Cost-effectiveness of provider-based HIV partner notification in urban Malawi

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Provider-initiated partner notification for HIV effectively identifies new cases of HIV in sub-Saharan Africa, but is not widely implemented. Our objective was to determine whether provider-based HIV partner notification strategies are cost-effective for preventing HIV transmission compared with passive referral. We conducted a cost-effectiveness analysis using a decision-analytic model from the health system perspective during a 1-year period. Costs and outcomes of all strategies were estimated with a decision-tree model. The study setting was an urban sexually transmitted infection clinic in Lilongwe, Malawi, using a hypothetical cohort of 5000 sex partners of 3500 HIV-positive index cases. We evaluated three partner notification strategies: provider notification (provider attempts to notify indexes' locatable partners), contract notification (index given 1 week to notify partners then provider attempts notification) and passive referral (index is encouraged to notify partners, standard of care). Our main outcomes included cost (US dollars) per transmission averted, cost per new case identified and cost per partner tested. Based on estimated transmissions in a 5000-person cohort, provider and contract notification averted 27.9 and 27.5 new infections, respectively, compared with passive referral. The incremental cost-effectiveness ratio (ICER) was $3560 per HIV transmission averted for contract notification compared with passive referral. Provider notification was more expensive and slightly more effective than contract notification, yielding an ICER of $51 421 per transmission averted. ICERs were sensitive to the proportion of partners not contacted, but likely HIV positive and the probability of transmission if not on antiretroviral therapy. The costs per new case identified were $36 (provider), $18 (contract) and $8 (passive). The costs per partner tested were $19 (provider), $9 (contract) and $4 (passive). We conclude that, in this population, provider-based notification strategies are potentially cost-effective for identifying new cases of HIV. These strategies offer a simple, effective and easily implementable opportunity to control HIV transmission.

Keywords Cost-benefit analysis, contact tracing, HIV, sub-Saharan Africa

Introduction

A substantial portion of HIV transmission is attributable to persons unaware of their HIV-positive status (Marks *et al.* 2006; CDC 2008). This transmission pattern is also expected in more resource-limited settings. Interventions targeting these individuals are critical for HIV prevention. One important and accessible group of persons unaware of their status is sexual partners of persons with newly diagnosed HIV infection. These partners, if not already infected, are at high risk of acquiring infection due to their ongoing exposure to the virus. Identifying and testing sexual partners of persons recently diagnosed with HIV may be an important component of expanded prevention and treatment services.

Partner notification effectively identifies new cases of HIV infection in high-income countries (Landis *et al.* 1992; Mathews *et al.* 2002; Brewer 2005; Hogben *et al.* 2007; Golden *et al.* 2009; Marcus *et al.* 2009). In partner notification, sexual partners of a newly diagnosed person with HIV (index) are notified of their potential exposure and encouraged to seek testing. Partner notification strategies include 'provider notification', where a medical provider notifies the exposed partner(s); 'contract notification', where the index patient attempts to notify partner(s) within 1–2 weeks, after which the provider completes the notification process and 'passive referral', where the index patient notifies partner(s) without any direct provider contact. Provider and contract notifications for syphilis and HIV infection have been mainstays of public health control efforts in high-income countries (European Partner Notification Study 2001; CDC 2003). Provider-based notification strategies increase the rate of partner testing (Mathews *et al.* 2002) and, although costs vary across sites (Shrestha *et al.* 2009), are believed to be cost-effective for preventing future cases of HIV infection in high-income countries (Rahman *et al.* 1998; Varghese *et al.* 1999).

Despite its success in high-income countries, provider-based partner notification has not been widely adopted in sub-Saharan Africa. However, in Malawi and Cameroon, provider and contract notification appear to be feasible and effective in identifying previously unknown infected persons and linking these persons to care (Muffih *et al.* 2009; Brown *et al.* 2011). In Malawi, rates of partner return were twice as high with provider-based notification, compared with passive referral in a randomized trial (Brown *et al.* 2011). Among partners who presented for testing, 64% tested HIV positive; of partners testing positive, most (81%) were new diagnoses. Many (28%) were eligible for antiretroviral therapy (ART) based on Malawi's national guidelines of CD4 $\leq$250 cells/mm^3. The programme was well accepted among sexually transmitted infection (STI) patients, with only 11% of eligible index cases refusing participation.

In this study, we evaluated the cost-effectiveness of partner notification strategies to identify sexual partners of HIV-infected index patients at STI clinics in Lilongwe, Malawi. We estimated the costs associated with tracing and testing locatable partners. We modelled transmission rates and behavioural modifications after testing to evaluate cost per partner tested, cost per new case identified and cost-effectiveness of HIV transmissions averted by each notification strategy. We compared our estimates of cost-effectiveness to those of widely accepted transmission prevention interventions, such as HIV testing and counselling (HTC) and nevirapine to prevent mother-to-child transmission (Sweat *et al.* 2004; Menzies *et al.* 2009; Orlando *et al.* 2010). To our knowledge, this study is the first cost-effectiveness analysis of partner notification in the sub-Saharan African context.

Methods

We developed a decision-tree model (Figure 1), constructed using Excel^{TM} 2010 (Microsoft Corp, Redmond, WA, USA), to simulate costs, outcomes and incremental cost-effectiveness ratios (ICERs) of implementing partner notification for HIV in STI clinics in Lilongwe, Malawi. We used a health system perspective, incorporating system-level costs incurred by tracing, testing and treating eligible partners. Indirect patient costs (i.e. travel time, lost wages, etc.) were not considered. Costs and outcomes were evaluated during 1 year of programme operation.

We used the trial of partner notification in an STI clinic in Lilongwe as the primary basis for the model (Table 1) (Brown *et al.* 2011). We obtained other parameter estimates from relevant studies conducted in Malawi or elsewhere in sub-Saharan Africa. The principal outcome was the number and cost per secondary infection avoided as a result of integrating partner notification in this setting. Additional outcomes included the cost per new case identified and cost per partner tested.

