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Screening for acute HIV infection in community-based settings: Cost-effectiveness and impact on transmissions

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Summary *Objectives:* To determine cost-effectiveness of three community-based acute HIV infection (AHI) testing algorithms compared to HIV antibody testing alone by focusing on the potential of averting new infections occurring within a one-year time horizon among men who have sex with men (MSM).
Methods: Data sources for model parameters included actual cost and prevalence data derived from a community-based AHI screening program in San Diego, and published studies. Main outcome measure was costs per infection averted (IA). The lower end of the cost range of discounted lifetime costs of an HIV infection (i.e. $236,948) was used for defining cost-effectiveness.
Results: The most sensitive algorithm for AHI detection, which was based on HIV nucleic acid amplification testing, was estimated to prevent between 5 and 45 transmissions, with simulated costs per infection averted between $965 and $141,256 when compared to HIV antibody testing alone.
Conclusion: AHI testing was cost-effective in preventing new HIV infections among at risk MSM in

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San Diego, and also among other MSM populations with similar HIV prevalence but lower proportions of AHI diagnoses. These results indicate that community-based AHI testing among MSM in the United States can pay for itself over the long run.

Introduction

HIV antibody testing remains the most widely used approach to diagnose HIV infection in community-based settings in the United States.[1] HIV antibody tests, however, fail to detect acute HIV infection (AHI), which is the earliest stage of HIV disease and lasts until the body develops antibodies against HIV.[2] AHI is associated with transient levels of extremely high titer viremia[3] resulting in a high level of infectiousness that serves as a major driver of HIV transmission in the United States and other resource rich countries.[4–6] As many as half of HIV transmissions occur from persons with AHI,[7] which makes detection of AHI critical to HIV prevention strategies.[4–6,8] While guidelines support early initiation of antiretroviral therapy (ART) for the prevention of HIV transmission (i.e. treatment as prevention),[9,10] AHI diagnosis may reduce transmission risk even in the absence of other interventions, as evidence suggests that individuals generally reduce their risk behavior after being diagnosed with HIV.[5,11]

Although detection of AHI offers opportunities to reduce infectivity (primarily ART and risk reduction) and transmission risk, screening for AHI is not widely performed in community-based settings. Commercially available point-of-care (POC) assays for AHI have limited sensitivity, while non-POC assays require follow up for results and are generally more costly to perform. By comparing four community-based testing strategies, we have recently shown that costs for detection of one case of AHI may be below US $20,000 in at risk men who have sex with men (MSM).[12,13] Calculation of cost-effectiveness per transmission prevented (i.e. infection averted [IA]) is more complicated, but has two major advantages: i) cost thresholds are easier to define, as there are comprehensive estimates of lifetime treatment- and healthcare costs per HIV infection,[14,15] and ii) the measure is more complete in terms of costs to the healthcare system. Consistent with federal efforts to reduce the costs of healthcare through the deployment of effective prevention measures, calculation of costs per IA will allow us to determine if testing can pay for itself over the long run.

The objective of this study was to determine cost-effectiveness of three community-based AHI testing algorithms compared to HIV antibody testing alone by focusing on the potential of averting new infections.

Material and methods

This one-year cost analysis compared community-based HIV testing strategies based upon the cost per IA in 2014 US dollars. Cost analyses were conducted using an established HIV testing program perspective. The study evaluated four community based HIV testing strategies,[12] including three that detect AHI (Early Test [i.e. routine HIV nucleic-acid-amplification testing in all antibody negative persons], Architect, and Determine [both based on HIV p24 antigen detection]), and one that relies on HIV antibody testing alone. The model was built on our recent cost-model that compared these four algorithms with regard to costs per AHI diagnosis in 2014 US dollars,[12] which was based on published risk data and HIV observed in MSM undergoing community-based AHI screening in San Diego between 2006 and 2014.[16–20] Detailed description of the algorithms and methods can be found elsewhere,[12] and is summarized in the supplementary appendix (SI Appendix, SI Appendix Table S1, SI Appendix Fig. S1).

