About These Slide

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British Medical Journal

- In publication since 1840
- ‘original research articles, review and educational articles, news, letters, investigative journalism, and articles commenting on the clinical, scientific, social, political, and economic factors affecting health’
- Published weekly
- Impact factor: 20.785 (2016)
NEWS: New HIV strain drives growing Philippines epidemic

Dyer, O.

- 11 103 new cases in 2017
- 20% increase from 9264 reported in 2016
- Shift from Western subtype B to more aggressive subtype AE

The country’s president, Rodrigo Duterte, drew criticism from public health agencies last month when he advised a crowd against using condoms because “it is not satisfying.” Putting a wrapped sweet in his mouth during a public address, Duterte said, “Here, try eating it without unwrapping it. Eat it. That’s what a condom is like.”

BMJ 2018; 360: 1323

Medical Journal of Australia

- In publication since 1914
- ‘important issues affecting Australian health care, publishing the latest Australian clinical research, evidence-based reviews, clinical practice updates, authoritative medical opinion and debate, and developments within the humanities with respect to medicine’
- Published twice a month, with double issues in January and December (22 issues a year)
- Impact factor: 3.369 (2015)
Letters: Crusted scabies in northern and central Australia – now is the time for eradication. Quilty et al

- High rates in remote Indigenous Australia communities > skin infections > invasive streptococcal and staphylococcal sepsis, post-streptococcal glomerulonephritis and ARF
- Katherine Hospital - audit of presentations over 5 years
- 42 admissions, 4 with multiple presentations
- 14 dx confirmed by skin scraping; 16 presumptive
- Homelessness as a key issue
- Listed as a notifiable disease in NT

MJA 206 (2) 6 Feb 2017


Background
Burden of cervical abnormalities/cancer is higher whilst participation in cervical screening is significantly lower in Indigenous women in Queensland

Study Design
- Population based retrospective cohort analysis
- 34 980 women aged 20-68 including 1592 Indigenous women
- First HGA smear result on Pap Smear Registry during 2000-2009
- Outcome measure: Time from index smear to clinical investigation

MJA 206 (2) 6 February 2017

Results

- Indigenous women in QLD are less likely to have had clinical investigation (colposcopy/biopsy) within the recommended 2 months after a high-grade abnormal smear result.
- Indigenous women who had not been followed up within 2 months were then more likely to have a clinical investigation than non-Indigenous women.
- By 6 months the follow up rate is similar for Indigenous and non-Indigenous women.

<table>
<thead>
<tr>
<th>2 Queensland resident women aged 20–68 years having a clinical investigation after a high grade abnormal Pap smear result, 2000–2009, by 2-month interval.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigenous women</td>
</tr>
<tr>
<td>Women with clinical investigation</td>
</tr>
<tr>
<td>Total number of women</td>
</tr>
<tr>
<td>2-month interval</td>
</tr>
<tr>
<td>0 to &lt; 2 months</td>
</tr>
<tr>
<td>2 to &lt; 4 months</td>
</tr>
<tr>
<td>4 to &lt; 6 months</td>
</tr>
<tr>
<td>6 to &lt; 8 months</td>
</tr>
<tr>
<td>8 to &lt; 10 months</td>
</tr>
<tr>
<td>10 to &lt; 12 months</td>
</tr>
</tbody>
</table>

Conclusion

- Prompt follow up needs to improve for Indigenous women.
- BUT: Slow follow up is a smaller contributor to higher cervical cancer incidence and mortality than low participation in screening.
- Known barriers to Indigenous women participating in screening.
- Changes to NCSP – will they make a difference?
Clinical experience of patients with hepatitis C virus infection among Australian GP trainees. *Davis et al*

- Data collected on 150,000+ consultations by GP trainees
- **Aim**: Determine prevalence of management for and testing for HCV in trainee encounters
- **Findings**: Only 0.08% of consultations; older than other patients, male or Indigenous Australians
- **Testing**: 0.7% consultations; testing younger, female, Indigenous or from non-English speaking background
- **Doctors**: younger, female, Australian university graduates, city practices

*MJA 206 (7) 17 April 2017*

The Australasian Society for Infectious Diseases and Refugee Health Network of Australia recommendations for health assessment for people from refugee-like backgrounds: an abridged outline. *Chaves et al*