Transmissions and infections averted

We built a partner-centric model following a hypothetical cohort of 5000 men and women aged 15–49 years who are partners of indexes at an STI clinic. Index cases on average report 1.4 locatable partners (Brown *et al.* 2011). Therefore, the 5000 partner hypothetical cohort corresponds to ~3500 index cases. In this cohort, locatable partners of the index case received provider notification, contract notification or passive
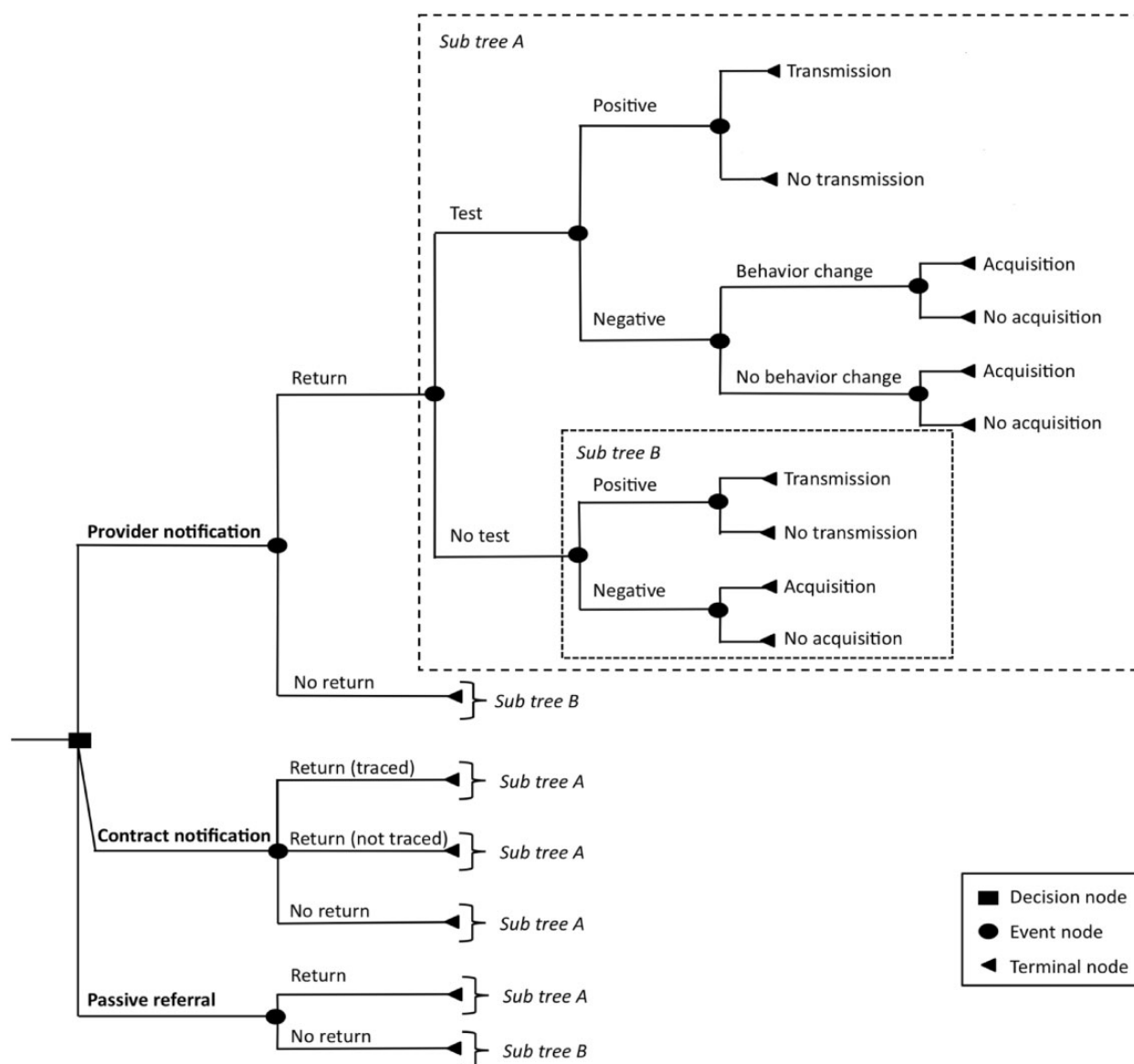
Figure 1 Decision tree modelling three strategies for partner notification. Partners of index patients may be notified of their exposure to HIV by provider notification, contract notification or passive referral. Partners who return to the clinic and agree to HIV testing may test positive or negative, and those partners who test positive may be in the chronic phase of infection and not treatment eligible, or may be eligible for treatment (CD4 $\leq$250 cells/mm^3). Persons who test and are HIV negative may change their sexual risk behaviours, affecting their risk of acquisition in their serodiscordant partnership with the index partner. Transmission probabilities from positive partners account for the variability of infectivity at different stages of infection, as well as reduced infectiousness for those who are eligible and retained on ART. Transmission also accounts for the probability of HIV-infected partners in the cohort having sexual partnerships with HIV-negative persons outside of the index partnership.

referral. Locatable partners are partners that the index reports having had sexual contact with within the past 3 months and for whom the index has either a phone number or address. Success of the programme was modelled based on varying partner return rates (Brown *et al.* 2011, Antelman *et al.* 1999, Kilewo *et al.* 1999, and Temmerman *et al.* 1995). Transmission events can be from the index to a negative partner or from a positive partner to a person other than the index.

