Technical Appendix S1

Cost-effectiveness of More Frequent HIV Screening of Populations at High Risk in the United States

Hutchinson et al.

Word count: 2,050

1.0 HIV Detection and Transmission Model

The HIV detection and transmission model is a simple, two-part mathematical model that estimates HIV infections detected and averted transmissions. It was applied to assess outcomes of HIV testing every 3 months and 6 months compared to annual testing and 3-month versus 6-month testing using two HIV testing methods: point-of-care rapid testing and conventional testing with a fourth-generation HIV test. In this analysis, averted transmissions were based on differences in the number of new HIV infections detected and persons made aware under each testing interval as well as disease stage: acute infection, the first stage of HIV during which infectiousness and the likelihood of transmission are highest before antibodies are detectable; or established infection, when antibodies are fully detectable. We assumed that all diagnosed infections were new infections, the incidence rate was constant, testing occurred on day 90 or 180, and there was no migration of persons into or out of the model.

1.1 HIV Infections Detected

Using annual incidence estimates, we first calculated the number of HIV infections occurring and detected under the two tests during each testing interval for cohorts of 10,000
MSM and IDU. We assessed the probability infection was detectable for a given testing frequency and type of test using the window period of detection for each test: conventional fourth-generation, 16 days and rapid testing, 54 days\textsuperscript{1–3}. The probability of detection was calculated as the ratio of the detectable period (the testing interval minus the window period plus 1) and the full testing interval. Thus, the probability of detection of a new HIV infection with fourth-generation test assuming testing on day 90 was 0.811. This probability was applied to the number of new infections (incidence) during the period to estimate HIV infections detected. We assumed infections that occurred during the window period of one testing interval would be detected during the subsequent interval. For example, in the case of quarterly fourth-generation testing, infections that occurred during the window period of the first quarter (day 74–90 assuming testing occurs on day 90) are undetectable and will be detectable at the second quarterly testing interval. For the second to fourth intervals for quarterly testing, detectable infections included those that occurred within the window period of the prior testing interval and newly detectable infections in the current interval. Figure S1 depicts the detectable period for each test for quarterly testing. Next, we applied the probability of notification to detected infections for each testing strategy (80% for conventional fourth-generation testing and 99% for rapid testing) to estimate the number of newly-diagnosed persons who are aware of their infections.

We estimated the benefits of early detection of infection for each testing interval based on the time of detection and awareness of HIV infection and the comparison testing interval. For example, in the case of quarterly detection, infected persons detected in the first quarter would be aware of their infection 9 months earlier compared to annual testing and 3 months
earlier compared to testing every 6 months. Window period infections from the third quarter and detectable infections from the fourth quarter did not constitute early detection because testing would otherwise occur annually.

Because an HIV-infected person’s awareness of their infection during the acute phase of infection provided additional transmission benefits, we added the benefits of transmissions averted because of acute-phase detection. Acute-phase infection awareness was based on the probability that the person was both detected and notified of infection while in the acute phase of infection, which lasts for 49 days\(^4-5\). To estimate acute-phase detection and awareness, we calculated the shortest (1 day) and longest (24 days) possible periods of awareness of infection during the acute phase based on time of infection and test window periods (Figure S2). Our calculations are described for quarterly testing. We assumed a 7-day time to receipt of results following a fourth-generation test. The longest period of awareness was calculated as follows: assuming testing occurred on day 90, the last day of the testing interval, infection can occur on day 73 with detection on day 90 (assuming a 16 day window period), awareness on day 97 and the acute phase lasting until day 122, yielding a maximum 24 days duration of acute-phase awareness. Infection can occur as early as day 49 for a person to be aware during the acute phase; assuming detection on day 90, awareness on day 97. However the acute phase only lasts until day 98, leaving 1 day of acute-phase awareness. We then applied the mean value (12) of the shortest and longest possible period of acute phase awareness. For persons with cases of HIV that were detectable with a fourth-generation test who were notified of their infection (current, point-of-care rapid tests do not detect acute-phase infection), we applied acute-phase transmission benefits (the difference in transmission between the acute unaware
and aware) to the mean of 12 days of acute-phase awareness, (Figure S2). Thus, total transmissions averted are the sum of transmissions averted during the established and acute phase of infection.