**Update to 2009 Guidelines**
- **Recommendations**: Risk based rather than universal screening for Hepatitis C, malaria, schistosomiasis and sexually transmissible infections
- **Current Pre-departure Screening**
  - CXR – current or previous TB, age 11+ years
  - Interferon gamma or tuberculin skin test (children age 2-10, humanitarian visas, high prevalence countries, prior household contact)
  - HIV serology (age 15+, unaccompanied minors)
  - Hepatitis B surface antigen (pregnant women, unaccompanied minors, onshore protection visas, health care workers)
  - HCV antibody (onshore protection visas, healthcare workers)
  - Syphilis serology (age 15+, humanitarian visas, onshore protection visas)

- **Full version at** [http://www.asid.net.au/documents/item/1225](http://www.asid.net.au/documents/item/1225)

*MJA 206 (7) 17 April 2017*
**General Recommendations**

**All**
- HIV: Offer to all people aged 15 years and all unaccompanied or separated minors

**Risk based**
- First pass urine or self obtained vaginal swabs for NG and chlamydia PCR (Risk factors for STIs or on request)
- Syphilis serology (part of IME in humanitarian entrants age 15+, unaccompanied or separated minors; risk factors for STIs)
- No evidence for universal post-arrival screening

**Country based**
- HCV
  - High risk: Congo, Egypt, Iraq, Pakistan, Syria (consider)
  - Risk factors, uncertain history of travel
  - HCV Ab, HCV RNA if HCV Ab positive (HCV, test if risk factors regardless of country of origin)

**Letters:** Invasive Neisseria gonorrhoeae producing pre-septal cellulitis and keratoconjunctivitis: diagnosis and management. *Varma et al*

- 53 year old female: rapid onset left eyelid pain, swelling and purulent discharge
- Visual acuity was 6/24 in the left and 6/9 in the right with normal ocular motility

*MJA 207 (6) 18 September 2017*
**Letter**: Invasive Neisseria gonorrhoeae producing pre-septal cellulitis and keratoconjunctivitis: diagnosis and management. Varma et al

‘The Australian Gonococcal Surveillance Programme has shown an emerging resistance to ceftriaxone – the antibiotic of choice - from 0.6% in 2005 to 5.4% in 2014’

<table>
<thead>
<tr>
<th>Ceftriaxone</th>
</tr>
</thead>
<tbody>
<tr>
<td>From 2001 onwards, gonococcal isolates categorised as having decreased susceptibility to ceftriaxone, by the AGSP criteria (MIC values 0.06–0.125 mg/L), have been reported in Australia. The proportion increased incrementally from 0.6% in 2006, to 4.4% in 2012, then in 2013 doubled to 8.8%. In 2014, the proportion of gonococci with decreased susceptibility to ceftriaxone nationally decreased to 5.4% (Table 4).</td>
</tr>
</tbody>
</table>

**Integrated (one-stop shop) youth health care: best available evidence and future directions. Hetrick et al**

- Mental health problems represent the largest burden of disease for young people but access to care is poor
- **Integrated care**: physical and mental health care plus social services in one location
- **Method**: Literature review: academic peer reviewed literature, grey literature, international experts via email
- Identified 49 documents, 45 evaluations, 18 different services worldwide
- **Looked at**: Youth participation, access, levels of distress, presenting issues, services received, satisfaction/acceptability/appropriateness
- **Limitations**: evaluation process, outcome data and measurement, tracking, variable quality of included studies, unavailable data
- **Message**: Accessibility is key; Traditional approaches do not work

MJA 207 (10) 20 November 2017

- So far little information regarding indigenous populations globally regarding HPV vaccination, impact and genital wart prevalence
- Authors conducted a systematic review and could not find any studies reporting on these issues.