The stage of infection at diagnosis [acute, chronic or treatment eligible (i.e. CD4 $\leq$250 cells/mm^3)] predicts likelihood of HIV transmission (Leynaert *et al.* 1998; Wawer *et al.* 2005; Girardi *et al.* 2007; Hollingsworth *et al.* 2008). We used estimates that reflect

the distribution of disease stage at diagnosis as observed at a Lilongwe STI clinic, excluding acute infection in that it is not screened for in the setting of interest. Twenty-eight per cent of partners (range 0.224–0.336) were eligible for ART at baseline (CD4 $\leq$250 cells/mm^3) (Powers *et al.* 2007; Brown *et al.* 2011). Transmission probabilities were based on observed transmissions among serodiscordant couples in Uganda and are independent of coital frequency, representing probability of transmission during 12 months (Hollingsworth *et al.* 2008). We assumed that all partners who are tested and eligible for treatment according to Malawian guidelines will begin ART immediately, with retention in care across 1 year at $\sim$70% (Rosen and Fox 2011). The reduced

Table 1 Model input parameters

Parameter	Base case (range)	References
Probability of partner return and testing		
Return (PN)	0.51 (0.4–0.73)	Brown *et al.* (2011)
Return—traced (CN)	0.18 (0.144–0.216)	Brown *et al.* (2011) and Muffih *et al.* (2009)
Return—not traced (CN)	0.33 (0.264–0.396)	Brown *et al.* (2011)
Return (PR)	0.24 (0.14–0.34)	Brown *et al.* (2011), Antelman *et al.* (1999), Kilewo *et al* (1999) and Temmerman *et al* (1995)
Test (PN)	0.95 (0.8–1.0)	Brown *et al.* (2011) and Muffih *et al.* (2009)
Test (CN) among traced partners	0.97 (0.8–1.0)	Brown *et al.* (2011) and Muffih *et al.* (2009)
Test (CN) among not traced partners	1.0 (0.8–1.0)	Brown *et al.* (2011)
Test (PR)	1.0 (0.8–1.0)	Brown *et al.* (2011)
HIV prevalence and disease stage among partners (%)		
Antibody positive (PN, CN and PR)	0.64 (0.51–0.77)	Brown *et al.* (2011), Muffih *et al.* (2009) and Temmerman *et al* (1995)
Antibody positive, no return (PN, CN and PR)	0.64 (0.34–0.94)	Assumed
End-stage if antibody positive	0.28 (0.224–0.336)	Brown *et al.* (2011)
New diagnosis if antibody positive	0.81 (0.648–0.972)	Brown *et al.* (2011)
Acute if antibody negative	0.0325 (0.02–0.045)	Brown *et al.* (2011), Powers *et al.* (2007) Pilcher *et al.* 2004 and Pilcher *et al* (2007)
Behaviour change and transmission probabilities		
Behaviour change if negative	0.35 (0.2–0.5)	Allen *et al.* (1992, 2003), Baeten *et al.* (2012), Celum *et al.* (2010), Voluntary HIV-1 Counseling and Testing Efficacy Study Group (2000), Cohen *et al.* (2011), Denison *et al.* (2008), Hughes *et al.* (2012), Kennedy *et al.* (2010) and Rosenberg *et al.* (2012)
Transmission if behaviour change	0	Assumed
Partnership probabilities		
Index patient is sole partner	0.7 (0.5–0.82)	Brown *et al.* (2011) and Allen *et al.* (2003)
Outside partner is HIV positive	0.141 (0.069–0.214)	UNAIDS (2009) and WHO (2008)
Probability of transmission (no behaviour change)		
Acute	0.1975 (0.105–0.2875)	Hollingsworth *et al.* (2008)
Chronic	0.1 (0.05–0.15)	Hollingsworth *et al.* (2008)
Treatment eligible[a] (no ART)	0.43 (0.27–0.62)	Hollingsworth *et al.* (2008)
Treatment eligible[a] (ART)	0.003	Del Romero *et al.* (2010), Wilson *et al.* (2008) and Donnell *et al.* (2010)
Acquisition if negative	0.075 (0.03–0.1)	Brown *et al.* (2011) and Hollingsworth *et al.* (2008)

Costs (in 2010 US$)[b]

Parameter	Base case (range)	References
Personnel		
Provider hourly wage	$2 ($1.40–$2)	
Provider time (additional counselling for index patients) (min)	5 (3–10)	
Provider time (tracing) (min)	35 (25–90)	
Provider time (testing notified partners) (min)	30 (20–45)	
Driver hourly wage	$1.40 ($1–$2.40)	
Driver time (tracing) (min)	35 (25–90)	
Supervisor cost[c]	$532 ($304–$760)	
Tracing and transportation		
Tracing distance (km)	15 (5–25)	
Fuel costs per km (car)	$0.24 ($0.19–$0.29)	
Fuel costs per km (motorbike)	$0.09 ($0.07–$0.10)	
Yearly cost of vehicle (car)[c]	$3750 ($3000–$4500)	
Yearly cost of vehicle (motorbike)[c]	$400 ($320–$480)	

(continued)

Table 1 Continued

Parameter	Base case (range)	References
Cost of insurance (car)[c]	$2667 ($2400–$2933)	
Cost of insurance (motorbike)[c]	$267 ($240–$293)	
Testing and treatment		
Cost of condoms (10 per person tested)	$0.30 ($0.10–$0.50)	
Rapid antibody HIV test kits	$2 ($1–$3)	
Consumables	$1 ($0.80–$1.20)	
Cost of care (non-ART)	$100 ($80–$120)	Malawi Ministry of Health (Kamoto and Schouten 2007), CHAI 2012 ART Pricing List
Cost of care (ART)	$285 ($228–$342)	Malawi Ministry of Health (Kamoto and Schouten 2007), CHAI 2012 ART Pricing List
Training[c]	$152 ($122–$183)	

CN, contract notification; PN, provider notification; PR, passive referral.

[a]Treatment eligible are those persons testing with a CD4 ≤ 250 cells/mm^3.

[b]All costs from personal communication with administrators at UNC Project in Lilongwe unless otherwise indicated.