1.2 HIV Transmissions Averted

Averted HIV transmissions were transmissions averted during the extra period of awareness conferred by more frequent HIV testing compared to when testing would otherwise occur (e.g., based on the additional infections detected and persons notified at 6 months compared to annual detection or 3 months compared to 6 months). The model estimates infections detected and one generation of averted secondary transmissions based on the difference in transmission due to sexual behavior change because of awareness of HIV infection, disease stage, and viral load suppression due to earlier ART initiation\(^6\).

There were three overall categories of transmissions averted (transmission rates can be found in Table S1): 1) Acute-phase transmission, the difference in acute unaware and acute aware. 2) Established transmission, the difference in established unaware and established aware without viral suppression (includes sexual behavior change because of awareness of positive status); 3) Established transmission with viral suppression, the difference in established unaware and established aware with viral suppression and sexual behavior change benefits. We assigned viral suppression benefits to 42% and 36% of newly diagnosed MSM and IDU, respectively, based on national HIV surveillance data on the proportion of prevalent cases with viral suppression at most recent viral load test\(^7\)\(^{-8}\). For example, for MSM, total established transmissions averted were calculated as the weighted average of the transmission benefit of established transmission with viral suppression \(0.121 - 0.003 = 0.118 \times 0.42 = 0.049\) and the
transmission benefit of established transmission without viral suppression (0.121 – 0.069 = 0.052 x 0.58 = 0.0030; 0.064 + 0.022 = 0.086) (Table S1). Total acute transmissions were the product of the benefit of acute-transmission detection expressed as a daily rate (1.146 – 0.330 = 0.816 / 365 = 0.002) and 12, the mean number of days of acute phase awareness (0.002 x 12 = 0.024).

1.3 Bernoulli-model based HIV transmission rates

We used Bernoulli-model based HIV transmission rates by Lin et al., who incorporated awareness of positive status and viral suppression in their transmission rate estimation (Table S1). The Bernoulli model is given below (Lin, unpublished-revision).

\[
R = m(1 - \pi)(1 - o)\left(1 - (1 - \theta)\alpha\right)^{n(1-Qe)},
\]

where, \(R\): the annual risk of transmitting HIV; \(\pi\): HIV prevalence; \(m\): Average annual number of partners; \(o\): Rate of partnership overlap; \(\alpha\): Per-contact transmission probability; \(n\): Annual number of sexual contacts; \(Q\): Proportion of protected sexual contacts of type; \(\theta\): Reduction in HIV sexual infectivity based on the viral load status; \(e\): Condom effectiveness.

We also adjusted Lin’s transmission estimates for our sensitivity analysis on the transmission reduction because of awareness of HIV status (53%; sensitivity analysis, 22%–75%) and the reduction in infectivity for infected persons who achieve viral load suppressions (96%; sensitivity analysis, 70%–99%)\(^9,10\). For the established aware group, we used transmission rates that include behavioral benefits because of awareness of infection both with and without the benefits of viral suppression. To estimate transmission for acutely infected persons aware and
unaware of their infection, a modifier on per-act transmission of 12.0 for acute HIV transmission was applied\textsuperscript{11–13}.

1.4 HIV Detection and Transmission Model Formula

Formulas for the model are given below. For each test type, the following formulas applied:

(1) Established HIV detection and transmission,

The number of persons detected and notified in each testing event:

\[ N_t^{\text{notified}} = P_{\text{notify}} \times N \times I_t \times \frac{[t-(WP+1)]}{t} \]

The number of persons who were in the window period notified during next testing event:

\[ WN_t^{\text{notified}} = P_{\text{notify}} \times N \times I_t \times \left(1 - \frac{[t-(WP+1)]}{t}\right) \]

Total transmission due to established HIV awareness in testing event \( i \):

\[ \Delta Trans_i = N_t^{\text{notified}} \times \Delta \beta^j_{\text{annual}} \times \frac{TI-i}{TI} \] (tested and notified in the same interval)

and

\[ \Delta TransW_{i+1} = WN_t^{\text{notified}} \times \Delta \beta^j_{\text{annual}} \times \frac{TI-i}{TI} \] (tested in one interval and notified in the next interval)

\[ \Delta TransW_1 = 0 \] (There is no notification of window period infections during the first event)

