Partner Notification for Reduction of HIV-1 Transmission and Related Costs among Men Who Have Sex with Men: A Mathematical Modeling Study

Brooke E. Nichols¹*, Hannelore M. Götz²,³, Eric C. M. van Gorp¹,⁴, Annelies Verbon⁴, Casper Rokx⁴, Charles A. B. Boucher¹, David A. M. C. van de Vijver¹

¹ Department of Viroscience, Erasmus Medical Center, Rotterdam, the Netherlands, ² Department Infectious Disease Control, Public Health Service Rotterdam-Rijnmond, Rotterdam, the Netherlands, ³ Department of Public Health, Erasmus Medical Center, Rotterdam, the Netherlands, ⁴ Department of Internal Medicine and Infectious Diseases, Erasmus Medical Center, Rotterdam, the Netherlands

* b.nichols@erasmusmc.nl

Abstract

Background

Earlier antiretroviral treatment initiation prevents new HIV infections. A key problem in HIV prevention and care is the high number of patients diagnosed late, as these undiagnosed patients can continue forward HIV transmission. We modeled the impact on the Dutch men-who-have-sex-with-men (MSM) HIV epidemic and cost-effectiveness of an existing partner notification process for earlier identification of HIV-infected individuals to reduce HIV transmission.

Methods

Reduction in new infections and cost-effectiveness ratios were obtained for the use of partner notification to identify 5% of all new diagnoses (Scenario 1) and 20% of all new diagnoses (Scenario 2), versus no partner notification. Costs and quality adjusted life years (QALYs) were assigned to each disease state and calculated over 5 year increments for a 20 year period.

Results

Partner notification is predicted to avert 18–69 infections (interquartile range [IQR] 13–24; 51–93) over the course of 5 years countrywide to 221–830 (IQR 140–299; 530–1,127) over 20 years for Scenario 1 and 2 respectively. Partner notification was considered cost-effective in the short term, with increasing cost-effectiveness over time: from €41,476 - €41,736 (IQR €40,529-€42,147; €40,791-€42,397) to €5,773 - €5,887 (€5,134-€7,196; €5,411-€6,552) per QALY gained over a 5 and 20 year period, respectively. The full monetary benefits of partner notification by preventing new HIV infections become more apparent over time.
Conclusions

Partner notification will not lead to the end of the HIV epidemic, but will prevent new infections and be increasingly cost-effectiveness over time.

Introduction

In 2012, the HIV epidemic among men who have sex with men (MSM) was increasing across the world [1, 2]. MSM are disproportionately affected by HIV infection in the Netherlands comprising 71% of new HIV-infections in 2013 [3]. Next to behavior change and condom use, the use of treatment as prevention has shown to be an effective way to prevent HIV [4]. Among men and women in a generalized epidemic, the initiation of antiretroviral therapy (ART) at a CD4 cell count between 350–550 cells/μl was shown to prevent 96% of new infections as compared to treatment initiation at CD4 <250 cells/μl [4, 5]. It is hypothesized that the effect of treatment as prevention is similar among MSM [6].

Treatment as prevention cannot succeed unless patients are diagnosed early in infection. Early identification of patients is key from both clinical and preventative perspectives. Patients who are identified early and initiate antiretroviral therapy at a higher CD4 cell count have lower mortality, and fewer long-term complications and opportunistic infections compared to patients who initiate treatment late [4, 7]. Unfortunately, a significant problem in HIV prevention and care is the substantial number of patients diagnosed late [8]. Across Europe, MSM are diagnosed late in infection, with 44% diagnosed at a CD4 count <350, and 24% diagnosed with a CD4 <200 cells/μl [8]. The number of late diagnoses is similar among MSM in the Netherlands, with 37% of individuals diagnosed with a CD4 count <350 cells/μl, of which approximately half are diagnosed with CD4 <200 cells/μl [3]. These undiagnosed patients can then continue the forward transmission of HIV-1. It has been estimated that 50% of new infections are due to the 20% who are unaware of their infection [9], though these percentages may vary by setting.

Partner notification can play a role in identifying a proportion of HIV-infected individuals who are unaware of their infection, and getting them into care earlier in infection [10]. Notified partners have a higher rate of HIV positivity than those who come in for screening without being notified [10–13]. If HIV is diagnosed in a notified partner, these individuals can then initiate treatment earlier which can in turn reduce the number of HIV infections to others. Partner notification is therefore a method that can be used to control sexually transmitted infections (STIs) and HIV [14]. The cost-effectiveness and full monetary benefit of partner notification is not yet known.

The aim of this study is to use mathematical modeling to determine the preventative impact on new HIV-1 infections and cost-effectiveness of partner notification. For this purpose, we used data from the Rotterdam-Rijnmond Public Health Service (the Netherlands) which utilizes partner notification supported by an online partner notification system.