[c]Fixed year-one costs, not dependent on partner return or testing rate.

risk of transmission for persons on ART was accounted for and adjusted based on the likelihood of loss to follow-up across 1 year (Wilson *et al.* 2008; Del Romero *et al.* 2010; Donnell *et al.* 2010). This retention in care and associated transmission probabilities were also applied to index patients who could then transmit to HIV-negative partners in the model. All HIV-infected patients are eligible to transmit to HIV-uninfected persons for the full year. Given the heterogeneity of treatment efficacy, comorbidities and acquired or developed resistance to therapy, differential 1-year ART survival projections are beyond the scope of this study.

We estimated rates of infection among partners who declined testing or did not return. Given the high risk of HIV infection among sexual partners of HIV-infected persons, the Malawian adult HIV prevalence was an inadequate estimate (WHO 2008; UNAIDS 2009). Therefore, we assumed the prevalence of partners who did not test was the same as the prevalence of those who did according to the empirical results of the trial (WHO 2008; UNAIDS 2009; Brown *et al.* 2011). Uncertainty in this estimate is reflected in the wide range used in sensitivity analyses to explore this parameter's potentially substantial role in cost-effectiveness estimates.

Among partners agreeing to HIV testing there are three possible outcomes: (1) the partner is identified as HIV negative, (2) the partner is diagnosed as HIV positive for the first time or (3) the partner is diagnosed as HIV positive and was already aware of this serostatus. HIV-negative partners who do not dissolve the partnership with the index case are now in a serodiscordant partnership. The probability of reduced risk behaviours among HIV-serodiscordant couples is substantial (Allen *et al.* 1992, 2003; Voluntary HIV-1 Counseling and Testing Efficacy Study Group 2000; Denison *et al.* 2008; Celum *et al.* 2010; Kennedy *et al.* 2010; Cohen *et al.* 2011; Baeten *et al.* 2012; Hughes *et al.* 2012; Rosenberg *et al.* 2012). In this model, we assumed that 35% of partners who test HIV negative change behaviour, reducing the risk of HIV acquisition from the HIV-infected index partner. To account for uncertainty in this assumption, we varied this base-case value (20–50%). We assumed that persons who change behaviour modify risky

activities such that they are fully protected from acquisition or transmission (i.e. 100% condom use, abstinence, etc.) (Crepaz *et al.* 2006; Metsch *et al.* 2008; Kennedy *et al.* 2010). No behaviour change is assumed for partners who test HIV positive. This represents a conservative approach. In addition, no behaviour change is assumed for partners who are neither notified nor tested (Weinhardt *et al.* 1999; Denison *et al.* 2008). We conducted one-way and probabilistic sensitivity analyses to assess the impact of these assumptions on estimated ICERs.

The likelihood of HIV acquisition for partners assumes a stable partnership between the index and the tested partner; most partners who are locatable and who agree to testing are main or steady partners (Kissinger *et al.* 2003; Brown *et al.* 2011). Based on observed distribution of CD4 counts among index partners in the primary study, 37% of index cases were identified as being treatment eligible and were placed on therapy. Using the same estimated retention in ART care as applied to partners in the model (70%), transmission probability to an HIV-negative partner from the index partner was constructed as a weighted average, between index cases retained on ART and the remaining being in the chronic stage of infection and not on ART (Brown *et al.* 2011).

Cost inputs

The incremental costs associated with partner notification were derived from resources required to trace, test and counsel, and potentially treat partners of newly diagnosed HIV-positive indexes (Table 1). The incremental cost of integrating partner notification into an existing STI clinic is expressed in 2010 US dollars (US$). Many cost parameters were provided in Kwacha (Malawian currency) directly from a district hospital in Lilongwe.[1] We use a nominal exchange rate of 150 Kwacha/ 2010 US$ (Financial Management Service).

The costs of adverse events that may result from partner notification, including partner violence or partnership dissolution (Rothenberg *et al.* 1995; Maher *et al.* 2000; Maman *et al.* 2001), were excluded from this analysis. Adverse events were extremely rare in the Malawi-based trial (Brown *et al.* 2011). In

addition, among women visiting an antenatal clinic in a similar setting, adverse events were not increased among women who disclosed their HIV status to their partners (Semrau *et al.* 2005).

Personnel costs were captured as a proportion of full-time work dedicated to notification services. Salaries were transformed into hourly wages based on the assumption of full-time employment equivalent to 2000 h/year. We assumed that partners of indexes would not otherwise seek HIV testing during the 12-month period, and thus include the time for pre- and post-test counselling (Zanera and Miteka 2004).

Transportation costs (fuel, insurance and driver time) were calculated using the average distance travelled to notify partners in the Lilongwe catchment area, a base case of 15 km and a range of 5–25 km. Providers attempted to locate all partners in the provider notification arm. Tracing costs are lower in the contract notification arm, as a proportion of partners are expected to return within the predefined 1-week period after notification by the index. No tracing costs are associated with the passive referral arm.

The costs associated with care and treatment for HIV-positive persons are fully subsidized by the government in Malawian public clinics and were included as a cost for all who tested positive in this model. Costs in the model did not account for the expense of HIV-related hospitalizations. We assumed a 50% loss to follow-up from care among persons who test positive but are not eligible for ART, and conducted one-way sensitivity varying this from 30 to 70% (Zachariah *et al.* 2010; Rosen and Fox 2011). Persons not retained in care do not accumulate costs of pre-ART care, such as drugs for HIV-related opportunistic infections, broad-spectrum antibiotics for prophylaxis against opportunistic infections and other staff and laboratory support costs. ART expenses account for most treatment costs [inflated from 2007 US$ using Malawi gross domestic product (GDP) implicit price deflator] (Kamoto and Schouten 2007; Malawi Country Report). Prices were also estimated using Clinton Health Access Initiative (CHAI) price lists for ART in Malawi from May 2012. We assumed 70% of all eligible persons, as assessed by CD4 count at diagnosis, begin and adhere to ART.