Cost per infection (i.e. transmission) averted

Estimations of the potential impact of missed AHI diagnoses on subsequent spread of HIV were conducted by combining published transmission risk estimations with data on risk and testing behavior observed in MSM diagnosed with AHI between April 2008 and July 2014 with the "Early Test", a community-based, confidential AHI screening program in San Diego, California.[16] To assess the frequency of testing in those diagnosed with AHI, we calculated the time period between the last negative test and the day they tested positive by NAT and assumed that it would have taken those individuals exactly the same time period to test again. We also assumed that the risk behavior reported by those with AHI for the last 12 months before diagnosis [i.e. condomless insertive anal intercourse (CIAI) and number of male partners] would reflect the ongoing risk behavior in the absence of an HIV diagnosis. In addition, we focused only on direct transmission occurring from individuals with missed AHI diagnoses. Finally, we assumed that those diagnosed with AHI would not transmit HIV during the first year after diagnosis (immediate ART is routinely provided to "Early Test" participants diagnosed with AHI, in addition studies have shown that transmission risk behavior may decrease significantly in the months after HIV diagnosis[5]). Using these assumptions, we calculated estimated numbers of transmissions from undiagnosed (i.e. missed) acute HIV diagnoses. Incremental cost effectiveness ratios (ICERs) were calculated by comparing two different testing algorithms, with the numerator representing the difference in annual cost of the two algorithms and the denominator representing the difference in IA. Numbers of IA by each of the AHI were calculated by two different approaches: a) per-contact transmission risk and b) per-partner transmission risk.

Cost thresholds

Discounted lifetime costs of an HIV infection have recently been updated [i.e. between $229,800 and $338,400 depending on the time point of diagnosis and ART initiation[15]]. As those costs were calculated in 2012 US dollars, the thresholds were updated to 2014 US dollars by adding the cumulative rate of inflation (i.e. 3.1%), resulting in an

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updated cost range of $236,948 and $348,927. We conservatively used the lower end of this updated cost range (i.e. $236,948) for defining cost-effectiveness.

Per-contact transmission risk

Focusing on per-contact transmission risk is important as numbers of sexual contacts do not correlate with the number of partners. In previous studies, the number of sexual contacts was markedly higher and condomless anal sex was more frequent with the main partner *vs*. casual partners (80.7 annual contacts with main partner *vs*. 4.0 with casual partners).[21,22] However, number of contacts was not routinely assessed in our cohort of MSM and we therefore used estimates from a comparable study cohort.[23,24] In an Australian study that followed more than 1000 MSM over 4 years, a mean of 41 annual condomless insertive anal intercourse (CIAI) episodes were reported in those reporting any CIAI, however, actual numbers of contacts varied widely.[23,24] We used these estimates and assumed that in our setting every MSM who reported CIAI for the prior 12 months, would have 41 CIAI episodes (95% confidence interval [CI] 10–70 episodes) per year.

In recent analyses on per-contact HIV transmission risk, condomless receptive anal intercourse (CRAI) with an HIV-positive partner (either acute or chronic) carried the greatest risk of HIV acquisition, with an estimated 1.38% (95% CI 1.02%–1.86%) risk of seroconversion (more than 10 times higher than the risk of acquiring HIV infection during CIAI).[23,25,26] Therefore, we focused our transmission risk model on CIAI episodes by the transmitting HIV-positive partners, and assumed a 1.38% (95% CI 1.02%–1.86%) risk per act of transmitting the disease, although this may be an underestimation for those with AHI, where transmission risk is greatest during the initial weeks and months.[27,28]

We combined those two estimations (i.e. 41 CIAI episodes per year[23,24] and 1.38% risk of transmission per episode[23,25,26]), with risk behavior and testing data from individuals diagnosed with AHI by the "Early Test" between 2008 and 2014, and calculated a mean one-year risk of transmitting HIV. Data derived from "Early Test" included: i) proportion who reported CIAI and ii) median time period between the last negative test and the day they tested positive (proportion of a year) with a maximum of 1 year. We calculated a **mean one-year risk of HIV transmission per contact (β1)** using the following equation:

$$\beta 1 = \frac{0.0138 \times 41 \times t \times c}{365}$$

Considering:

(1) Estimation number of yearly CIAI episodes = 41[23,24]
(2) Per-contact transmission risk = 0.0138[23,25,26]
(3) t, Time between last negative and first positive HIV test (in days, range 1–365)
(4) c, Proportion who reported CIAI (range 0–1)

To calculate the risk of transmission for the proportion of individuals with missed AHI diagnoses in the different algorithms, we multiplied the respective number of missed AHI diagnoses by the mean risk calculated using the formula above.

Per-partner transmission risk

In a second approach, we assessed the risk of transmission by focusing on number of unique sexual partners. Again, we chose a conservative approach focusing on CIAI only. In a recent meta-analysis of studies evaluating HIV transmission risk through anal intercourse, per-partner HIV transmission probability was 39.9% in MSM (95% CI 22.5–57%).[29] The remaining variables were derived from individuals diagnosed with AHI by the "Early Test". As we did not have number of CIAI partners we assumed that all individuals with AHI that reported insertive anal intercourse (IAI) had IAI with every partner they reported. We calculated the proportion of partners with whom CIAI was performed by using the reported frequency of condom use during IAI episodes. As the frequency of condom use was reported as a percentage range (100% of the time, 50%–99%, 1%–49% or 0%) we chose the median of the percentage range if necessary [i.e. 75% for "condom use in 1%–49% of IAI episodes" and 25% for "condom use in 50%–100%"]. We calculated the **mean one-year risk of HIV transmission per partner (β2)** using the following equation:

$$\beta 2 = \frac{0.399 \times n \times \mu \times t \times c}{365}$$

Considering:

(1) Estimated per partner risk = 0.399[29]
(2) n, Mean reported number of male partners
(3) μ, Mean reported proportion of condom use during IAI (range 0–1)
(4) t, Time between last negative and first positive HIV test (in days, range 1–365)
(5) c, Proportion who reported CIAI (range 0–1)

Again, the result was multiplied with the respective number of missed AHI diagnoses to calculate transmission risks for the different algorithms.

Sensitivity analyses

We assessed the effect of a number of alternate plausible assumptions and employed a probabilistic sensitivity analysis (PSA) to examine the impact of cost parameter uncertainty. We performed PSA for two different proportions of AHI (0.24 and 0.10 of all HIV diagnoses). While AHI cases represented 24% of all newly diagnosed HIV cases among MSM in the San Diego Primary Infection Resource Consortium (SD PIRC), a lower proportion of 10%, may be more appropriate for settings where clients undergo screening less frequently.[30,31] For PSA we assigned uniformly distributed 95% CI to applicable cost items, test performance, and loss to follow up in algorithms that do not provide POC positive results for AHI, as described previously.[12] In addition, we assigned uniformly distributed 95% CI to all variables of per-contact and per-partner risk calculation. To determine the frequency at which each algorithm was cost-effective at the given threshold, we conducted Monte Carlo simulations

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to obtain 1000 samples from all distributions, and used these samples to calculate means and 95% CIs for ICERs per IA, by using the 2.9% HIV prevalence rate, and AHI proportions of 24% and 10%. The model and statistical analyses were performed using Excel 2010 (Microsoft, Seattle, WA, USA) and SPSS 21 (SPSS Inc. Chicago, IL, USA).

Results

Base model

The base model of costs per IA utilized data from 93 MSM diagnosed with AHI (Fiebig stage I–II) in the Early Test program between April 2008 and July 2014 in conjunction with previously published data and transmission risks. One-year transmission risks per AHI case missed were calculated with per-contact and per-partner analyses, input variables and results are depicted in Table 1. Estimated total annual costs associated with each of the four algorithms are displayed in Table 2.