AIM

- Examine the effect of the HPV vaccination program on diagnoses of genital warts in Indigenous Australians
- Compare this with data for non-Indigenous Australians

MJA 207 (10) 20 November 2017

Human papillomavirus vaccination and genital warts in young Indigenous Australians: national sentinel surveillance data

- 39 clinics in the Genital Wart Surveillance Network
- Collated routinely collected, de-identified data
  - Age, Sex, Indigenous status, Country of birth, sex of sexual partners
- Results are presented as summary rate ratios
- Analysis for 3 age groups: People under 21, 21-30, 30+
- 220761 Australian born patients seen for first time between 2004-2014
  - 5162 records were excluded due to lack of Indigenous status information
- Data on 215 599 patients
  - 15683 (7.3%) identified as Indigenous
  - 91689 (42.5%) were women
RESULTS: WOMEN
Rates of diagnosis of genital warts consistently lower for Indigenous than non-Indigenous women

RESULTS: Heterosexual Men
Average annual rates of diagnosis - consistently lower for Indigenous men in each age group

RESULTS: Men who have sex with men
Similar rates of diagnosis between Indigenous and non-Indigenous men

Discussion

- Marked declines in first visit presentations for genital warts in young women since introduction of HPV vaccine program
- Greater decline for Indigenous women age 21 and under than non-Indigenous
- Decreases in young Indigenous heterosexual men and non-Indigenous heterosexual men of all ages
- Clinics included in the study capture only a subset of Indigenous people
- MSM - significant decline in non-Indigenous diagnoses but not in Indigenous MSM
Discussion

**Strengths**
- First to examine trends in diagnoses of genital warts in Indigenous people attending sexual health clinics
- National surveillance network, wide geographical area
- Retrospective data was available

**Limitations**
- Ecological study
- Indigenous patient group are sexual health clinic attendees
- Small numbers in some patient groups – CI's for trends and SSRs are wide

**Comments**
- Vaccination works – overall rates of diagnosis have decreased
- How representative of the Indigenous population is this group
- Case ascertainment: May not have disclosed presence of warts at their first visit – unsure if everyone was examined or only those who requested it.
- First visit versus first visit complaining of genital lesions?
Peer Review
Disclosures

- *Opposites Attract* one-year study extension was partially funded from unrestricted grants from ViiV and Gilead.

- Honoraria received from Pharmaceutical Society of Australia for delivery of PrEP workshops to community pharmacists.
### Outline

- Defining biomedical HIV prevention
- Currently available biomedical approaches
- Biomedical approaches under investigation
- Challenges and questions

- This presentation will focus on the *sexual transmission* of HIV only

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**What is biomedical HIV prevention?**
Combination HIV prevention

- Although the categories are somewhat artificial, there are three broad types of HIV prevention.

- HIV prevention aims to:
  - Reduce infectiousness
  - Prevent exposure
  - Reduce susceptibility
  - Improve the enabling environment

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### Preventing sexual transmission of HIV

- Structural
- Behavioural
- Biomedical

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### Structural HIV prevention

- Structural interventions change or influence social, political, or economic environments in ways that help many people all at once – perhaps without their even knowing it.

- Examples include:
  - Decriminalising sex work, homosexual behaviour, and provision of needles/syringes
  - Education of girls and young women in resource-poor settings
  - Reducing stigma against HIV and/or key populations
  - Galvanising political will to fund and implement effective prevention activities

- Structural factors should be considered as part of any comprehensive HIV prevention effort, and can often explain why certain individual-level HIV prevention interventions fail.
## Behavioural HIV prevention strategies

- Broadly divided into **Condoms** and **Non-condom-based risk reduction strategies**

<table>
<thead>
<tr>
<th>Effective</th>
<th>Somewhat effective</th>
<th>Unrealistic / ineffective</th>
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<tbody>
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<td>Condoms</td>
<td>Serosorting</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>Strategic positioning</td>
<td>PrEP sorting</td>
<td>Abstinence</td>
</tr>
<tr>
<td>Negotiated safety</td>
<td>Viral load sorting</td>
<td>Partner reduction</td>
</tr>
<tr>
<td>Viral load agreements</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“**Relationship agreements**”

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## Behavioural HIV prevention strategies

- Broadly divided into **Condoms** and **Non-condom-based risk reduction strategies**

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</tr>
<tr>
<td>Viral load agreements</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“**Prevention by proxy**”
Behavioural approaches have been the mainstay of HIV prevention for the first decades of the epidemic.

Although HIV prevention has been successful in some places and in some populations, the global HIV epidemic was relatively out of control.

Some biomedical approaches have been in use for some time (e.g. PEP).

Since 2010, exciting new scientific findings in biomedical HIV prevention have shifted the focus.

All forms of ‘biomedical prevention’ still require one or more ‘behaviours’ and need to be incorporated into people’s everyday lives/practices.

