HOW SAFE IS PrEP?

An analysis of the safety of TDF/FTC as PrEP vs Control

Victoria Pilkington, Andrew Hill, Sophie Hughes, Nneka Nwokolo and Anton Pozniak
1.8 Million

New HIV infections worldwide every year
Prevention is Vital

NEW INFECTIONS 1.8 Million

LIVING WITH HIV 36.7 Million

DEATHS 1 Million

Success in Treatment

2018

Over 300,000 take PrEP worldwide

Est. numbers on PrEP:
- <100
- 100 - 1,000
- 1,000 - 10,000
- 10,000 - 100,000
- >100,000

Map from mapchart.net.
Data from AVAC.org 2018.
PrEP Costs
Cost of PrEP is widely variable

Depending on the availability of generics

BRANDED:  
$6,200/yr

GENERIC:  
$500/yr

$20,000/yr

$54/yr


PrEP

Costs  Uptake  Safety
TDF use in treatment: Boosted

- TDF/FTC + Booster Drugs
- Bone: Risk Increase p=0.04
- Renal: Risk increase p=0.002

Suggests there is TOXICITY

Unboosted

- TDF/FTC
- Bone: No significant risk
- Renal: No significant risk

NO TOXICITY
Primary research question:

Is TDF/FTC safe when used as PrEP?
Randomised, Placebo Controlled Trials
Comparing TDF(/FTC) as PrEP with Control (Placebo)

SEARCH
Embase, Medline, HMIC and Global Health
CROI, BHIVA, IAS conference abstracts

SCREENING + INCLUSION

EXTRACT SAFETY DATA
Meta-Analysis

METHODS
SAFETY ENDPOINTS

- Clinical - Grade 3 & 4 Adverse events
- Clinical - Protocol defined Serious Adverse Events
- Lab - Serum creatinine elevations (Grade 3+)
- Bone Fractures

Renal Damage
Loss BMD
RESULTS
606 Papers found on Medline
1055 Papers found on Embase
1133 Papers found on Global Health

2306 studies screened
488 Duplicates Removed
2105 studies irrelevant

201 studies assessed for full-text eligibility

13 RCT Included

188 studies excluded
47 = Wrong Outcomes
32 = Wrong study design
27 = Wrong Intervention
9 = Discussion/Editorial/Guidance
10 = Review
15 = Pharmacological/Histopathological study
8 = Wrong Patient Population
7 = Mathematical Model
1 = Ongoing study
35 = Related Sub-Studies or OLE (Used as contextual analysis in discussion)
4 months
IAVI

MSM
IAVI Kenya Study
TDF - 2
iPREX
PrEPare
IPERGAY
US Safety Study

On-Demand

4 years
BKK

IVDU
BKK TDF Study

Serodiscordant couples
IAVI Uganda Study

Women
West African Study
FEM-PrEP
VOICE

TDF alone

Daily TDF/FTC
In one treatment and one control arm

13 trials

15,678 participants

22,250 PYFU
Grade 3+4 Adverse Events

No significant increased in risk on PrEP

Control: 16.8%
PrEP: 17.4%

More risk on Control
More risk on PrEP

West African Study
IAVI Uganda Study
FEM-PrEP
IPERGAY
IAVI Kenya Study
PrEPare
iPRES
TDF – 2
VOICE
Partners
BKK TDF Study
US Safety Study

Risk Difference (95% CI)
RD = 0%
(-1% to 2%)
p = 0.53
Serious Adverse Events

<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>PrEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>West African Study</td>
<td>10.1%</td>
<td>9.4%</td>
</tr>
<tr>
<td>IAVI Kenya Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IAVI Uganda Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PrEPare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPERGAY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROUD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BKK TDF Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VOICE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF - 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>iPREX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partners</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US Safety Study</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No significant increased in risk on PrEP

Risk Difference (95% CI)

RD = 0%
(-1% to 1%)

p = 0.80
Bone Fractures

No significant increased in risk on PrEP

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Difference (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPERGAY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PrEPare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROUD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROUD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF – 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VOICE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>iPREX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BKK TDF Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US Safety Study</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RD = 0% (0% to 1%)
p = 0.50
Creatinine Elevations (Grade 3+)

%Events /Total people

Control: 0.1%  PrEP: 0.1%

More risk on Control  More risk on PrEP

IPERGAY  PROUD
West African Study  IAVI Kenya Study
IAVI Uganda Study  FEM-PrEP
PrEPare  iPREX
TDF – 2  US Safety Study
VOICE  Partners
BKK TDF Study

