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] We downgraded the quality of evidence by one level on account of instability of results since there are fewer than 200 events per arm.

NNT?

WRCResearch

Our case scenario

A 28 year old man comes in to your family practice to talk about PrEP. He has sex with other men and occasionally uses intravenous drugs.
Although he typically uses condoms during intercourse and does not share needles, sometimes he does not use STI protection and may share needles.
He has heard that PrEP may reduce his risk of contracting HIV from his partners and wants to start on the drug.

WRCResearch

How to evaluate the evidence …

(this is a generalization)

1
- Do the results **directly relate** to my question/patients/practice?
- Is the **study quality** good enough?

YES

2
- Are the effects **statistically significant**? (i.e., based on p-value, relative risk/benefit)

YES

3
- Are the results **clinically significant**? (i.e., based on change in absolute risk/NNT, precision)
- Are the harms small enough to justify?

YES

CONSIDER IT*

*Consider the cost-benefit compared to **all other** options.

WRCResearch

Let's Grade

- **Confidence in the evidence?**
  - Daily PrEP use can lower the risk of getting HIV from sex by about 50%
- **Strength of recommendation?**
  - Must commit to taking the drug every day and seeing their health care provider for follow-up every 3 months.
  - Absolute risk is ~ 4% (in ~ 2-3 years) .. Is it?
    - Infection incidence in Canada?
    - Cost of ART?