ICERs per IA are displayed in Fig. 1. Focusing on per-contact transmission risk, the mean calculated one-year HIV transmission risk for individuals with missed AHI diagnosis was 26.46%. Using these estimations, 5.28 infections were averted within a year using the Early Test algorithm when compared to the Ab alone algorithm (4.22 IA by Architect algorithm when compared to Ab alone, and 2.78 by Determine). The cost per IA by the Early Test algorithm when compared to the Ab alone algorithm was $22,894 (Architect *vs.* Ab alone was $26,542, and Determine *vs.* Ab alone $11,305). As these were significantly lower than the lower threshold of the discounted lifetime costs of an HIV infection (i.e. $236,948), all three algorithms that detect AHI were deemed cost-effective compared to the Ab alone algorithm. Numbers and incremental cost effectiveness ratios (ICERs) per IA for per-contact risk comparisons of all four algorithms and for HIV prevalence of 2.9% and AHI proportions of 24% and 10% are depicted in Table 3.

Using per-partner transmission risk calculations, the estimated number of HIV transmissions over one year was 2.2664 per undiagnosed AHI diagnosis. Using these estimations, 45 infections were averted by using the Early Test algorithm when compared to Ab alone, with costs per IA as low as $2673. Numbers and ICERs per IA for per-partner-risk comparisons are depicted in Table 4.

Probabilistic sensitivity analysis

Results of the probabilistic sensitivity analyses for a 2.9% HIV prevalence with AHI proportions of 24% and 10%, including 95% CI and ranges are depicted in Table 3 (per-contact transmission risk analysis), Table 4 (per-partner transmission risk analysis) and Fig. 1. We found that testing for AHI in the per-contact analysis was cost-effective (i.e. ICERs below $236,948 per IA) *vs.* Ab testing alone. Specifically, the Early Test was cost-effective 100% of the time (with 24% proportion of AHI) and 99.2% (when assuming a 10% proportion of AHI) *vs.* Ab alone, Architect was cost-effective 100% (24% AHI) and 98.4% (10% AHI) of the time *vs.* Ab alone, and Determine was always cost-effective *vs.* Ab alone. When comparing the three AHI algorithms, Early Test was cost-effective 100% of the time *vs.* Architect, 99.9% (24% AHI) and 92.4% (10% AHI) of the time *vs.* Determine, while Architect was cost-effective 96.3% (24% AHI) and 74.1% (10% AHI) of the time *vs.* Determine. In all six comparisons of the per-partner analysis those algorithms that were more sensitive for AHI diagnoses (i.e. detect more AHI) were cost-effective ≥99.9% of the time *vs.* those algorithms that were less sensitive for AHI (i.e. detect less AHI; Fig. 1).

Table 1 Input variables for calculation of per-contact and per-partner transmission risk, and one year transmission risk per acute HIV infection missed using per contact and per partner calculation.

	Base model (mean, 95% CI)	Probabilistic sensitivity analysis (mean, 95% CI)
Variables from 93 MSM diagnosed with AHI with the "Early Test" program between mid-2008 and mid-2014		
Proportion who reported recent CIAI	0.871 (0.804–0.938)	–
Time factor (i.e. testing frequency in proportions of one year)[a]	0.537 (0.465–0.609)	–
Number partners	24 (10–37)	–
Proportion of condom use in IAI partners	0.506 (0.438–0.573)	–
Variables from literature		
Number of CIAI contacts[23,24]	41 (10–70)	–
Risk per CIAI[26]	0.0138 (0.0102–0.0186)	–
Risk per partner[29]	0.399 (0.225–0.574)	–
Mean one-year risk of transmitting HIV per missed AHI diagnosis: **per-contact analysis**	0.2646	0.2701 (95% CI 0.0208–0.5193)
Mean one-year risk of transmitting HIV per missed AHI diagnosis: **per-partner analysis**	2.2664	2.1762 (95% CI 0.3029–4.0496)

Abbreviations: AHI, acute HIV infection; CI, confidence interval; CIAI, condomless insertive anal intercourse; IAI, insertive anal intercourse; MSM, men who have sex with men.