However, the key distinguishing feature is that biomedical strategies are mediated by the medical profession. This is why some people consider condoms ‘biomedical’ whereas I view them as ‘behavioural’.

<table>
<thead>
<tr>
<th>Available / Established</th>
<th>Currently under evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-exposure prophylaxis (PEP)</td>
<td>New forms of PrEP</td>
</tr>
<tr>
<td>Male circumcision</td>
<td>Microbicides &amp; vaginal rings</td>
</tr>
<tr>
<td>Treatment as Prevention (TasP)</td>
<td>Broadly neutralizing antibodies</td>
</tr>
<tr>
<td>Oral pre-exposure prophylaxis (PrEP)</td>
<td>Vaccines</td>
</tr>
</tbody>
</table>
Currently available biomedical approaches

Biomedical HIV prevention

PEP

- No clinical trial evidence for its effectiveness, but will remain part of the global HIV prevention response.

Male Circumcision

- Circumcision is about 75% effective in preventing transmission to males from female sexual partners from several clinical trials.
- Since most HIV infection in MSM is from receptive condomless anal intercourse (CLAI), it has little public health impact on MSM epidemics.
  - It may lower the risk for individual MSM who exclusively take the insertive position (~5-6% of gay men in Australia).
Treatment as Prevention (TasP)

- TasP refers to when an HIV-positive person takes antiretroviral treatments to prevent sexual transmission to an HIV-negative partner.

- TasP is often the term used to describe the population-level intervention rather than individuals’ use.

Three periods of research on TasP/UVL*

Prior to 2011: Observational research, primarily in untreated African heterosexual couples.


* TasP = Treatment as Prevention. UVL = Undetectable Viral Load.
**Efficacy of TasP in serodiscordant couples**

**HPTN 052: Original results (2011)**

- Total N = 1,763 couples
- 39 total seroconversions
- 28 linked infections
- 11 unlinked infections
- 96% reduction in HIV transmission risk (HR=0.04, 95%CI=0.01-0.27, p<0.001)

**HPTN 052: Final results (2015)**

- Total N = 1,763 couples
- 1,171 (66%) couples in trial until the end
- 9,822 CYFU
- 78 total seroconversions
- 44 linked infections
- 34 unlinked infections
- 93% reduction in HIV transmission risk
Efficacy of TasP in serodiscordant couples

**HPTN 052: Final results (2015)**

- Being on ART is not the same thing as having undetectable viral load.

- In *HPTN 052*, no linked transmissions occurred when the HIV-positive partner was *virally suppressed*.

- Of the 8 *linked infections* that occurred when the HIV-positive partner was *taking ART*:
  - 4 infections were diagnosed shortly after the HIV-positive partner started ART (i.e. not yet virally suppressed)
  - 4 infections were diagnosed after ART failure.

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**PARTNER Study: Final results, Phase 1 (2016)**

- MSM results from 340 couples:
  There were no linked HIV transmissions (transmission rate = 0 per 100 couple-years of follow-up, 95%CI = 0 – 0.89 per 100 PY).
Opposites Attract: *Transmission rates*

<table>
<thead>
<tr>
<th>Type of condomless anal intercourse (CLAI) reported by HIV-negative partner</th>
<th>Linked transmissions (n)</th>
<th>Couple-years of follow up (CYFU)</th>
<th>No. of CLAI acts</th>
<th>Incidence rate per 100 CYFU (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0</td>
<td>591.2</td>
<td>16,889</td>
<td>0 (0-0.62)</td>
</tr>
<tr>
<td>Any CLAI</td>
<td>0</td>
<td>318.0</td>
<td>16,889</td>
<td>0 (0-1.16)</td>
</tr>
<tr>
<td>Any CLAI while not on PrEP</td>
<td>0</td>
<td>241.3</td>
<td>12,928</td>
<td>0 (0-1.53)</td>
</tr>
<tr>
<td>Any CLAI when VL ≥200 copies</td>
<td>0</td>
<td>5.2</td>
<td>290</td>
<td>0 (0-71.4)</td>
</tr>
<tr>
<td>Any CLAI when VL &lt;200 copies</td>
<td>0</td>
<td>236.2</td>
<td>12,638</td>
<td>0 (0-1.56)</td>
</tr>
</tbody>
</table>