Risk Difference (95% CI)

RD = 0%  (0% to 0%)

p = 0.68

No significant increased in risk on PrEP

Pilkington et al. Glasgow HIV 2018. Poster 0143
Creatinine Elevations (Grade 1-4)

<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>PrEP</th>
<th>Risk Difference (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>West African Study</td>
<td>2.3%</td>
<td>4.3%</td>
<td>0.1 (0% to 3%)</td>
<td>0.04</td>
</tr>
<tr>
<td>PROUD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPERGAY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IAVI Uganda Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PrEPare</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IAVI Kenya Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US Safety Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF – 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partners</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iPREX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VOICE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BKK TDF Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Borderline significant increased in risk on PrEP

RD = 2%
(0% to 3%)
p = 0.04
## SENSITIVITY ANALYSES

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Effect on overall significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>Daily/intermittent or TDF/TDF+FTC</td>
<td>None</td>
</tr>
<tr>
<td>Reporting</td>
<td>Number of events vs number of people experiencing events</td>
<td>None</td>
</tr>
<tr>
<td>Sex</td>
<td>Studies in males, females and both</td>
<td>None</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>Studies split by those 1yr average follow-up time</td>
<td>SAE</td>
</tr>
</tbody>
</table>
Serious Adverse Events

Statistically significant decrease in risk on PrEP in longer-term follow-up studies

%Events / Total people

Control: 10.1%

PrEP: 9.4%

More risk on Control

More risk on PrEP

West African Study
IAVI Kenya Study
IAVI Uganda Study
PrEPare
FEM-PrEP
IPERGAY
PROUD

BKK TDF Study
VOICE
TDF -2
iPREX
Partners
US Safety Study

<1 year of follow-up
RD = 0.01
p = 0.19

>1 year of follow-up
RD = -0.01
p = 0.02

RD = 0.00
p = 0.80

Risk Difference (95% CI)
Significant Increase in Risk on PrEP?

<table>
<thead>
<tr>
<th>None</th>
<th>None</th>
<th>None</th>
<th>None</th>
<th>p=0.04</th>
</tr>
</thead>
</table>

- **Grade 3/4 Adverse Events**
  - PrEP Control: 17.4%
  - Control: 16.8%

- **Serious Adverse Events**
  - PrEP Control: 9.4%
  - Control: 10.1%

- **Fractures**
  - PrEP Control: 3.7%
  - Control: 3.3%

- **Creatinine Elevations (Grade 3+)**
  - PrEP Control: 0.1%
  - Control: 0.1%

- **Creatinine Elevations (Grades 1-4)**
  - PrEP Control: 4.3%
  - Control: 2.3%

n = 15,678
STRENGTHS

- Low baseline risk
- Low adherence
- Not all groups/world regions represented
- Low risk bias
- ~22,250 total PYFU

LIMITATIONS
This review found **no evidence** of any increased risk of **severe adverse events** on TDF/FTC as PrEP.
TDF vs TAF

If TDF is safe – is expenditure on TAF justified?

Newer drug
Better safety profile?
More expensive

Pilkington et al. Glasgow HIV 2018. Poster 0143
Hill et al. J Virus Erad 2018, 4:72-78
Unboosted TDF/FTC vs TAF/FTC (n=3181)

<table>
<thead>
<tr>
<th>Event</th>
<th>TDF/FTC</th>
<th>TAF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3+4 Serious Adverse Events</td>
<td>No risk difference</td>
<td>No risk difference</td>
</tr>
<tr>
<td>Bone Fractures</td>
<td>No risk difference</td>
<td>No risk difference</td>
</tr>
<tr>
<td>Renal D/C</td>
<td>No risk difference</td>
<td>No risk difference</td>
</tr>
</tbody>
</table>
CONCLUSIONS
PrEP has great potential

1.8 Million Infections

FEWER NEW INFECTIONS

Tens of Millions at risk

FEWER LIVING WITH HIV

Pilkington et al. Glasgow HIV 2018. Poster 0143

Pilkington et al, BHIVA 2018, Edinburgh, Poster 94
PrEP has great potential
PrEP is becoming more affordable
PrEP has great potential

