Undiagnosed HIV infections among gay and bisexual men increasingly contribute to new infections in Australia

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Some PLHIV are: undiagnosed, diagnosed but not on ART, on ART but with detectable VL

- Closely align with estimates of new infections
- Where do new infections come from?
- What is the contribution of undiagnosed gay and bisexual men?
Methods

Contribution of undiagnosed HIV infections to new infections

Estimating infectivity

Update of approach and estimates presented at ASHM 2015

\[ I = \beta_u N_u + \beta_d N_d + \beta_u^u N_u^u + \beta_t^s N_t^s \]

Where:
- \( I \) = number of new infections
- \( N_u \) = number of people with undiagnosed infection
- \( N_d \) = number of people with diagnosed infection but not on ART
- \( N_u^u \) = number of people on ART but with unsuppressed virus (> 200 copies/ml)
- \( N_t^s \) = number of people on ART but with undetectable viral load (< 200 copies/ml)
- \( \beta_u, \beta_d, \beta_u^u, \) and \( \beta_t^s \) are the corresponding annual rates of transmission attributable to each cascade step or infectivity of people in each step

From new infections and population sizes we can estimate the \( \beta \) values

Contribution of new infections from undiagnosed: \( \beta_u N_u / I \)
Number of new infections

Used the European Centre for Disease Prevention (ECDC) HIV modelling tool which uses CD4 count at diagnosis

What we use for estimating the proportion undiagnosed in the national HIV cascade (reported in the ASR)

Applied it to notifications attributable to male-to-male sex

Ran two scenarios
- Notifications of those previously diagnosed overseas included
- Notifications of those previously diagnosed overseas excluded

![Graph showing number of new infections](image)
HIV Cascade for GBM

- Used method from 2016 Annual Surveillance Report

- Diagnosed
  - All notifications attributed to male-to-male sex minus duplicates, deaths and emigrants
  - Gives number living with diagnosed HIV over time

- Treated
  - Diagnosed x proportion on treatment from GCPS

- Suppressed
  - Treated x proportion with VL < 200 at last test from AHOD

HIV Cascade for GBM - Undiagnosed

- Comes from the ECDC model

- % undiagnosed from 14.5% in 2004 to 7.5% in 2015
Contribution of undiagnosed HIV infections to new infections

HIV diagnosis and care cascade for GBM

\[ I = \beta_u N_u + \beta_d N_d + \beta^u_i N^u_i + \beta^s_i N^s_i \]

Just like a regression model but the $\beta$ values are not completely free
- They cannot be less than zero
- They could change over time
- We know people with suppressed virus are much less likely to transmit: HPTN-052, Partner Study, Opposites Attract

Used a **Bayesian methodology** to estimate each infectivity parameter $\beta$ using estimates for each step of a GBM HIV cascade and estimated number of new infections in GBM over 2004-2015

**Assumptions:**
- Uncertainty in cascade estimates: $\beta N = \beta' NE$
- $\beta$ changes linearly over 2004-2015 from $\beta_{\text{start}}$ to $\beta_{\text{end}}$
Estimating infectivity - Priors

Priors for $\beta_u$, $\beta_d$, and $\beta_t^u$ uniform with means satisfying $\beta_u > \beta_d > \beta_t^u$ but with wide ranges so they can overlap

- Assume start and end priors are the same

Prior for $\beta_t^z$ based on the results of clinical studies
- Assume no change over time

<table>
<thead>
<tr>
<th>Study</th>
<th>Prior</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partner study</td>
<td>Exponential mean: 1/2.8 per 1000 GBM with suppressed virus.</td>
<td>Zero transmissions but upper 95% confidence interval was 8.4 transmissions per 1000 couple-years</td>
</tr>
<tr>
<td>HPTN-052</td>
<td>Lognormal distribution: mean 0.04 (95% CI: 0.01-0.27) relative to $\beta_d$</td>
<td>$\beta_t^z = \text{prior} \times \beta_d$</td>
</tr>
<tr>
<td>Partner, Opposites Attract</td>
<td>$\beta_t^z = 0$</td>
<td>Zero transmission from suppressed</td>
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Estimating infectivity – Fitting Procedure

To fit the model to the estimates for new infections and each cascade step we used a **Bayesian melding** procedure

- Sampling-Importance-Resampling Procedure
- Took 5 million samples of the priors
- For each sample ran the model and calculated a weight based on the fit

To generate the posterior distributions for each $\beta$ we resampled 100,000 times based on the weights
- This set used to generate all the results
Sensitivity scenarios

Focus on 2015 cascade estimates with uncertainty ranges and Partner study prior

Also ran scenarios:
• 2015 cascade and HPTN-052 prior
• 2015 cascade and zero transmission from suppressed
• 2015 cascade with best estimates only and Partner prior
• HIV cascade over 2004-2014 using 2015 ASR methodology (higher estimates for diagnosed due to lower emigration) and Partner study prior

Results
Contribution of undiagnosed HIV infections to new infections

Fit to new infections

Estimate and range

- ECDC model estimates

New infections posterior

- Posterior simulations
- Posterior mean
- 95% credible interval

Year

New infections


Contribution of undiagnosed HIV infections to new infections

New infections attributable to each cascade step

Undiagnosed

Diagnosed untreated

On ART unsuppressed VL

On ART suppressed VL

Year

New infections

0 200 400 600

2005 2010 2015

Percentage of new infections

0% 25% 50% 75% 100%

2005 2010 2015
## New infections attributable to each cascade step

<table>
<thead>
<tr>
<th>Cascade step</th>
<th>New infections 2015</th>
<th>Percentage 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undiagnosed</td>
<td>423 (132-680)</td>
<td>59% (20.8-89.8%)</td>
</tr>
<tr>
<td>Diagnosed untreated</td>
<td>103 (8-221)</td>
<td>15% (1.2-34.4%)</td>
</tr>
<tr>
<td>Treated but unsuppressed</td>
<td>138 (6-307)</td>
<td>19.8% (0.9-45.3%)</td>
</tr>
<tr>
<td>Suppressed</td>
<td>44 (1-159)</td>
<td>6.2% (0.2-21.4%)</td>
</tr>
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## New infections attributable to undiagnosed

![Graph showing density over years](image)
Contribution of undiagnosed HIV infections to new infections

Rate of transmission for undiagnosed PLHIV

Increased from 110 per 1000 PLHIV in 2004 to 290 per 1000 PLHIV in 2015

Realistic?

- Increase in condomless anal intercourse
- Serosorting amongst HIV-negative
- Reduction in time between infection and diagnosis means larger proportion of time with high VL

Effect of variations in suppressed prior

Changing the prior for $\beta_s$ did not change the estimated contribution of undiagnosed infections to new infections substantially (57-65%)
- 65% if suppressed have zero transmission

Using the best estimates for the cascade without uncertainty pushes the contribution of undiagnosed infections to 74% (with much tighter posterior distribution)
Conclusions

Using this approach

- In 2015 around 59% of new infections in GBM are attributed to undiagnosed men
- Rate of HIV transmission from undiagnosed GBM increased substantially over 2004-2015
- Minimizing number of undiagnosed men and maximizing effective ART coverage would likely have a substantial impact on HIV incidence
- Also highlights the potential of PrEP but will need a more complex model to assess the contribution of PrEP

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