Combining TasP evidence

- Combining the data for vaginal sex in heterosexual couples:

<table>
<thead>
<tr>
<th></th>
<th>Couple-years</th>
<th>Condomless sex acts</th>
<th>Upper confidence limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational studies + HPTN052</td>
<td>330</td>
<td>?</td>
<td>1.1 / 100 PY</td>
</tr>
<tr>
<td><strong>PARTNER</strong></td>
<td>629</td>
<td>35,940</td>
<td>0.59 / 100 PY</td>
</tr>
<tr>
<td><strong>Opposites Attract</strong></td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>959</td>
<td>&gt; 35,940</td>
<td>~ 0.38 / 100 PY</td>
</tr>
</tbody>
</table>
Combining TasP evidence

- Combining the data for anal sex in homosexual couples:

<table>
<thead>
<tr>
<th></th>
<th>Couple-years</th>
<th>Condomless sex acts</th>
<th>Upper confidence limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational studies + HPTN052</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>PARTNER</td>
<td>415</td>
<td>22,273</td>
<td>0.89 / 100 PY</td>
</tr>
<tr>
<td>Opposites Attract</td>
<td>236</td>
<td>12,638</td>
<td>1.56 / 100 PY</td>
</tr>
<tr>
<td>Total</td>
<td>651</td>
<td>34,911</td>
<td>0.56 / 100 PY</td>
</tr>
</tbody>
</table>

PARTNER will report results from Phase 2 (MSM only) in 2018 or 2019.
Combining TasP evidence

- By combining the available data, it is now clear that CLAI when the HIV-positive partner has UVL is a form of ‘safe sex’.

- While we cannot say that a transmission with UVL is absolutely impossible, the risk is negligible to non-existent.

- We are as close to certainty on this as science really ever gets.

Are there any caveats to TasP in couples?

First six months of ART

- Four infections in HPTN 052 were in this category.

- No infections in PARTNER or OA in this category.

- But in OA, we had less than 10 CYFU where HIV-positive partners were in their first six months – not enough to say anything useful.

- At this stage, might be best to stick to the Swiss Statement line of “UVL for at least six months”.

Cohen et al. 2015, IAS; Rodger et al., 2016, JAMA; Opposites Attract unpublished main analysis
Are there any caveats to TasP in couples?

First six months of ART

- How quickly do people become undetectable from other research?
  - On average, there is a 2-log decline in the first 2 weeks followed by another 1-log decline by 1 month after starting ART.
  - Most people would be undetectable by 1 month if starting with a VL of 100,000 copies or less. If on integrase inhibitors, it may be faster.
  - But... we can’t apply these results directly to the question of transmission within serodiscordant couples.

<table>
<thead>
<tr>
<th>Starting point</th>
<th>By 14 days</th>
<th>By 1 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,000,000</td>
<td>50,000</td>
<td>5,000</td>
</tr>
<tr>
<td>1,000,000</td>
<td>10,000</td>
<td>1,000</td>
</tr>
<tr>
<td>500,000</td>
<td>5,000</td>
<td>500</td>
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<td>100,000</td>
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<td>5,000</td>
<td>50</td>
<td>&lt;20</td>
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<tr>
<td>1,000</td>
<td>&lt;20</td>
<td>&lt;20</td>
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<tr>
<td>500</td>
<td>&lt;20</td>
<td>&lt;20</td>
</tr>
<tr>
<td>100</td>
<td>&lt;20</td>
<td>&lt;20</td>
</tr>
</tbody>
</table>

Are there any caveats to TasP in couples?

Virological failure

- Four infections in HPTN 052 were in this category.
- No infections in PARTNER or OA in this category. OA had no cases of virological failure at all.
- Since we know that transmission can happen due to virological failure, we need to emphasise optimal adherence (at least 80% or greater) and the importance of regular viral load monitoring.
- What are the implications of less frequent viral load monitoring?
Are there any caveats to TasP in couples?

Viral blips

- From all the studies, it would appear that viral blips don’t make a difference to the transmission rate.
- But this may be simply because they were rare.
  - In PARTNER, only 13 CYFU were removed from the main analysis because VL was <200 at the start of a period and became >200 during the period. PARTNER did not report on how many CYFU were excluded due to VL being >200 for the entire period.
  - In OA, out of 343 HIV-positive partners, only 3% (n=11) had a blip of any kind (one man had 2 blips). All the blips in Australia were less than 1,000 copies/mL, and only 2 were higher than 400 copies.

