Effectiveness of PrEP

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Content

- Evidence for PrEP effectiveness and safety
- Risk compensation and impact on STIs,
- Influence on current clinical practice
- Current and future challenges for PrEP implementation
HIV prevention

- Combination approach to HIV prevention gives us the tools to dramatically reduce HIV transmission
  - Condom use
  - Testing
  - Treatment as Prevention
  - PrEP

- For maximal impact interventions need to be targeted at those most at risk
  - On-going HIV high incidence in MSM
  - Incidence unclear in other ‘at risk’ groups
Back-calculation estimate of HIV incidence and prevalence of undiagnosed infection among men who have sex with men: United Kingdom, 2005 - 2014

- Undiagnosed HIV infection
- Estimated incidence
- 95% credible interval of estimated incidence

Estimated through the CD4 back-calculation
## HIV incidence

### Estimated HIV incidence among sexual health clinic attendees in 2012

<table>
<thead>
<tr>
<th>Group of attendees</th>
<th>Estimated incidence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.15%</td>
<td>0.13% - 0.17%</td>
</tr>
<tr>
<td>MSM</td>
<td>1.34%</td>
<td>1.15% - 1.53%</td>
</tr>
<tr>
<td>Heterosexuals</td>
<td>0.03%</td>
<td>0.02% - 0.04%</td>
</tr>
<tr>
<td>Black African Heterosexuals</td>
<td>0.17%</td>
<td>0.08% - 0.27%</td>
</tr>
</tbody>
</table>

HIV incidence among people who attend sexual health clinics in England in 2012

*Sex Transm Infect 2015;91:A2 doi:10.1136/sextrans-2015-052126.4*

### HIV incidence in HIV negative MSM who re-attended at STI clinics in 2012

<table>
<thead>
<tr>
<th>Category</th>
<th>HIV incidence (per 100 py)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV test 42-365 days prior to current attendance</td>
<td>2.4</td>
<td>2.0 – 2.8</td>
</tr>
<tr>
<td>Bacterial STI in previous year and/or at current attendance</td>
<td>3.3</td>
<td>2.8 – 4.0</td>
</tr>
<tr>
<td><strong>Rectal</strong> bacterial STI in previous year and/or at current attendance</td>
<td>5.2</td>
<td>3.7 – 6.7</td>
</tr>
<tr>
<td>PEP in previous year</td>
<td>3.3</td>
<td>1.7 – 6.3</td>
</tr>
</tbody>
</table>

Source: GUMCAD, PHE, HIV incidence analyses 2012
The journey to PrEP implementation

- Research findings
  PROUD study

- Policy
  Politics
  Commissioning

- Community activism
  Campaigning

- Clinical service support
Effectiveness: MSM

**iPREX (TDF/FTC)**
- Sth America, US, SA
- 2499 MSM/TGW
- Daily TDF/FTC or placebo
- 2499: MSM (88%) and TGW (12%)
- Adherence 50%

**PROUD (TDF/FTC)**
- UK
- 544 MSM, 1 TGW
- Immediate vs def daily TDF/FTC
- Adherence 88%

**IPERGAY (on demand TDF/FTC)**
- France, 414 MSM
- On demand FTC/TDF or placebo
- Adherence 86% (TDF in blood)


Grant et al, NEJM, 2010
Effectiveness: Heterosexuals

**TDF2**
- Botswana. HT men and women (1219)
- Randomised to TDF/FTC or placebo
- Adherence: 84%

**Partners PrEP study**
- Kenya and Uganda
- HT men and women randomised to placebo (1586) or TDF (1589) or TDF/FTC (1583)
- Adherence: 92%
Effectiveness: Heterosexuals

**VOICE**
- South Africa, Uganda, Zimbabwe
- 5029 women, randomised to oral TDF, oral TDF/FTC, vaginal TFV gel, placebo
- Zero evidence effectiveness
- Adherence: 25-30%

**FEM-PrEP**
- South Africa, Kenya, Tanzania
- 2120 women, randomised 1:1 to TDF/FTC or placebo
- No evidence effectiveness
- Adherence <40%
Other at risk groups: Trans women, trans men and people who inject drugs

- Subgroup analysis iPrEx trial\(^1\): 339 TGW
  - 11 infections PrEP arm (none had detectable TDF/FTC in blood) and 10 in placebo (HR: 1.1, 95% CI: 0.5–2.7)

- No PrEP studies in Trans women which are specifically designed for and focussed on trans women and trans issues,

- No data at all in TGM

- The Bangkok Tenofovir Study\(^2\): 1:1 male and female PWID randomized to TDF or placebo.
  - 48.9% reduction incidence (95% CI 9.6-72.2)
  - Adherence 83%