PrEP is becoming more affordable

TDF/FTC as PrEP is safe
THANK YOU
<table>
<thead>
<tr>
<th>Event</th>
<th>PrEP Events / People</th>
<th>Control Events / People</th>
<th>Risk Difference (95% CI)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3/4 AE</td>
<td>1306 / 7504</td>
<td>1259 / 7502</td>
<td>0% (-1% to 2%)</td>
<td>p = 0.53</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>740 / 7843</td>
<td>795 / 7835</td>
<td>0% (-1% to 1%)</td>
<td>p = 0.80</td>
</tr>
<tr>
<td>Bone Fractures</td>
<td>217 / 5789</td>
<td>189 / 5795</td>
<td>0% (0% to 1%)</td>
<td>p = 0.50</td>
</tr>
<tr>
<td>Grade 3+ Creatinine Elevations</td>
<td>8 / 7843</td>
<td>4 / 7835</td>
<td>0% (0% to 0%)</td>
<td>p = 0.68</td>
</tr>
<tr>
<td>All Creatinine Elevations</td>
<td>336 / 7843</td>
<td>178 / 7835</td>
<td>2% (0% to 3%)</td>
<td>p = 0.04</td>
</tr>
</tbody>
</table>
### Risk of Bias

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data addressed (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US SAFETY STUDY</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>PrEPare - ATN 082</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>IAVI Uganda Study</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IAVI Kenya Study</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PROUD</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>IPERGAY</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Partners</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>West African Safety Study</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>TDF 2</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>iPREX</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>VOICE</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
</tbody>
</table>

**KEY**

- **Low Risk of Bias**
- **Unclear Risk of Bias**
- **High Risk of Bias**
<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>DISEASE</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exposure prophylaxis/</td>
<td>HIV/</td>
<td>drug efficacy/</td>
</tr>
<tr>
<td>Chemoprophylaxis/</td>
<td>Human immunodeficiency virus/</td>
<td>safety/</td>
</tr>
<tr>
<td>Pre-Exposure Prophylaxis.mp</td>
<td>Human Immunodeficiency Virus.mp.</td>
<td>adverse drug reaction/ adverse outcome/</td>
</tr>
<tr>
<td>PrEP.mp</td>
<td>HIV.mp.</td>
<td>adverse event/</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment Outcome/</td>
</tr>
<tr>
<td></td>
<td></td>
<td>safety/</td>
</tr>
<tr>
<td></td>
<td></td>
<td>efficacy.mp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Safety.mp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>adverse.mp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>adverse event*.mp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>adverse outcome*.mp.</td>
</tr>
</tbody>
</table>
### PREP TRIALS

<table>
<thead>
<tr>
<th>INCLUSION</th>
<th>EXCLUSION</th>
</tr>
</thead>
</table>
| • Controlled randomised controlled trials, with a placebo or comparison arm.  
• Published in a peer reviewed journal  
• Clinical trials which assess safety of the treatment drug and report absolute numbers of adverse events occurring in both arms. | • Non Human Trials  
• Earlier than phase III.  
• Trials of non-oral PrEP (eg. Microbicide)  
• Substudies looking at the wrong outcome eg. Measures of adherence and dosing, and measure of qualitative wellbeing or commitment etc |
Average Price of PrEP by World Region

Max = $20,350/yr  
Min = $33/yr

North America: 11,725
Europe & Central Asia: 3,471
Middle East & North Africa: 2,756
East Asia & Pacific: 2,216
Latin America & Caribbean: 2,894
Sub-Saharan Africa: 66
South Asia: 132

Pilkington et al. Glasgow HIV 2018. Poster 0143
Summary of Efficacies of Oral PrEP Trials

- PROUD - MSM
- IPERGAY - MSM
- Partners (TDF/FTC) – Serodiscordant Couples
- Partners (TDF) – Serodiscordant Couples
- West African Safety Study - Women
- TDF-2 – MSM + Women
- Bangkok Tenofovir Study - IVDU
- iPREX - MSM
- FEM-PrEP - Women
- VOICE (TDF/FTC) - Women
- VOICE (TDF) - Women
Pooled incidence by Risk Group

Range of Incidences:

- IVDU: 1.7
- FSW: 1.7
- Adolescent: 2.0
- MSM: 3.3
NNTB falls as incidence increases
Countries with higher HIV incidence can treat fewer to prevent new infections

Incidence/100PY

NNTB

Population by country

MSM

Pilkington et al. Glasgow HIV 2018. Poster 0143
SOUTH AFRICA

HIV Incidence: 270,000
Number on PrEP: 9,500
RATIO: 28:1

AUSTRALIA

HIV Incidence: 1,100
Number on PrEP: 14,600
RATIO: 1:13

Data from AVAC.org 2018
Data from UNAIDS Data report 2017.