Are there any caveats to TasP in couples?

Sexually transmitted infections (STIs)

- STIs also don’t appear to increase the HIV transmission rate.
- But this may simply be because our data to-date are very limited.
- Although STI rates were relatively high in PARTNER and Opposites Attract, the number of CYFU in periods where there was an STI was low.
Are there any conditions?

Viral load in semen

- No data on this yet in the context of a transmission study with serodiscordant couples – *but still no observed transmissions*.

- OA collected semen samples from HIV-positive partners in Sydney, Bangkok and Rio de Janeiro. But these have not yet been analysed to see if there were any “semen VL blips” even when blood VL was undetectable.

- Other research suggests that VL can be detectable in semen 25% of the time that it is undetectable in blood (50% of the time in those with detectable blood VL) and was strongly associated with having a urethral STI.

What remains for TasP research?

TasP at the population level

- The couple-level efficacy/effectiveness of TasP is proven.
- The UNAIDS 90-90-90 goals have been set, and the world is pushing towards them.
- The population-level effects of TasP are difficult to measure.

Implementation science questions

- How quickly can we move newly diagnosed people onto ART?
- Why do some PLHIV still refuse ART? (Especially overseas)
- Improving the delivery of ART programs
Pre-exposure prophylaxis (PrEP) is when an HIV-negative individual takes antiretroviral drugs before exposure to prevent HIV infection.

The term ‘PrEP’ currently refers to oral medication, but delivery options are likely to expand in the future.

Currently, one fixed-dose combination is approved for PrEP by the TGA:
- Tenofovir Disoproxil Fumarate (TDF), 300mg (and equivalents)
- Emtricitabine (FTC), 200mg

Available as brand-name Truvada® and several generic equivalents.

iPrEx Results

Total Participants = 2,499
Peru, Ecuador, Thailand, Brazil, South Africa, U.S.

Incident infections

PrEP arm: 36
Placebo arm: 64

44% reduction in HIV transmission risk
(HR=0.56, 95%CI=0.15-0.63, p<0.005)

Source: Grant et al, 2012, New England Journal of Medicine
iPrEx Results

iPrEx seemed to show that PrEP was much less effective than expected...

• BUT... Participants said they were taking more pills than they actually were (measured by drug levels in blood).

![Bar graph showing self-report vs. drug levels adherence]

The pills need to be taken for them to work!

iPrEx Results: Adherence and HIV infections

![Graph showing HIV incidence per 100 person-years by adherence level]

Source: Grant et al, 2012, New England Journal of Medicine

Source: Bob Grant 2015
**PROUD Study Results**

Total Participants = 544

United Kingdom

- Incident infections: 23
  - Immediate arm: 3 (Incidence: 1.3% per year)
  - Delayed arm: 20 (Incidence: 8.9% per year)

86% reduction in HIV transmission risk

(90%CI=58-96%, \( p=0.0002 \))

Source: McCormack et al, 2015, The Lancet

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**IPERGAY Study Design**

Placebo-controlled randomised clinical trial

- IPERGAY aimed to determine the efficacy of event-driven PrEP rather than daily PrEP.
  - Taking PrEP around the time of sex may help to increase adherence and to increase cost-effectiveness.

- Half of the participants randomly assigned to each group.
  - **PrEP arm:** Event-driven Truvada
  - **Placebo arm:** Event-driven placebo pill

- Study population was 414 high risk gay men in France and Canada.

Source: Molina et al, 2015, Conference on Retroviruses and Opportunistic Infections
**IPERGAY Study Design**

**Dosing schedule**

- 2 tablets (TDF/FTC or placebo) 2-24 hours before sex
- 1 tablet (TDF/FTC or placebo) 24 hours later
- 1 tablet (TDF/FTC or placebo) 48 hours after first intake

- If they continued to have sex in the following days, they would keep going with one pill per day.