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Effectiveness in open label extension studies - MSM

iPrEx-OLE\textsuperscript{1}

• 76% of 1603 iPrEX participants, MSM/TGW

• No seroconversions if drug levels compatible with ≥four pills/week

IPERGAY-OLE\textsuperscript{2}

• 362 MSM

• 97% reduction in risk compared to the placebo arm of the IPERGAY randomised phase

Effectiveness in open label extension studies – Heterosexual

Partners PrEP OLE

- 89% of 1418 heterosexual men and women
- Efficacy of TDF (67%) & FTC/TDF (75%)

TDF2 OLE

- 229 men and women, 33% did not complete follow up
- No new HIV infections during the 12 month F/U
- 87% women and 96% men had detectable drug levels at visits

2. Chirwa LI et al. Enrollment into open-label phase of TDF2 PrEP Study. 20th IAC; 2014; Melbourne, Australia.
Differences in efficacy largely explained by adherence
Pragmatic Open-Label Randomised Trial of Pre-Exposure Prophylaxis: the PROUD study

http://www.proud.mrc.ac.uk/
PROUD Study

MSM and TGW reporting unprotected anal sex in last and next 90 days

Truvada AFTER 12M

Randomise HIV negative MSM

Main endpoints in Pilot: recruitment and retention
From April 2014: HIV infection in first 12 months
Follow 3 monthly for up to 24 months


86% reduction in HIV Transmission
No increased rates of other STIs
Number of screens differed between the groups:

- e.g. Rectal gonorrhoea/chlamydia
- 974 in the IMM group and 749 in the DEF
PrEP interruptions for medical event

- **PrEP interrupted** by 28 participants (*both groups*) but only *13* had events considered related to drug:
  - nausea alone or with diarrhoea/abdominal pain/aches and fatigue (*n*=5)
  - decline in creatinine clearance (*n*=2)
  - headache (*n*=2)
  - joint pain, with fatigue in one case (*n*=2)
  - sleep disturbance (*n*=1)
  - flu-like illness (*n*=1)

- **PrEP re-started** by 11 of 13 participants above
Study Design

Double-Blinded Randomised Placebo-Controlled Trial

- HIV negative high risk MSM
- Condomless anal sex with > 2 partners within 6 m
- eGFR > 60 mL/mn

Full prevention services*
TDF/FTC before and after sex

Full prevention services*
Placebo before and after sex

* Counseling, condoms, testing and treatment for STIs, vaccination for HBV and HAV, PEP

- End-point driven study: with 64 HIV-1 infections, 80% power to detect a 50% relative decrease in HIV-1 incidence with TDF/FTC (expected incidence: 3/100 PY with placebo)
- Follow-up visits: month 1, 2 and every two months thereafter
276 STIs were diagnosed in 141 participants

<table>
<thead>
<tr>
<th></th>
<th>TDF/FTC n=199</th>
<th>Placebo n=201</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nb Pt (%)</td>
<td>Nb Events</td>
<td>Nb Pt (%)</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>43 (22)</td>
<td>61</td>
<td>34 (17)</td>
</tr>
<tr>
<td>Gonorrhoea</td>
<td>38 (19)</td>
<td>50</td>
<td>45 (22)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>19 (10)</td>
<td>19</td>
<td>19 (10)</td>
</tr>
<tr>
<td>HCV</td>
<td>3 (&lt;2)</td>
<td>3</td>
<td>3 (&lt;2)</td>
</tr>
<tr>
<td>Any STI</td>
<td>76 (38)</td>
<td>133</td>
<td>65 (32)</td>
</tr>
</tbody>
</table>
- **Median number of pills/month (IQR):** 16 pills (10-23) in the placebo arm and 16 pills (12-24) in the TDF/FTC arm (p=0.84)

- **48 participants (12%) received PEP**
  25 (13%) in the TDF/FTC arm and 23 (11%) in the placebo arm (p=0.73)
## Adverse Events

<table>
<thead>
<tr>
<th>Nb of Participants (%)</th>
<th>TDF/FTC n=199</th>
<th>Placebo n=201</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>184 (92)</td>
<td>178 (89)</td>
<td>0.18</td>
</tr>
<tr>
<td>Any Serious AE</td>
<td>18 (9)</td>
<td>16 (8)</td>
<td>0.70</td>
</tr>
<tr>
<td>Any Grade 3 or 4 AE</td>
<td>17 (9)</td>
<td>14 (7)</td>
<td>0.56</td>
</tr>
<tr>
<td>Treatment D/C due to AE</td>
<td>1*</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Drug-Related GI AEs</td>
<td>25 (13)</td>
<td>11 (6)</td>
<td>0.013</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>15</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