Sensitivity analyses

Deterministic (one-way univariate) and probabilistic (multivariate) sensitivity analyses were performed to assess the robustness of the assumptions in the decision model (Briggs 2000). One-way sensitivity analyses were conducted for parameters identified as major drivers of the ICER for either provider or contract notification. Probabilistic sensitivity analyses using Monte Carlo simulations (5000 trials) were executed with Crystal Ball version 11.1.2 (Oracle, Redwood Shores, CA, USA). To assess variation in input parameters and assumptions, probabilities assumed beta distributions and all costs assumed gamma distributions. Distribution of probabilities was based on observed ranges reported in primary literature (Table 1). Where data were lacking or unavailable, assumption ranges were generally set to ±0.25.

An alternative scenario assessed the use of a motorbike for tracing in the provider and contract notification arms, instead of the base-case assumption of a car and driver. Cost savings in the motorbike scenario include reduced vehicle and driver costs, improved gas efficiency, faster travel time and lower insurance premiums. An additional scenario considered the possibility of patients who test negative being in the acute phase of HIV infection.

Results

In our model of 5000 locatable partners of HIV-positive indexes, we estimated that 2436 and 2537 would receive HIV testing services in the provider and contract notification arms, respectively, compared with 1207 returning for testing with passive referral. Provider notification identified 1267 new HIV cases and contract notification identified 1320 new cases compared with 627 in the passive referral arm.

We conducted sequential comparisons rank ordered by total cost (Gold *et al.* 1996; Muennig 2008). Passive referral was the least expensive, followed by contract notification. Provider notification was the most costly. The effectiveness of each alternative strategy was evaluated as transmissions averted, compared with the next most expensive strategy. We estimated that compared with passive referral, contract notification would avert 27.5 transmissions over 1 year. Our base-case analysis comparing contract notification with passive referral resulted in an ICER of $3560 per transmission averted (Table 2). Although more expensive than contract notification, provider notification averts an additional 0.4 transmissions over 1 year, corresponding to an ICER of $51 421 per transmission averted.

In some settings, provider notification may be a more viable or operationally preferable option compared with contract notification based on site-specific factors such as staffing constraints, clinic catchment areas and testing volumes. In light of this, we compared provider notification with passive

Table 2 Base-case cost-effectiveness of provider-based partner notification strategies

	Total costs	Total transmissions	Incremental costs	Incremental effectiveness	ICER ($/transmission averted)
Passive referral	$77 411	233.9	–	–	–
Contract notification	$175 468	206.4	$98 058	27.5	$3560
Provider notification	$191 798	206.0	$16 330	0.4	$51 421
Provider notification vs passive referral scenario					
Passive referral	$77 411	234.0	–	–	–
Provider notification	$191 798	206.0	$114 387	28.0	$4106

Table 3 One-way sensitivity analyses comparing partner notification strategies[a]

Parameter	Input		CN vs PR ($/transmission averted)		PN vs CN ($/transmission averted)		PN vs PR ($/transmission averted)	
	Low	High	Low	High	Low	High	Low	High
Probability positive PR (no return)	0.34	0.94	$2843	$4760	$51 421	$51 421	$3287	$5459
Probability of transmission if treatment eligible (no ART)	0.27	0.62	$4707	$2769	$19 532	Dominated	$5284	$3254
Probability IP only sexual partner	0.5	0.82	$2683	$4525	Dominated	$13 771	$3167	$5008
Probability acquire infection if negative (no behaviour change)	0.03	0.1	$4462	$3200	Dominated	$18 429	$5378	$3628
Probability positive (PN)	0.51	0.77	$3560	$3560	$8956	$21 664	$3252	$4855
Probability retained in care among ART-eligible patients	0.5	0.9	$4440	$2960	$22 807	Dominated	$5010	$3468
Probability positive (CN)	0.51	0.77	$2705	$4263	$15 628	$6095	$4106	$4106
Probability positive PN (no return)	0.34	0.94	$3560	$3560	Dominated	$3406	$4891	$3537
Probability return PN	0.4	0.73	$3560	$3560	$1570	$3625	$4900	$3590
Probability positive CN (no return)	0.34	0.94	$4251	$3062	$3406	Dominated	$4106	$4106
Probability behaviour change if negative	0.2	0.5	$4161	$3111	$24 350	Dominated	$4730	$3627
Probability test after notification (PN)	0.8	1	$3560	$3560	$20 187	$43 715	$3305	$4363
Probability return PR	0.14	0.34	$3434	$3840	$51 421	$51 421	$3832	$4707
Average tracing distance (km)	5	25	$3482	$3639	$20 629	$82 213	$3678	$4534
Probability lost to follow-up among non-ART-eligible patients	0.3	0.7	$4006	$3114	$54 360	$48 482	$4513	$3698
Probability positive (PR)	0.51	0.77	$3912	$3174	$51 421	$51 421	$4430	$3750
Cost of ART + care	$228	$342	$3207	$3918	$53 761	$49 081	$3783	$4433

CN, contract notification; IP, index partners; PN, provider notification; PR, passive referral.

[a]Only parameters with a CN or PN ICER difference >$650 listed.

referral. The associated ICER is $4106 per transmission averted (Table 2—'provider notification vs passive referral scenario').

Excluding the cost of treatment for persons identified as positive, the cost per new case identified was $36, $18 and $8 for provider notification, contract notification and passive referral, respectively. New identified cases are patients who are traced or voluntarily return to the clinic and subsequently receive an HIV-positive test result, excluding the proportion of persons who test positive and were already aware of their HIV status. The cost per partner contacted and tested, again excluding costs associated with treatment for positive partners, was $19, $9 and $4 for provider notification, contract notification and passive referral, respectively. We used costs obtained directly from the site at which all trial activities were conducted. We excluded costs that would not be incurred outside of the trial setting.

