Presented by: Dr Katelin Haynes, PhD
Senior Project Officer
Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine
2016 Australasian Sexual Health Conference
14-16 November 2016
The National Cervical Screening Program: On the Cusp of Change
A/Prof Marion Saville
VCS Pathology

HPV Vaccination:

- In 2015, 77.4% 15 year old Australian girls were vaccinated, along with 66.4% of boys
- Declines in rates of high grade histologically confirmed cervical abnormalities observed in women <30 years
- Australia is likely to move to a two-dose, nine-valent HPV vaccine
“Renewal” of the National Cervical Cancer Screening Program

From 1 May 2017:

• the Pap smear will be replaced with the Cervical Screening Test
• time between tests will be 5 years
• first age of screening is 25 years
• women aged 70-74 will be invited to have an exit screen
• women will be invited to participate via the National Cancer Screening Register
• vaccinated women still require regular screening

“Renewal” of the National Cervical Cancer Screening Program

Three-year average cervical cancer incidence (with 95% CIs), by age and histological type, 1982-2010

Marion Saville
“Renewal” of the National Cervical Cancer Screening Program

• National Cervical Screening Program 2016 Guidelines will be published early 2017

• Management:
  • Low risk
    HPV not detected - Repeat in 5 years
  • Higher risk
    HPV (16/18) detected OR HPV (not 16/18) + abnormalities
    Refer for colposcopy
  • Intermediate risk
    HPV (not 16/18) detected, no abnormalities
    Repeat in 12 months
The likely impact of the renewal of the cervical screening program in Australia on the prevalence of *Trichomonas vaginalis*: a modelling study

David Regan, Kirby Institute

- Trichomonas vaginalis (TV) prevalence <1% in urban Australia
- Testing not recommended for asymptomatic individuals
- Detected opportunistically through Pap smears
- Hypothesis: In the absence of further changes to guidelines, the renewal of the cervical cancer screening program will lead to an increase in TV prevalence in urban Australia over time
Renewal and TV

Results (3)

- **Scenario 3:** HPV testing replaces cytology, screening commences at age 25 and screening interval is 5-yearly
- **Model predictions at t = 25 yrs**
  - HR HPV prevalence remains constant: prevalence of TV infection will increase from 0.4% to 5.7%
  - HR HPV prevalence continues to decrease at current rate: prevalence of TV infection will increase from 0.4% to 6.0%

---

HIV, viral hepatitis and sexually transmissible infections in Australia
Annual Surveillance Report 2016
The Kirby Institute

HIV

• Notification rate stable
• 29% of new diagnoses were estimated to have an infection duration of longer than 4 years, based on immune function
• 27% increase in HIV testing in MSM in last 5 years
• 45% increase in treatment in MSM in last 10 years
• Zero mother to child transmissions from 2013 onward
Kirby Annual Surveillance Report 2016

The 2015 HIV diagnosis and care cascade

- **Target 1**: 90% living with HIV and diagnosed with HIV
- **Target 2**: 90% diagnosed with HIV and on antiretroviral therapy
- **Target 3**: 90% of people on treatment with suppressed viral load

<table>
<thead>
<tr>
<th>Step</th>
<th>Percentage</th>
<th>Number of People</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living with HIV</td>
<td>90%</td>
<td>30,000</td>
</tr>
<tr>
<td>Living and diagnosed with HIV</td>
<td>90%</td>
<td>25,000</td>
</tr>
<tr>
<td>Retained in care</td>
<td>84%</td>
<td>20,000</td>
</tr>
<tr>
<td>Receiving antiretroviral therapy</td>
<td>84%</td>
<td>15,000</td>
</tr>
<tr>
<td>Suppressed viral load</td>
<td>92%</td>
<td>10,000</td>
</tr>
</tbody>
</table>

© ASHM 2016
Kirby Annual Surveillance Report 2016

Hepatitis C
• Notifications stable since 2011
• 57% among those attending NSPs
• 29,070 severe fibrosis, 17,149 cirrhosis, 818 deaths

Hepatitis B
• Declining in Australian-born under 25yrs (due to vaccination)
• 24 months vaccination coverage 95% non-indigenous, 96% Aboriginal and Torres Strait Islander
Kirby Annual Surveillance Report 2016

Sexually transmissible infections

- 19% decline in chlamydia in 15-19yr in last 5 years
- Chlamydia testing rate in general practice has doubled to 16%
- Increasing gonorrhoea notifications, particularly in men
- Infectious syphilis rates increased from 6.5 per 100,000 in 2006 to 21.0 per 100,000 in 2015
- Four notifications of congenital syphilis in 2015 (3 in Qld), down from 11 in 2006 (1 in 2012, 7 in 2013)
Aboriginal and Torres Strait Islander Sexual Health