Total transmission due to established HIV awareness:

\[ \Delta \text{Total}_{\text{non-acute}} = \sum_{i=1}^{TI} \Delta Trans_i + \sum_{i=1}^{TI-1} \Delta TransW_i \]

(2) Acute-phase detection and transmissions,

The mean number of days acute (AHI) awareness will be:

\[ \sigma_{\text{acute}} = \frac{\max[D_{\text{acute}}-(WP+TTN+1),0]}{2} \]

Total transmission(s) due to acute awareness in testing event \( i \):

\[ \Delta \text{TransAcute}_i = N_t^{\text{notified}} \times \Delta \beta^j_{\text{daily}} \times \sigma_{\text{acute}} \]
Total transmissions due to acute (AHI) awareness:

$$\Delta Total_{acute} = \sum_{i=1}^{TI-1} \Delta TransAcute_i$$

Then, overall transmission due to acute and established HIV awareness:

$$\Delta Total = \Delta Total_{established} + \Delta Total_{acute}$$

or

$$\Delta Total = \sum_{i=1}^{TI} \Delta Trans_i + \sum_{i=1}^{TI-1}[\Delta TransW_i + \Delta TransAcute_i]$$

Where:

- $N = \text{Cohort size}$
- $WP = \text{Window period}$
- $P_{notify} = \text{probability of notification (differs by rapid and conventional test)}$
- $t = \text{Test interval (e.g. 90 days for testing every 3 months)}$
- $TI = \text{number of testing events annually}$

For example, $TI = 4$ for testing every 3 months and $TI = 2$ for testing every 6 months

- $i = \text{index for testing event, } i = 1, ..., TI$
- $I_t = \text{HIV incidence in the test interval } t$ (e.g. $I_{90\text{days}} = \frac{I_{\text{annual}}}{4}$)
- $\Delta \beta_j^{\text{annual}} = \text{Annual difference in transmission rate of unaware and aware for risk population } j, j = \text{MSM and IDU}$
- $\Delta \beta_j^{\text{daily}} = \text{Daily difference in transmission rate of acute unaware and acute aware for risk population } j, j = \text{MSM and IDU}$
- $D_{acute} = \text{Duration of acute period}$
- $TTN = \text{Time between the test day and notification day}$

**2.0 Annual Incidence Rate Estimation**
We calculated an annual HIV incidence rate for MSM age 14–64 using the following formula:

$$\text{Annual HIV Incidence, 2009} = \frac{\text{Number of new cases}}{\text{Susceptible population}}.$$ 

We defined MSM as MSM and MSM/IDU age 14–64. We utilized the following data on incident cases among MSM and MSM/IDU (2009): 30,600 (95% CI, 26,190-35,000)\(^14\). The susceptible population was calculated by applying the estimated proportion of males, 2.9% (95% CI, 2.6–3.2%), who had sex with another male in the last 12 months to U.S. census data on the population of males in the United States in 2009 (102,385,336)\(^15\)–\(^16\) and subtracting out prevalent HIV cases among MSM based on a 19% prevalence for MSM\(^8\). We estimated the susceptible population to be 2,405,032 with a range of 2,156,235–2,653,827. Our annual HIV incidence rate for MSM was 1.27% (0.99–1.62%). We calculated the lower bound of the incidence rate based on the lower bound in the annual incidence estimate and the upper bound in the susceptible population. We calculated the upper bound using the upper bound of the incidence estimate and the lower bound susceptible–population estimate. For IDU, we used 2009 data on HIV incidence 4,673 (95% CI, 3,100–5,900), which includes a prorated portion of MSM/IDU, for the numerator, and for the denominator, meta-analytic survey data on the susceptible population IDU age 13 and older in 2009, 759,759 (95% CI, 481,181–1,038,338)\(^14\)\(^17\). These calculations yielded an annual HIV incidence rate for IDU of 0.62 (0.21–1.20). The lower bound of the annual incidence rate range was calculated using the lower bound of incident IDU cases and an alternate recent estimate of the IDU population (1,520,054 in 2007) (personal communication, Dr. Barbara Tempalski, The Institute for AIDS research, New York, NY). The upper bound was calculated using the upper bound of the incident cases and the lower bound
of the IDU population estimates by Lansky et al.\textsuperscript{17}. Incidence rates for each testing interval were calculated in proportion to the annual incidence rate.