Methods

Study design and partner notification

We based our model on the outcomes of partner notification supported by an online partner notification tool in the Rotterdam region. The online tool, known as Suggest-A-Test, has been implemented by both the Rotterdam-Rijnmond and Amsterdam health municipalities since
Suggest-A-Test is a tool in which people diagnosed with an STI/HIV can easily and anonymously notify recent partners. After a patient is diagnosed, there is an intensive counseling process at the STI clinic in which partner notification is discussed. Patients can choose whether to contact their partners on their own or through the Suggest-A-Test system, and most choose to notify partners outside the Suggest-A-Test tool. For an HIV diagnosis, it is advised that the patient notifies all partners from the last 12 months and longer if possible.

We modeled two partner notification scenarios using the partner notification outcome data. In 2013, there were nine new HIV diagnoses via partner notification out of 366 MSM notified for any STI/HIV and tested for HIV. These nine new diagnoses represent approximately 4.7% of all new diagnoses in the entire Rotterdam region. Therefore in Scenario 1, we assume that approximately 5% of diagnoses in the Netherlands can be ascertained through partner notification. The nine new diagnoses also represent 19.6% of new diagnoses at the Rotterdam Public Health Municipality. We then model this in Scenario 2, in which we assume approximately 20% of individuals are diagnosed through partner notification. Scenario 1 therefore represents a decrease in effectiveness that may be observed with a nationwide scale-up of partner notification.

Model assumptions and calibration

A compartmental deterministic mathematical model was constructed and parameters were chosen to represent the Dutch HIV epidemic among MSM from 2008–2012 (Table 1) [15, 16]. We estimated that there were approximately 176,000 (164,000–190,000) MSM in the Netherlands in 2014 over the age of 15 [17, 18], with the number of new HIV diagnoses declining from 800 in 2008 to 700 in 2012 among MSM [3]. We model the partner notification process when treatment is initiated at CD4 cell count of <500 cells/μl, in line with current World Health Organization guidelines [19], and when treatment is initiated immediately, in line with current Dutch guidelines [20]. Partner notification is implemented in 2015, and the model is run until 2035. We compare our partner notification scenarios with treatment at CD4 <500 cells/μl, with a baseline of no partner notification and treatment at CD4 <500 cells/μl; and similarly our partner notification scenarios with immediate treatment, with a baseline of no partner notification and immediate treatment.

Our model stratifies disease progression into an acute stage, three chronic stages, and two AIDS stages (the full model schematic can be found in S1 Fig). Three chronic stages were chosen to be able to evaluate the model when treatment is initiated at different CD4 cell count thresholds: CD4 cell count <200, <350, <500 cells/μl, and immediate treatment. The duration and infectivity of each stage of infection differ (Table 1) [22, 23]. Treatment is assumed to reduce infectivity by 90–100% [4, 6]. In the model, approximately 25–30% of patients are diagnosed with a CD4 cell count >500 cells/μl, and approximately 35–40% diagnosed with a CD4 cell count <350 cells/μl, in line with current data [3]. In our baseline scenarios with no partner notification, we assume that individuals are tested at the rates that allow the modelled CD4 cell count distribution at diagnosis to match the current CD4 cell count distribution at diagnosis in the Dutch HIV epidemic among MSM. As the CD4 cell count at diagnosis of notified partners follows approximately the same distribution as those who were tested without being notified, we increased the test rate at all stages of infection in our partner notification scenarios. Full model equations and description can be found in S1 Text of the supporting information.

We matched our model to the previous epidemic based on: estimated Dutch MSM population size, number diagnosed with HIV, percentage diagnosed with a CD4 <200 cells/μl, and percentage diagnosed with CD4 200–350 cells/μl. Using Monte Carlo filtering techniques [29], we accepted 129 of 100,000 simulations that matched these parameters (value ranges of accepted parameters can be found in S1 Table). The model calibration to the number
Table 1. Key model parameters and costs.