- HIV rate double the Australian-born non-indigenous population (6.8 vs 3.1 per 100,000)
- Hepatitis C rate 4 times greater, 43% increase in the past five years
- Hepatitis B rate 3 times higher, declining in young people
- Chlamydia rate 3 times higher
- Gonorrhoea 10 times higher, but a 22% reduction in 4 years (compared to a 94% increase in non-indigenous)
- Infectious syphilis 6 times higher
Men’s role in childbearing decision making: implications for public education
Prof Robert McLachlan - Monash

• 1:20 men are “subfertile” – 60% with no identifiable cause

Five reasons to assess the male partner:
• Identify treatable disorders
• Provide a diagnosis
• Diagnose co-existent disease
• Consider genetic issues
• Counsel re ART safety (man & offspring)

Physical examination is essential

https://www.andrologyaustralia.org/
2016 Australasian HIV & AIDS Conference
16-18 November
HIV Cure - Where’s the science up to?
Tony Kelleher – Kirby Institute & St Vincents

Latency – virus not transcribing
Mechanisms:
• Integration into silent gene / gene becomes silent
• Viral promoter competition with host gene
• Defective virus – not replication competent
• Epigenetic silencing

Only a small fraction (~0.1%) of total HIV DNA is replication competent and inducible
HIV Cure – Where’s the science up to?

Cellular reservoirs

- T cells – all CD4+ T cells
  - Naïve, memory, follicular T helper cells
- Monocytes, macrophages and dendritic cells
- Brain
- Gut, genitourinary tract

How to control the reservoir?

- “Kick and kill” – activate virus in presence of ART
- Immunotherapies to enhance anti-HIV immune response
  ie. monoclonal antibodies
HIV Cure – Where’s the science up to?

Kick and kill

• “kick” ie. with histone deacetylase (HDAC) inhibitors
  • HDACi non-specifically activate viral transcription (including defective virus)
• IL-2: massive T cell activation, reduction in viral RNA but no assessment of reservoir
• IL-7: increases the reservoir
• Therapeutic vaccines: best reduced viral load by $1 \log_{10}$

Reservoir is small, but widely disseminated
Non-specific activation may have unwanted off target effects
HIV Cure – What do the Clinical trials and cohorts tell us?
James McMahon – Monash & Burnet Institute

Current approaches to cure:
• Reduce the reservoir (kick & kill)
• Boost immunity to HIV
• Develop a HIV resistant immune system
• Early ART

HIV Cure – What do the Clinical trials and cohorts tell us?

Reduce the reservoir (kick & kill)

<table>
<thead>
<tr>
<th>Latency reversing agent</th>
<th>Site of action</th>
<th>HIV latency</th>
<th>US HIV RNA</th>
<th>Plasma RNA</th>
<th>HIV DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vorinostat</td>
<td>HDACi</td>
<td>Single dose(^1) Intermittent(^2) Continuous(^3)</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>HDACi</td>
<td>Intermittent(^4)</td>
<td>↑</td>
<td>+/-</td>
<td>↔</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>HDACi</td>
<td>Weekly(^5)</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↔</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>AKT activation</td>
<td>High dose(^6)</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Bryostatin</td>
<td>PKC agonist</td>
<td>Low dose(^7)</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

# HIV Cure – What do the Clinical trials and cohorts tell us?

## Boost immunity to HIV – Immune checkpoint blockade

<table>
<thead>
<tr>
<th>Immune checkpoint blocker</th>
<th>Study design</th>
<th>Patient population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-PDL1 (BMS)</td>
<td>Dose escalation phase 1</td>
<td>Healthy</td>
<td>Ceased due to pre-clinical toxicity</td>
</tr>
<tr>
<td>Anti-PD1 (Merck)</td>
<td>Multi-dose phase 1B</td>
<td>Malignancy: AIDS defining or non-AIDS</td>
<td>Reservoir substudy</td>
</tr>
<tr>
<td>Anti-PD1 + Anti-CTLA4 (BMS)</td>
<td>Phase 1 Dose escalation</td>
<td>Malignancy: HIV-associated tumours including lung, anal, and Kaposi’s sarcoma</td>
<td>Reservoir substudy</td>
</tr>
<tr>
<td>All immune checkpoint blockers</td>
<td>Observational study</td>
<td>Malignancy: melanoma or small cell lung cancer</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
HIV Cure – What do the Clinical trials and cohorts tell us?