Sensitivity analyses

In one-way sensitivity analyses, we estimated the potential range of ICERs for the strategies, evaluating contract notification compared with passive referral, provider notification compared with contract notification and provider notification compared with passive referral across the probable range of input parameters. The results from the most influential input parameters are presented in Table 3. ICERs were most sensitive to the probability of persons who did not return being HIV positive. The wide confidence interval reflects uncertainty of this estimate (0.34–0.94). The transmission probability for persons eligible for ART but not on therapy also had a

substantial influence on ICERs, as did the probability that the index partner was the only partner, with greater partnership dissolutions resulting in more favourable ICERs. At certain extremes, provider notification was dominated by contract notification, demonstrating a scenario in which the provider notification strategy was less effective and more expensive.

Probabilistic sensitivity analysis demonstrates an overall robust model, where each input parameter is simultaneously varied across a given range of values from the parameter's defined distribution. With each 'draw', a new incremental cost and incremental effectiveness is calculated, as compared with the referent passive referral. The resulting point estimates are presented in Figure 2 (ICER planes), representing the ICERs of the 5000 draws executed through Monte Carlo simulation. The contract notification strategy is dominated (i.e. the strategy is both less effective and more costly compared with passive referral) 7.2% of the time. The provider notification strategy is dominated 22.9% of the time when compared with contract notification, and 7.7% of the time when compared with passive referral.

Alternative scenarios

Motorbike tracing

Assuming the same number of cases identified when providers use a motorbike, and excluding the cost of treatment, the motorbike scenario resulted in an ICER of $3248 per transmission averted for contract notification, compared with passive referral. Comparing motorbike tracing to our base case (car and driver), this ICER corresponds to a cost savings of $312 per case
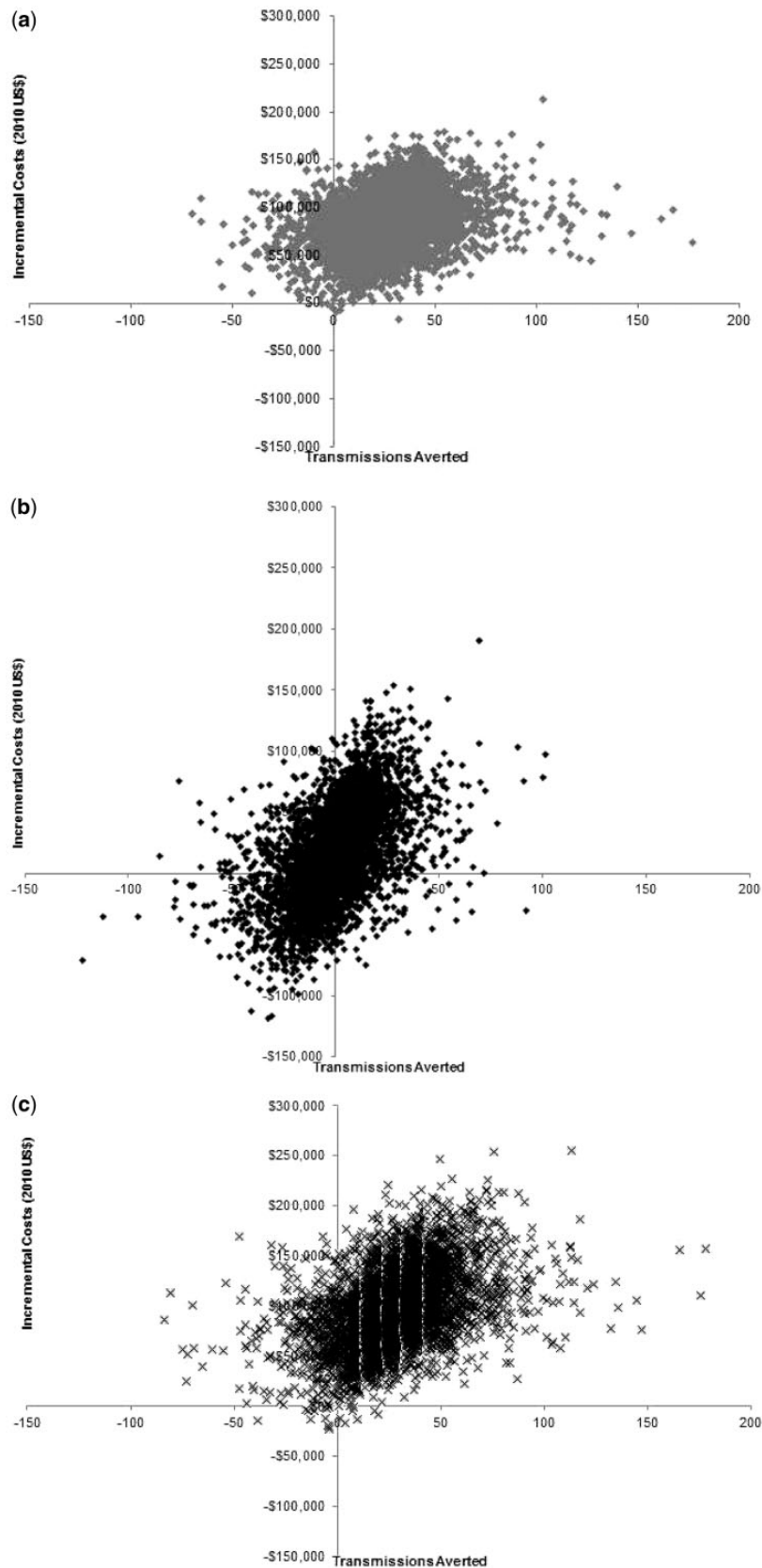
Figure 2 ICER planes. (a) Contract notification vs passive referral. (b) Provider notification vs contract notification. (c) Provider notification vs passive referral. The probabilistic sensitivity analysis simultaneously varies the input parameters across a given range of values from the parameter's distribution. With each draw, a new incremental cost and incremental effectiveness is calculated, as compared with the next least expensive arm. The resulting point estimates represent the ICERs of the 5000 draws executed with probabilistic sensitivity analyses. In (a) contract notification is compared with passive referral. In (b) the next most expensive option (provider notification) is compared with contract notification. Finally, in (c) we compare provider notification with passive referral.

averted. As with the base-case scenario, provider notification is slightly more effective but considerably more expensive than contract notification. Using a motorbike, the cost per new case identified was $19, $11 and $8 for provider, contract and passive referral, respectively.