3.0 HIV Testing and Treatment Cost

HIV test costs assume a routine testing approach, so costs for counseling uninfected persons and risk assessment are not included (Table S2). Costs included cost data on laboratory testing costs for fourth-generation antigen/antibody combination assays and Western blot that include reagent costs, supplies and controls\textsuperscript{18}. We also included costs for recruitment and outreach ($16.07) for all persons tested\textsuperscript{19}. We assumed use of the 1989 testing algorithm with confirmation of repeatedly reactive antibody tests and preliminary positive rapid tests with Western blot. Annual treatment costs ($16,318) include the following: costs for antiretroviral therapy ($15,196), CD4 ($149) and viral load monitoring ($371), resistance testing ($35) and outpatient costs ($566)\textsuperscript{20}. 
Table S1. Annual per Person HIV Transmission Rates

<table>
<thead>
<tr>
<th>Transmission Category</th>
<th>MSM</th>
<th>IDU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Unaware</td>
<td>1.146</td>
<td>0.327</td>
</tr>
<tr>
<td>Acute Aware</td>
<td>0.330</td>
<td>0.094</td>
</tr>
<tr>
<td>Established Unaware</td>
<td>0.121</td>
<td>0.060</td>
</tr>
<tr>
<td>Established Aware (no viral suppression)*</td>
<td>0.069</td>
<td>0.037</td>
</tr>
<tr>
<td>Established Aware (viral suppression)**</td>
<td>0.003</td>
<td>0.011</td>
</tr>
</tbody>
</table>

# transmissions per person per year. Calculated from Lin et al. (CDC unpublished data)
*includes behavioral benefits due to awareness of infection
**includes behavioral benefits due to awareness of infection and viral suppression benefits

Transmission Benefit:
- Acute phase transmission: acute unaware – acute aware
- Established transmission: established unaware – established aware
- Established transmission with viral suppression: established unaware – established with viral suppression
Table S2. HIV Testing Cost Detail

<table>
<thead>
<tr>
<th>Cost Component</th>
<th>Fourth-generation,$</th>
<th>Rapid,$</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV-</td>
<td>(HIV+)</td>
<td>HIV-</td>
</tr>
<tr>
<td>Assay, test kit costs†</td>
<td>6.81</td>
<td>19.36</td>
<td>17.08</td>
</tr>
<tr>
<td>Labor costs: specimen collection, pretest information</td>
<td>4.03</td>
<td>10.25</td>
<td>5.60</td>
</tr>
<tr>
<td>Western blot, labor, controls</td>
<td>---</td>
<td>43.90</td>
<td>---</td>
</tr>
<tr>
<td>Total test cost</td>
<td>10.84</td>
<td>73.51</td>
<td>22.62</td>
</tr>
</tbody>
</table>

†Includes reagent costs, supplies and labor costs adjusted for controls 2012 dollars
Figure S1. Relationship Between Test Window Period and Detectable Transmissions with Rapid and Fourth-Generation Quarterly Testing

The figure depicts 1 year of quarterly testing with detection and window periods (shown in the dark shaded area) with testing occurring the last day of the quarterly interval. Infections occurring in the light shaded area are detectable in the current testing interval. The arrow depicts window period transmissions that become detectable in the subsequent testing interval.

Window period for 4G = 16 days, and rapid test = 54 days. T1 to T4 are quarterly testing intervals. 4G = fourth generation test.
Figure S2. Acute-phase Awareness with Fourth-Generation Quarterly Testing

The patterned area depicts the maximum number of days (24 days) of acute-phase awareness of HIV infection assuming a 16-day window period for fourth-generation testing, 7-day results notification, and 49-day acute phase.

4G=fourth generation test
T = number of days
References