[a] 17% of MSM diagnosed with AHI reported that they have never been tested before. Among those with previous test results, the most recent HIV test before diagnosis was in median 128 days ago (IQR 65–240 days; 14% reported that their most recent test was more than a year ago).

Table 2 Number of diagnoses, total costs and cost differences of the four testing algorithms in the San Diego men who have sex with men model [Modified from previously published supplementary materials[12]].

Annual costs of the testing algorithms base model	Algorithms							
	Actual costs of early test		Estimated costs of architect		Estimated costs of determine		Estimated costs of rapid Ab alone	
Base model	N	USD	N	USD	N	USD	N	USD
Acute HIV (i.e. seronegative)	19.95	1815.65	15.96	1405.12	10.5	1394.40	—	—
Acute HIV, but MSM lost to follow up and not informed about diagnosis	1.05	68.48	0.84	52.29	—	—	—	—
Early or chronic HIV (i.e. seropositive)	66	3686.10	66	3686.10	66	5025.24	66	4372.50
True negative test result	2913	206,764.74	2913	198,142.26	2913	116,053.92	2913	86,486.97
False negative test result	—	—	4.2	285.68	10.5	418.32	21	623,49
Total costs per year	3000	**212,334.97**	3000	**203,571.45**	3000	**122,891.88**	3000	**91,482.96**
Cost difference *vs.* rapid antibody alone		**120,852.01**		**112,088.49**		**31,408.92**		—
Cost difference *vs.* Determine		**89,443.09**		**80,659.57**		—		—
Cost difference *vs.* Architect		**8763.53**		—		—		—

Abbreviations: MSM, men who have sex with men.
Total costs of the algorithms and cost differences are highlighted in bold.

Discussion

We compared four different community-based HIV testing strategies to estimate cost per infection (i.e. transmission) averted, and found that all three algorithms that detect AHI were cost-effective (i.e. one IA costs less than the lifetime medical costs of one HIV infection), when compared to testing relying on Ab testing alone. Among the algorithms that detect AHI, the Early Test algorithm was cost-effective *vs.* both other algorithms, with Architect being the second best alternative. Cost-effectiveness was established not only among at risk MSM in San Diego, but also among other MSM populations with similar HIV prevalence but lower proportions of AHI diagnoses. By accounting