**IPERGAY Study Results**

Total Participants = **414**
France, Canada

<table>
<thead>
<tr>
<th>Incidence:</th>
<th>PrEP arm</th>
<th>Placebo arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence:</strong></td>
<td><strong>0.9%</strong> per year</td>
<td><strong>6.6%</strong> per year</td>
</tr>
</tbody>
</table>

**16** Incident infections

- **PrEP arm**: 2
- **Placebo arm**: 14

**86% reduction in HIV transmission risk**

(90%CI=40-99%, \( p=0.002 \))

Source: Molina et al, 2015, Conference on Retroviruses and Opportunistic Infections
PrEP relies on adherence

PrEP failure / breakthrough infections

- Three cases worldwide of HIV infection despite confirmed adherence to PrEP.
  - Two cases likely due to sexually transmitted drug-resistant virus.
  - One case was not drug-resistant – the researchers hypothesised that PrEP contained a localised HIV infection in rectal tissue which only became systemic once PrEP was discontinued.

- All other cases of HIV infection when people were on PrEP trials have been due to poor adherence.

- PrEP is still extremely effective despite these 3 cases of failure.
Australian PrEP trials

Key
On trial
Trial cap

• In NSW, we plan to continue following up EPIC participants for a further 18 months in a new, optional study.

PrEP implementation


Australia:
• >16,000 people on PrEP currently
• Listed on the PBS
Biomedical approaches under evaluation

New forms of PrEP

- Several new forms of PrEP are in development or currently being trialed.
- These include:
  - New drug formulations for daily oral PrEP (TAF)
  - Long-acting injectable PrEP (cabotegravir, rilviripine)
  - Once-a-week oral pill
  - Once-a-week ingestible capsule
  - Implantable mini-pump
- Injectable cabotegravir and oral TAF are the most advanced.
Long-acting injectable PrEP (cabotegravir)

Population: 4,500 MSM & TGW
Locations: USA, Peru, Brazil, India, Thailand, Vietnam, Argentina, South Africa
Results: Expected in 2021

Population: 3,200 women, 18-45yrs
Locations: 5 African countries
Results: Expected in 2022

- Double-blind, double dummy
- HPTN 083 is a ‘non-inferiority’ trial
- HPTN 084 is a ‘superiority’ trial

Microbicides and vaginal rings

- Microbicides are products designed to be applied in the vagina and/or rectum to reduce the risk of getting HIV if exposed to it during sex.
- No licensed microbicide is available.
- In large Phase III studies, the dapivirine vaginal ring showed 56% decrease in HIV infection.
  - This product may be approved by regulators (Europe, South Africa) in 2019.
- There are only early stage trials underway for rectal microbicides, either in the form of gels or douches.
Broadly neutralising antibodies

- Broadly neutralising HIV antibodies (bNAbs) can be detected in about 25% of untreated HIV-positive people.
- They can be isolated and reproduced in labs.
- Hundreds of bNAbs have been identified, but research is focused on those that neutralize the largest number of HIV strains.
- Initially, they were identified to assist with HIV vaccine research.
- However, bNAbs themselves can be infused into HIV-negative individuals and may be able to prevent or reduce HIV infection.
- One bNAb (VRC01) is in Phase IIb research, while others are in Phase I research.

Broadly neutralising antibodies: VRC01

Population: 2,700 MSM & TGW
Locations: USA, Peru, Brazil

Population: 1,500 women
Locations: 7 African countries

Randomisation

- VRC01 30mg/kg
- VRC01 10mg/kg
- Placebo

Procedure: 10 infusions every 8 weeks
Follow-up: Further 20 week follow-up
Outcomes: HIV infection, dosage, safety
Results: Expected in 2022
Broadly neutralising antibodies: VRC01

Population: 2,700 MSM & TGW
Locations: USA, Peru, Brazil

Population: 1,500 women
Locations: 7 African countries

Randomisation

VRC01 30mg/kg
VRC01 10mg/kg
Placebo

Participants are allowed to use condoms, PEP and PrEP while on-study, according to standard-of-care in their setting.