* deep veinous thrombosis with suspected DDI with dabigatran
Risk compensation

- In the iPrEx study, there was no evidence of risk compensation.
- In the iPrEx-OLE study, both groups reported decreases in reported condomless receptive anal intercourse.
- In the PROUD study, there was no difference in the total number of sexual partners at 1 year or in the frequency of bacterial STIs.
- However, a greater proportion of the immediate group reported condomless receptive anal sex with 10+ partners at 1 year compared to the deferred group (21% vs 12%, p=0.03).
Risk compensation

- In IPERGAY, there were no significant differences between Truvada and placebo groups in the proportion of condomless receptive anal sex and incident STIs.

- In the open label phase (Ipergay OLE) there was an increase in overall reported condom use over time.
Evidence – summary

- PrEP is highly effective – when good adherence is achieved
- HIV incidence in PROUD was much higher than expected
- On demand PrEP was as effective as regular PrEP
- No major safety concerns
- No evidence of ‘risk compensation’ or increase in STIs
- PROUD demonstrated that PrEP was highly effective in a more ‘real world’ setting
- Clinics were able to adapt routine practice to incorporate PrEP (PROUD)
Evidence – summary

- All data for PrEP in heterosexuals is from sub-Saharan Africa
- We have no data to support risk assessment in heterosexuals in the UK
- There are no specifically designed studies in trans women and trans men
- NHSE study will address issues re:
  - Large scale experience
  - Access an eligibility (regular and on-demand PrEP)
  - Ongoing risk and need for PrEP
  - STI and HIV incidence
Clinical implications

- Generics
- Clinical support and service provision
Access to generics

• www.iwantprepnow.co.uk

• Tenvir-EM (Cipla)
  • Tavin-EM (Emcure)
  • Ricovir-EM (Mylan)
  • Tencitab (Aspen)
IwantPrEPnow on-line activity
Clinical Service support

- 56 Dean Street opens PrEP clinic in September 2015
  - Private prescriptions of Truvada
  - Support for those buying generic drug
  - STI and HIV testing and renal monitoring
  - Therapeutic drug monitoring for those taking generic TDF/FTC
Time-dependent concentration of plasma tenofovir following generic oral PrEP consumption

- Reference Truvada pK
- Sample generics pK
- Predicted Truvada pK

Courtesy of Dr Nneka Nwokolo et al, 56 Dean Street, BASHH 2016
Time-dependent concentration of plasma emtricitabine following generic oral PrEP consumption

- Sample generics pK
- Reference Truvada pK
- Predicted sample generics pK
- Predicted Truvada pK
Clinical Service support

- Support and advice about PrEP is being provided by sexual health services (GMC advice)

- PrEP is not commissioned and can’t be prescribed

- National guidance recommends 3 month STI and HIV tests for high risk MSM

- Services focus on MSM and providing a range of prevention services:
  - HIV and STI testing,
  - Renal monitoring
  - Drug and alcohol support (chemsex),
  - Behavioural interventions and condom provision
Our new #HIV diagnoses this year in gay/bi men down by a whopping 40%
#EndHIV #SexualHealth #Hackney

So, joining @56deanstreet and @HomertonSHS we have also seen big decreases in new HIV diagnoses in 2016. More than 50% drop! Wow!!
#EndHIV

Barts Health Sexual Health have seen a 36% drop in new #HIV diagnoses in MSM in 2016 compared to 2015, similar to other London clinics

Gay Times are spreading the good news. Condoms, PrEP, Early diagnosis, Immediate treatment. We can beat HIV in 2017.

40% drop in new HIV diagnoses at leading London sexual health clinic
56 Dean Street gave 373 new diagnoses of HIV in 2016, compared to 526 in 2015.
Similar reduction in HIV diagnoses in MSM (England)
Summary (1)

- Getting closer to PrEP access has required collaborative working between academics, clinicians, activists and community groups.
- Community engagement will be key to ensuring awareness, access and efficacy of national PrEP programme.
- For maximal impact of PrEP it is essential to target those most at risk.
- Strategies are required to engage with the most ‘hard to reach’ groups to ensure equity of access.
Summary (2)

- Stigma around HIV remains a potential barrier to implementation and access
- Clinical service delivery has potential for most impact when PrEP is delivered in a combination approach with other HIV prevention and health improvement strategies
- Early experience suggests the impact on HIV transmission can be significant
- Monitoring for impact on other STIs will be important
  - Regular testing may result in earlier diagnosis and treatment
Acknowledgments

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Consultant, HV and Sexual Health

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Co-founder of www.iwantprepnlow.co.uk