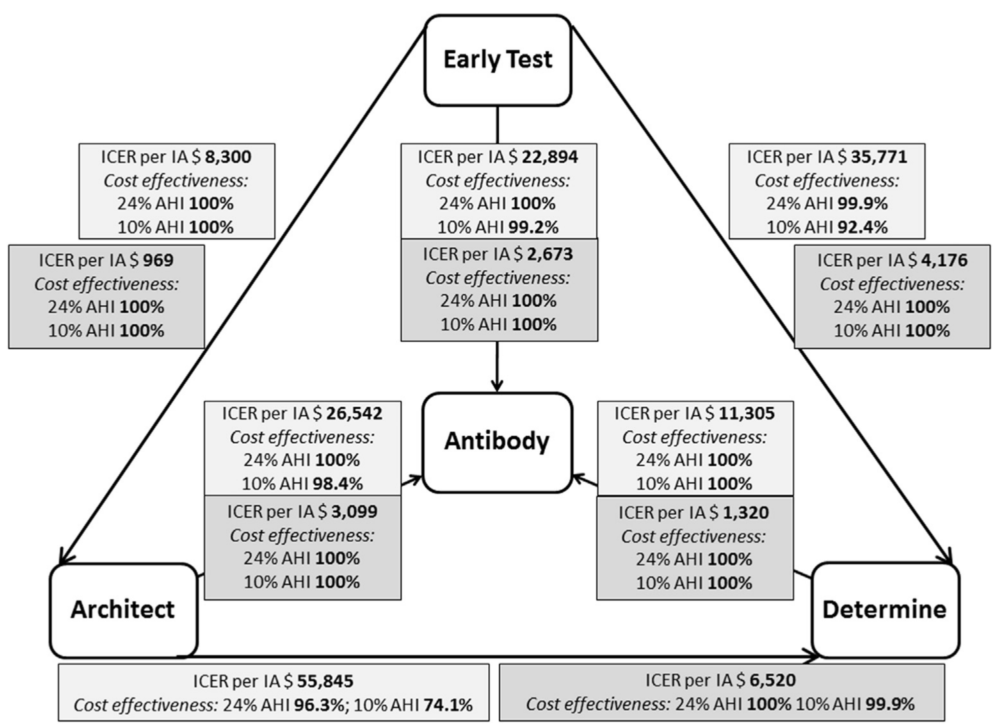

Figure 1 Incremental cost effectiveness ratios (ICERs) per infection (i.e. transmission) averted for comparing each of the four algorithms in the San Diego men who have sex with men model (i.e. base model), and results of probabilistic sensitivity analyses (percentage of cost-effectiveness in Monte Carlo simulations displayed for 24% AHI proportion and 10% AHI proportion). Light gray boxes represent results of per-contact analysis, dark gray boxes represent results of per-partner analysis.

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Table 3 Per-contact analysis: costs per infection (i.e. transmission) averted (i.e. incremental cost effectiveness ratio) for comparisons of all four algorithms. Base costs and results of probabilistic sensitivity analyses are displayed.

Costs per infection (i.e. transmission) averted (i.e. ICER)	HIV prevalence/AHI proportion (%)	Algorithms							
Per-contact analysis		Early test		Architect		Determine		Rapid Ab alone	
		N[a]	USD[b]	N[a]	USD[b]	N[a]	USD[b]	N[a]	USD[b]
ICER per IA *vs.* rapid Ab alone									
ICER per IA (base costs)	0.029/24%	**5.28**	**22,893.95**	**4.22**	**26,542.29**	**2.78**	**11,305.10**	—	—
ICER per IA, probabilistic sensitivity analysis	0.029/24%	—	—	—	—	—	—	—	—
95% CI of mean	—	29,045–31,402		33,799–36,552		14,326–15,487			
Range (**% above $236,948, if applicable**)	—	8779–141,256		9655–179,714		3932–69,804			
ICER per IA, probabilistic sensitivity analysis	0.029/10%	—	—	—	—	—	—	—	—
95% CI	—	69,590–75,239		80,999–87,596		33,934–36,685			
Range (**% above $236,948, if applicable**)	—	21,012–338,095 **(0.8%)**		23,113–430,429 **(1.6%)**		9280–165,917			
ICER per IA *vs.* Determine									
ICER per IA (base costs)	0.029/24%	**2.50**	**35,770.52**	**1.44**	**55,844.67**	—	—	—	—
ICER per IA, probabilistic sensitivity analysis	0.029/24%	—	—	—	—	—	—	—	—
95% CI of mean	—	46,211–50,164		77,540–85,560					
Range (**% above $236,948, if applicable**)	—	13,267–246,923 **(0.1%)**		17,356–601,868 **(3.7%)**					
ICER per IA, probabilistic sensitivity analysis	0.029/10%	—	—	—	—	—	—	—	—
95% CI of mean	—	111,167–120,682		186,692–206,018					
Range (**% above $236,948, if applicable**)	—	31,873–593,844 **(7.6%)**		41,711–1,449,498 **(25.9%)**					
ICER per IA *vs.* Architect									
ICER per IA (base costs)	0.029/24%	**1.06**	**8300.71**	—	—	—	—	—	—
ICER per IA, probabilistic sensitivity analysis	0.029/24%	—	—	—	—	—	—	—	—
95% CI of mean	—	10,865–11,836							
Range (**% above $236,948, if applicable**)	—	2885–53,197							
ICER per IA, probabilistic sensitivity analysis	0.029/10%	—	—	—	—	—	—	—	—
95% CI of mean	—	25,964–28,287							
Range (**% above $236,948, if applicable**)	—	6851–127,425							

Abbreviations: 95% CI, 95% confidence interval; IA, infection (i.e. transmission) averted; ICER, incremental cost effectiveness ratio.
Highlighted in bold are number of transmissions averted and costs per transmission averted in the base model as well as proportion of simulations in the probabilistic sensitivity analyses that exceeded the cost-effectiveness threshold.
[a] N corresponds to the total number of HIV transmissions averted when compared to alternative algorithm.
[b] USD corresponds to costs (in 2014 USD) per singleHIV transmission averted when compared to alternative algorithm.