HIV vaccine

• An effective preventive vaccine is the holy-grail of HIV prevention.
• HIV vaccine research has been underway for 35 years.
• One vaccine candidate has shown positive results (RV144), with 31% efficacy.
• This candidate has been improved and is currently being trialed in an RCT called HVTN 702, with results due in 2021.
• There is also another trial of a different candidate underway.
Biomedical prevention: Challenges and questions

Effectiveness in clinical studies versus in the “real world”

- TasP implementation trials have shown much lower effects than found in clinical studies.
  - In a population-level African trial, there was no reduction in HIV incidence; this was thought to be because of lower than expected treatment uptake.
  - In any setting, the “Achilles Heel” of TasP is undiagnosed infection.
  - But even in settings with massive increases in testing, and which have already reached the 90-90-90 Targets (e.g. NSW), we don’t always see large decreases in diagnoses.

- By contrast, PrEP is typically more effective in the “real world” than in clinical trials.
TasP & PrEP: Impact in San Francisco?

Figure 1.2 New HIV diagnoses, deaths, and prevalence, 2006-2016, San Francisco

TasP & PrEP: Impact in NSW?

Number of NSW residents notified with newly diagnosed HIV infection in 1 January 2013 to 31 March 2018

ART for all

EPIC-NSW

90-90-90 already achieved
Challenges and questions

Biomedical prevention highlights and possibly exacerbates health inequities

- Everywhere it has been studied, biomedical prevention (especially PrEP) becomes unequally distributed very quickly.
  - In NSW, we are seeing stunning reductions in ‘newly acquired’ HIV diagnoses among Australian-born men, but increases among overseas-born MSM.
  - In the USA, black and Latino MSM are taking up PrEP at a much lower rate than white MSM.

- This is most likely because biomedical approaches rely on knowledge, access and navigation of the health system.

National, all new diagnoses

<table>
<thead>
<tr>
<th>Year</th>
<th>Born overseas</th>
<th>Born in Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>190</td>
<td>436</td>
</tr>
<tr>
<td>2008</td>
<td>179</td>
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<td>2015</td>
<td>297</td>
<td>403</td>
</tr>
<tr>
<td>2016</td>
<td>311</td>
<td>401</td>
</tr>
</tbody>
</table>

Number of diagnoses by birthplace from 2007 to 2016.
Biomedical prevention highlights and possibly exacerbates health inequities

Challenges and questions

Inequities don’t explain everything

- An increasing and appropriate response to the current Australian epidemic is a major focus on overseas-born MSM and others at the “margins”.
  - e.g. those living outside of the inner-city, those not connected to community, etc.

- However, there are a lot of gay men eligible for PrEP who are still choosing not to take it.
  - Many of these men are centrally-located and connected to community.

- We need a better understanding of why many high-risk gay men choose not to take PrEP.
Impacts on sexual cultures/norms and changing meanings of ‘safe sex’

• We are in a period of major upheaval in gay men’s sexual practices and understandings of HIV risk.

• HIV prevention messaging is becoming more complex (and is only going to become more so).

• We now have a very uneven landscape of knowledge and attitudes about what is and isn’t “safe sex”.

Changing nature of ‘safe sex’
Changing nature of ‘safe sex’

One way to look at it is: “Oh no! Condomless sex has increased!”

But another way is that the proportion having “risky” condomless sex is really the same.
Changing nature of ‘safe sex’

This graph shows just the four condomless anal sex categories…

Even though condomless sex has increased overall, the proportion that is “risky” has decreased…

There may be a “herd immunity” effect happening in areas where PrEP is highly concentrated.

Changing nature of ‘safe sex’

Consistent condom use
No anal intercourse
Understanding the “men in red”

- We do not have a strong understanding of these men.
  - Some of them may just be “winging it” – that is, not really applying any risk reduction strategies and just hoping that they’ll be okay
  - Some are using “prevention by proxy” – that is, not taking PrEP themselves but only have condomless sex with negative guys on PrEP, positive guys with UVL, or serosorting
  - Most of them are likely to be using various forms of risk reduction and very few would be consistently not using any strategy – this is one of the main weaknesses of data from one time point

Challenges and questions

Future biomedical prevention research is going to become harder

- We now have a tool that is >99% effective if taken properly (PrEP).
- It becomes unethical to run clinical trials without allowing access to PrEP.
- But if everyone is on PrEP, there will be no infections, and thus no way to determine relative reductions in risk between ‘placebo’ and ‘experimental’ arms of the study.
- Studies will have to be:
  - Very large
  - Designed as non-inferiority trials rather than superiority trials
  - Use a non-HIV infection outcome (WHO is working on this)
Questions and comments

Thank you