Acute infection

A small percentage of persons who test negative with traditional antibody tests will actually be in the highly infectious stage of acute HIV infection (AHI) (Pilcher *et al.* 2004; Powers *et al.* 2007; Brown *et al.* 2011; Pilcher *et al.* 2007). AHI testing is not routinely available in STI clinics and these patients will be misclassified as HIV negative. In this scenario, 3% of patients who tested negative were assigned transmission probabilities consistent with AHI (0.178, range 0.09–0.25) (Hollingsworth *et al.* 2008; Brown *et al.* 2011). Including AHI as an infection state among partners who tested antibody negative did not qualitatively alter our results.

Discussion

To combat the HIV epidemic in sub-Saharan Africa, cost-effective, acceptable and feasible interventions to reduce HIV transmission are necessary. Currently, substantial efforts are being directed towards prevention strategies that require significant logistical effort and expense, such as pre-exposure prophylaxis and provision of ART for prevention. But active partner notification, a simple, effective and easily implementable strategy, has been largely neglected, relying solely on passive referral and HIV status disclosure.

We have demonstrated that provider and contract notification for HIV compare favourably to existing interventions in terms of cost per HIV case averted, and may be cost-effective strategies for identifying new cases and averting subsequent infections in Malawi (Sweat *et al.* 2004; Menzies *et al.* 2009). In our model, provider and contract notification cost only $28 and $10 more than passive referral, per new case identified. Using a motorbike for transportation reduces these costs further to only an additional $11 (provider) and $3 (contract) per new case identified, compared with passive referral. Contract and provider notification were more effective than passive referral in identifying cases and averting secondary transmissions over a wide range of probability estimates. This work builds upon our previous trial which demonstrated a high yield of provider-based notification strategies with minimal adverse consequences (Brown *et al.* 2011).

Our outcomes, in terms of cost per partner tested and cost per new HIV case identified, compare favourably to other HTC strategies. In Uganda, comparing stand-alone, hospital-based, household-member and door-to-door HTC, cost per HTC client ranged from $8.29 (door-to-door) to $19.26 (stand-alone) (2007 US$) (Menzies *et al.* 2009), comparable to the costs of provider or contract referral in 2010 US$. However, the cost per HIV infection identified observed in Uganda was much higher than the cost per HIV infection identified estimated in the model, ranging from $43 for hospital-based HTC to $232 for household-member HTC. We observed a cost per new HIV positive diagnosis of $36 (provider) and $18 (contract), demonstrating the efficiency of identifying new positives in

the high-risk population of partners of HIV-positive indexes. These findings likely generalize to other urban STI clinics in sub-Saharan Africa. Key parameters in our study, including partner return rates and prevalence of infection, are consistent with results of partner notification in Cameroon, where more than 56% of partners were tested through provider notification and 51% of partners tested were HIV positive, comparable to the 64% who tested positive in the Malawi trial (Muffih *et al.* 2009; Brown *et al.* 2011). Our parameter estimates and model results may be less applicable to rural settings given potentially different HIV prevalence, partnership patterns and tracing distances and associated costs.

Despite the compelling outcomes of the cost per new case identified, the cost-effectiveness of these provider-initiated partner notification strategies compared with passive referral is less certain as no accepted cost-effectiveness threshold exists for cost per infection averted. The commonly accepted World Health Organization (WHO) standards of <3 times GDP per capita as cost effective and <1 times GDP per capita as highly cost-effective relate to dollar per quality-adjusted life year outcomes. Importantly, evaluating cost-effectiveness based on country-specific ability to pay may not apply to the poorest countries, especially when most resources for HIV prevention and treatment are provided by external donors (Haacker 2008). Cost-effectiveness of provider-initiated partner notification strategies is better assessed through comparison with similar prevention strategies which evaluate averted infections, such as the use of nevirapine for prevention of mother-to-child transmission (PMTCT). This strategy is a widely adopted policy across sub-Saharan Africa and its cost per infection averted compares favourably with those ICERs observed in this analysis: a 2004 study found that the cost per infant case averted ranged from $1808 (Botswana) to $9258 (Côte d'Ivoire) (2000 US$) (Sweat *et al.* 2004). Further contextualizing the outcomes from this study to the Malawian setting, an evaluation of PMTCT from two Malawi health centres identified an ICER of $998 per infant case averted (2007 US$) (Orlando *et al.* 2010). Another Malawi-based cost-effectiveness analysis evaluated the opportunity to avert HIV infections through expanded treatment for STI among high-risk males, estimating an ICER of $15.42 per HIV case averted (2000 US$) (Price *et al.* 2006). Importantly, policy makers must consider the cost-effectiveness of alternative HIV-prevention strategies and the potential ethical obligations to inform persons who have been exposed to an HIV-infected partner.