Table 4 Per-partner analysis: costs per infection (i.e. transmission) averted (i.e. incremental cost effectiveness ratio) for comparisons of all four algorithms. Base costs and results of probabilistic sensitivity analyses are displayed.

Costs per infection (i.e. transmission) averted (i.e. ICER)	HIV prevalence/AHI proportion (%)	Algorithms							
Per-partner analysis		Early test		Architect		Determine		Rapid Ab alone	
		N[a]	USD[b]	N[a]	USD[b]	N[a]	USD[b]	N[a]	USD[b]
ICER per IA *vs*. rapid Ab alone									
ICER per IA (base costs)	0.029/24%	**45.21**	**2672.85**	**36.17**	**3098.79**	**23.90**	**1319.86**	–	–
ICER per IA, probabilistic sensitivity analysis	0.029/24%	–	–	–	–	–	–	–	–
95% CI of mean	–	3330–3540		3832–3501		1643–1748			
Range (**% above $236,948, if applicable**)	–	965–10,944		1199–13,863		484–6207			
ICER per IA, probabilistic sensitivity analysis	0.029/10%	–	–	–	–	–	–	–	–
95% CI	–	7979–8482		9300–9897		3892–4140			
Range (**% above $236,948, if applicable**)	–	2315–26,228		2876–33,237		1144–14,762			
ICER per IA *vs*. Determine									
ICER per IA (base costs)	0.029/24%	**21.42**	**4176.17**	**12.37**	**6519.81**	–	–	–	–
ICER per IA, probabilistic sensitivity analysis	0.029/24%	–	–	–	–	–	–	–	–
95% CI of mean	–	5294–5647		8911–9802					
Range (**% above $236,948, if applicable**)	–	**1451–19,733**		**1921–108,022**					
ICER per IA, probabilistic sensitivity analysis	0.029/10%	–	–	–	–	–	–	–	–
95% CI of mean	–	12,735–13,585		21,455–23,602					
Range (**% above $236,948, if applicable**)	–	3494–47,504		4617–260,681 **(0.1%)**					
ICER per IA *vs*. Architect									
ICER per IA (base costs)	0.029/24%	**9.04**	**969.10**	–	–	–	–	–	–
ICER per IA, probabilistic sensitivity analysis	0.029/24%	–	–	–	–	–	–	–	–
95% CI of mean	–	1238–1325							
Range (**% above $236,948, if applicable**)	–	282–4428							
ICER per IA, probabilistic sensitivity analysis	0.029/10%	–	–	–	–	–	–	–	–
95% CI of mean	–	2959–3168							
Range (**% above $236,948, if applicable**)	–	675–10,620							

Abbreviations: 95% CI, 95% confidence interval; IA, infection (i.e. transmission) averted; ICER, incremental cost effectiveness ratio. Highlighted in bold are number of transmissions averted and costs per transmission averted in the base model as well as proportion of simulations in the probabilistic sensitivity analyses that exceeded the cost-effectiveness threshold.

[a] N corresponds to the total number of HIV transmission averted when compared to alternative algorithm.

[b] USD corresponds to costs (in 2014 USD) per single HIV transmission averted when compared to alternative algorithm.

for parameter uncertainty, sensitivity analysis showed that cost-effectiveness of algorithms that detect AHI *vs*. Ab testing alone is likely to hold over a wide range of parameter values.