Develop a HIV resistant immune system

- ART + α4β7 monoclonal antibody in macaques → prolonged virological control and restoration of CD4+ cells (persisted after termination)
- Clinical trial ongoing of Vedolizumab (α4β7) infusions followed by ART interruption
- Gene therapy – CCR5 knockout ie. CRISPR
HIV Cure – What’s in it for me? – Balancing hope and scepticism about HIV cure research
Brent Allen – Living Positive Victoria

Australia has an outstanding history of people living with HIV participating in many different kinds of research

How do you prepare yourself or others for a cure? If it’s tomorrow, or in ten years time, how do you prepare to change your identity?
Pre-clinical evaluation of a mucosal HIV vaccine strategy
Charani Ranasinghe – ANU

- Mucosal (intranasal) immunisation gives broad protection of the genitorectal mucosa
- In non-human primates, a single dose of a poxviral vector-based HIV/SIV gag/pol/env vaccine induced excellent env-specific antibodies post-challenge (similar to HIV elite controllers)
A Novel Mucosal HIV Vaccination Regimen Involving Live Recombinant Human Rhinovirus and DNA Vaccines to Elicit Protective HIV-Specific Immunity
Danushka Wijesundara – The University of Adelaide

• “HIV vaccine research: Adelaide team achieves ‘glimpse in right direction’” – ABC News, 21 Nov 2016

• Vaccinated mice had a 10 fold lower viral load compared to unvaccinated after 7 days, with non-classical neutralizing antibodies to Tat (HIV encoded transcription factor)

• First evidence that a rHRV-DNA vaccination can elicit protective HIV-specific immunity

Descovy

- Available on the PBS 1\textsuperscript{st} December 2016
- Emtricitabine 200mg / Tenofovir alafenamide (TAF) 25mg

![Mechanism of Action: TAF vs TDF\textsuperscript{1-6}](image)

Levin J, EACS 2015
Pharmacokinetic-pharmacodynamic (PK-PD) of Emtricitabine/Tenofovir alafenamide (F/TAF) demonstrated wide exposure range associated with clinical safety

Paul Slade – Gilead Sciences

• F/TAF compared to F/TDF
• No difference in drug-related serious adverse events or discontinuation due to adverse events
• No difference in hip and spine BMD or fasting lipids after 48 weeks
A Case Study of HIV Detection Following Post-Exposure Prophylaxis

Julian Langton-Lockton – Nepean Sexual Health and HIV Clinic

• 21 yr old MSM university student
• Presented 36 hrs after high risk HIV exposure (involving “Ice” and multiple casual male partners)
• Prescribed Tenofovir/Emtricitabine and Raltegravir
## PEP Case Study

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Ab/Ag</td>
<td>Negative</td>
</tr>
<tr>
<td>Syphilis</td>
<td><strong>TPPA Positive</strong></td>
</tr>
<tr>
<td></td>
<td>FTA Negative</td>
</tr>
<tr>
<td></td>
<td>VDRL Negative</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>Negative by PCR</td>
</tr>
<tr>
<td>Gonorrhoea</td>
<td></td>
</tr>
<tr>
<td>Liver Function</td>
<td>ALT 103</td>
</tr>
<tr>
<td>Test</td>
<td>AST 164</td>
</tr>
<tr>
<td></td>
<td>CK 4138</td>
</tr>
<tr>
<td>Hepatitis BsAb</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Hepatitis C Ab</td>
<td>Negative</td>
</tr>
</tbody>
</table>
PEP Case Study

- Diagnosed with HIV 3 weeks into PEP
- Viral load undetectable
- Recommended to continue Tenofovir/Emtricitabine and Raltegravir
- Used Single Copy Assay to monitor at 4, 7, 9, 17 and 67 weeks
- At 67 weeks, HIV RNA levels were <0.3-0.5 copies/ml for 4-7ml samples (limit of detection of assay)

- Was this failed PEP? Was 36hrs too late?
- Can treatment in “hyper acute infection” achieve functional cure?
PrEP at age 6
Jared Baeten – University of Washington

What should we expect from a 6 year-old? Developmental milestones?

1. Begin to understand cause-and-effect relationships
   = take it, it works

2. Magical thinking quickly fades
   = only 5 year olds believe in magic bullets

3. Starts to understand the feelings of others
   = PrEP is wanted, and wanted in deep ways

4. Becomes more flexible in their thinking
   = PrEP makes us think differently

5. Understands more about their place in the world
   = Time to think big
Contact me

Dr Katelin Haynes, PhD
Senior Project Officer
0423 058 692
Katelin.Haynes@ashm.org.au