Our findings are likely a conservative estimate of the cost-effectiveness associated with provider-assisted notification strategies. The model permits only a single transmission for each HIV-positive person in serodiscordant partnerships. This restriction underestimates the total number of transmissions that may be attributed to an individual, as persons may have multiple partners. We selected conservative estimates for behaviour change within serodiscordant couples based on observed rates of protective behaviour (Kennedy *et al.* 2010), and did not include any behaviour change for partners who test positive. The model also addresses only the first year after diagnosis, which will underestimate future transmission events if behaviour change is sustained. In addition, we did not explicitly model additional expenses, such as hospitalizations

and lost productivity. Incorporation of these expenses would improve the cost-effectiveness of strategies that linked persons into care earlier. Although the cost per new case identified was higher with the provider-based notification strategies, earlier entrance into care may be associated with considerable future savings. Costs due to hospitalization and outpatient visits are reduced when ART is initiated prior to an AIDS-defining illness (Harling and Wood 2007). Other costs associated with delayed linkage into care, such as lost productivity, are difficult to capture, but their omission from this evaluation likely leads to a conservative assessment of cost-effectiveness.

As a policy model intended to inform policy makers regarding the potential consequences of incorporating different notification strategies into existing voluntary HIV counselling and testing programmes, all costs are limited to a 1-year time frame—appropriate for budget planning, but limited in that we are not able to account for costs or transmissions that occur outside of this time frame. The appropriate strategy and feasible scalability of a provider-initiated partner notification programme will vary by setting, and staffing constraints are not considered in this model. However, clinic catchment area and associated tracing distances, which may vary clinic-to-clinic, had only a minor effect on estimated ICERs. The acceptability of provider-based partner notification in the urban STI clinic setting was encouraging, with only 11% refusal in the initial trial (Brown *et al.* 2011). However, if index cases were unwilling to provide partner names or locator information, the estimated cost-effectiveness of provider-initiated partner notification programmes would be less favourable. Importantly, among patients who refused trial participation, 20% refused for reasons related to fear or unwillingness to notify partners, which translates to approximately 2% of all potential participants.

Despite robust, trial-based data, our model assumptions introduce uncertainty into cost-effectiveness estimates. We modelled HIV protective behaviour as an all-or-nothing change for 35% of the HIV-negative partners. We would see a similar result if a higher percentage of persons 'reduced' their risky behaviour after testing, as suggested by recent meta-analysis focused on HIV behaviour change in low- and middle-income countries (Kennedy *et al.* 2010). Lower rates of behaviour change would reduce the benefits of provider and contract notification relative to passive referral; higher rates would increase the benefit. We evaluated the impact of behaviour change in sensitivity analyses—behaviour change among partners testing HIV negative had a meaningful impact on estimated cost-effectiveness: varying the probability of behaviour change from 20 to 50% changes the estimated ICER to $1050 for contract notification compared with passive referral. Importantly, in the partner notification setting, partners who test negative are now likely aware of their being in a serodiscordant couple, which is associated with high rates of protective behaviour change (Allen *et al.* 1992, 2003; Denison *et al.* 2008; Celum *et al.* 2010; Cohen *et al.* 2011; Hughes *et al.* 2012; Rosenberg *et al.* 2012). Even if the partnership has dissolved, this testing scenario may have a more substantial impact on reducing risk behaviours as the individual has been directly informed of HIV exposure. Not shown are scenario analyses in which partners who test HIV positive are also given a 35% probability of protective behaviour change, thereby reducing their likelihood of

transmitting to any HIV-negative partners. Behaviour change among this group decreased the ICER comparing contract notification to passive referral by ∼$700.

Our primary effectiveness outcome depends on the reliability of partner return rates and the HIV prevalence among returning and non-returning partners. The former was empirically measured by the trial, whereas the latter relied on our modelling an assumed rate of infection. Data to support higher or lower rates of infection among partners who did not return are not available, and compelling arguments can be made for both scenarios. We accounted for this uncertainty by incorporating a wide probability distribution. Some notified partners may have sought alternative testing locations, but the likelihood of partners seeking testing outside of the trial-designated clinic was minimized by co-ordinating with area STI clinics and using study-specific referral cards (Brown *et al.* 2011). According to the most recent available data, annual testing rates for the general population in Lilongwe are ∼14% (MOH 2007). We assessed the influence of the underlying natural testing rate on the model in sensitivity analyses (not shown). There was no meaningful change in estimated ICERs when this testing rate was incorporated into the model for persons who were not notified and, therefore, not tested through one of the three partner notification strategies. As such, all testing costs are included in this model as they are considered incremental expenses that would not otherwise be incurred. Scenario analyses in which these costs were excluded had only a minor effect on ICERs. Accurately estimating transmission rates relies on properly describing infectiousness of HIV-positive partners. HIV transmission is dynamic, varying by gender, partner susceptibility, stage of infection, viral characteristics and treatment. We modelled transmission variability as amplified by stage of infection, but did not account for other biological co-factors that contribute to transmission probability differences, such as STIs. We accounted for the reduced infectiousness for persons on ART, assuming all eligible persons immediately began therapy, as occurred in our trial, estimating retention in care which is relevant for transmission probabilities and ART-associated costs (Wilson *et al.* 2008; Del Romero *et al.* 2010; Donnell *et al.* 2010; Brown *et al.* 2011; Rosen and Fox 2011). Accounting for the heterogeneity of ART efficacy across individuals was beyond the scope of this study and differential survival projections are not included in this model. The effect that delayed ART initiation and differential survival would have on model estimates is unknown as it would reduce costs in all arms, but would also affect expected transmissions.

Partner notification is a logistically feasible HIV prevention intervention that has been underutilized in sub-Saharan Africa, and may be a cost-effective addition to existing testing and prevention strategies. Alternative solutions that identify persons earlier in the course of infection may include community- or home-based testing, and these approaches should be considered in future cost-effectiveness analyses. Many of the most promising prevention interventions require reaching large segments of the population for HIV testing. Active partner notification, either contract or provider-based, provides an effective, efficient and likely cost-effective strategy in a resource-limited setting. Increasing efforts to reach partners of

known HIV-infected persons is a reasonable and appropriate adjunct to any HIV prevention programme.

Endnote

[1] Data obtained from UNC Project administrators, Lilongwe, Malawi.

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