While this study indicates that AHI testing is cost-effective among MSM undergoing community-based screening in San Diego and other similar MSM populations in the United States, a previous cost analysis conducted in 2008 found that pooled NAT screening for AHI following negative third-generation antibody or rapid tests was not cost-effective for unselected municipal sexually transmitted diseases clinics and testing and counseling populations.[32,33] Interestingly, that study used a very low AHI rate of 0.02% for determining cost-effectiveness.[32] Assuming a 10% proportion of AHI, this would relate to a per-test HIV positivity rate of 0.2% (the national HIV

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prevalence rate is 0.6%). In contrast, the AHI rates of 0.7% and 0.3% evaluated for determining cost-effectiveness in this study are not only more than 10 times higher than the AHI rate used in that previous study, but also in line with AHI rates reported previously for high risk individuals and MSM.[30,31] While differing study populations may be the main explanation for differing findings,[34] other factors such as lower costs for AHI tests in 2014 when compared to 2008 may provide additional explanation.

Costs per IA by algorithms that detect AHI *vs*. Ab testing alone stayed below $30,000 in the base model, and costs per IA by the Early Test (i.e. the most sensitive algorithm for AHI, but also the most expensive algorithm) *vs*. the other two algorithms that detect AHI were below $40,000. Costs per IA were therefore markedly below most recently published estimated medical costs saved by avoiding one single HIV infection [i.e. updated costs in 2014 US dollars between $236,948 and $348,927 depending on the time point of diagnosis and ART initiation[15]], and also markedly below prior estimations of these costs.[14] Among MSM, community-based HIV testing with algorithms that detect AHI was therefore clearly cost effective. Our results further indicate that the most sensitive and most expensive AHI testing algorithm — based on NAT testing — was cost-effective *vs*. the two other (less sensitive and less expensive) AHI testing algorithms. Probabilistic sensitivity analyses indicated, however, that the latter finding may be more uncertain in other MSM settings with lower AHI proportions.

Our study has several limitations. First, calculations were based on 3000 tests per year with 2.9% HIV prevalence and proportions of 24% and 10% AHI cases among all newly diagnosed HIV cases. The magnitude of effects will vary in other settings with differing numbers of annual tests/proportion of AHI diagnoses. Second, calculations of per-contact and per-partner transmission risk, which formed the basis for calculations of costs per IA, were — at least in part — based on assumptions and utilization of previously published data from other MSM cohorts. Although we did our best to prevent overestimation of transmission risk by choosing conservative approaches, we can't rule out that real world transmission risks may have been lower. When AHI algorithms were compared to the Ab alone algorithm, however, cost-effectiveness per IA was met by quite a margin (costs per IA below $30,000 for all comparisons of the base model, costs might have been more than eight times higher and still below the cost-effectiveness threshold). Therefore, we argue that it is unlikely that differing approaches would have changed our outcome. Further, this model was based on the assumption that HIV transmission will drop to zero for the year after AHI diagnosis. While it has been shown previously that risk behavior decreases after diagnosis,[5,11] and early ART may substantially decrease HIV transmission,[9,10] the risk for HIV transmission after AHI diagnosis may still differ in other settings/populations. Our model also focused only on direct transmission occurring from individuals with missed AHI diagnoses and did not account for increased transmission risk during the AHI phase, which may have led to an underestimation of IA. Costs of very early ART were not included in the model, as early ART independent of infection stage (or CD4 cell count) is the standard of care in the United States.[9,10] Further, the number of annual CIAI contacts in the per-contact analysis (i.e. n = 41) was derived from a cohort study in Australian MSM and it remains unclear if this number is a realistic estimate also for MSM in the United States. Finally, this analysis was built on a previous cost model, and additional limitations published previously for that model[12] may apply to the current model.

In conclusion, our analysis showed that AHI screening was cost-effective in preventing new HIV infections not only among at risk MSM in San Diego, but also among other MSM populations with similar HIV prevalence (i.e. 2.9%) and lower proportions of AHI diagnoses. The results indicate that community-based AHI testing among MSM in the United States can pay for itself over the long run. When comparing the three algorithms that detect AHI, those algorithms that were more sensitive for AHI were cost effective despite higher costs.

Conflicts of interest

Dr. Hoenigl served on the speakers' bureau of Merck. Dr. Little reported grant funding from Gilead Sciences, Inc. All other authors no conflicts.

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Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jinf.2016.07.019.

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