| Description | Estimate or Range* | Reference |
|-------------|--------------------|-----------|
| **Model parameters** | | |
| Disease stages duration | | [21, 22] |
| Acute stage | 10–16 weeks | |
| Chronic stage >500 cells/μL | 0.87–1 year | |
| Chronic stage 350–500 cells/μL | 2.9–3.1 years | |
| Chronic stage 200–350 cells/μL | 3.6–3.9 years | |
| AIDS stage** | 6–12 months | |
| Final AIDS stage** | 7–13 months | |
| Infectivity; per partnership transmissibility per year | | [23]; Model Calibration |
| Acute stage | 0.024–0.59% | |
| Chronic stage (all) | 0.023–0.22% | |
| AIDS stage** | 0.006–0.27% | |
| Final AIDS stage** | 0% | |
| Proportion of people in sexual risk groups | | Model Calibration |
| Highest | 1.0–3.8% | |
| 2nd | 11–40% | |
| 3rd | 10–60% | |
| Lowest | 12–70% | |
| Number of partners per year in each sexual risk group | | Model Calibration |
| Highest | 92–556 | |
| 2nd | 10–91 | |
| 3rd | 1–9 | |
| Lowest | 0.4–2 | |
| Mortality rates per year | | [24–26] |
| Population | 0.0155 | |
| Chronic HIV stage | 0.098 | |
| AIDS stage | 0.63 | |
| On treatment during chronic stage, first 3 months | 0.0172–0.0175 | |
| On treatment during AIDS stage, first 3 months | 0.0184–0.0196 | |
| On treatment 3+ months | 0.0172–0.0175 | |
| HIV Test Rate | | |
| Baseline | 15.5–20% | Model Calibration |
| Rate of being tested in the acute stage of HIV | 80–87.5% of the baseline rate | Assumption*** |
| Linkage to care from test to treat | 90–98% | Model Calibration |
| Reduction in transmissibility of those patients on treatment | 90–100% | [4, 6, 27] |
| **Cost Parameters (Costs listed are in 2015 euros)** | | |
| **Testing** | | |
| Primary HIV test† | €20.32 | Local data |
| Confirmatory testing | €45.83 | Local data |
| All-inclusive cost charged to STI clinic for all STI tests (chlamydia, gonorrhea, syphilis, hepatitis B and HIV combined) | €124 | Local data |
| **ART costs** | | |
| Yearly cost of ART (averaged across regimens by number of people on regimen) | €10293 | Local data |
| CD4 cell count test | €97.75 | Local data |
| Viral load test | €66.54 | Local data |
| Outpatient visit at clinic/primary care | €31 | [28] |
| Outpatient visit after diagnosis† | €124 | [28], Local data |

(Continued)
diagnosed is shown in S2 Fig. All reported results are the median and interquartile range (IQR) of the accepted simulations.

Cost-effectiveness of partner notification

Each compartment in our deterministic model was assigned a cost and quality adjusted life year (QALY) depending on the intervention (Table 1, QALY weights can be found in S2 Table). In this analysis we take a third-party-payer perspective, and as such we take local costs for hospitalization of HIV infected persons, opportunistic infections, HIV testing, and ART, into account. We calculated incremental cost-effectiveness ratios over a 5, 10, 15, and 20 year period where we compared incremental costs and QALYs of partner notification scenarios to the baseline of no partner notification by treatment initiation threshold. Costs were discounted at 4% per year, and QALYs at 1/C5% per year, as per Dutch guidelines [30].

Sensitivity analysis

We performed a univariate sensitivity analysis of the cost-effectiveness of partner notification of Scenario 1- identifying approximately 5% of new HIV cases via partner notification. Five key input variables—number needed to test via partner notification for a positive HIV diagnosis, cost of antiretroviral drugs, cost of HIV testing, cost discounting, and QALY discounting—were considered to identify the sensitivity of our model. Recursive partitioning [31, 32] was conducted to determine the most influential parameters on the number of infections averted when using partner notification (S3 Fig shows the recursive partitioning analysis).

Results

Impact on Dutch HIV epidemic

Scenario 1. When 5% of new infections are identified through partner notification, partner notification is predicted to avert a total of 18 and 19 infections (interquartile range [IQR]
13–24; 14–26) over the course of 5 years countrywide when initiating at CD4 <500 cells/µl and immediately, respectively compared to treatment at those two thresholds with no partner notification use. Over 20 years, partner notification is predicted to avert between 221 and 222 infections (IQR 140–299; 140–304) (Fig 1) when initiating at CD4 <500 cells/µl and immediately, respectively. This represents approximately 1.5% of new infections over the 20 year timeframe.

**Scenario 2.** When 20% of new infections are identified via partner notification, on average 69 and 76 infections (IQR 51–93; 56–102) are predicted to be averted over 5 years. Over 20 years, between 830 and 832 infections (IQR 530–1,127; 537–1,135) are predicted to be averted when initiating at CD4 <500 cells/µl and immediately, respectively. Averting nearly four times more infections than Scenario 1, the number of infections averted represents approximately 5.7% of new infections over 20 years.

**Cost-effectiveness of partner notification**

Partner notification had substantial increasing cost-effectiveness over time: from €41,736 (IQR €40,791–€42,397) per QALY gained over 5 years to €5,887 (€5,411–€6,552) per QALY gained over 20 years in Scenario 1 when treatment is initiated at CD4 <500 cells/µl (Table 2). When treatment is initiated immediately, the cost per QALY decreases slightly to €41,065 (IQR €39,261–€42,134) per QALY gained at 5 years and €5,719 (IQR €5,113–€6,339) per QALY gained at 20 years in Scenario 1. The cost-effectiveness ratios for Scenario 2, where 20% of HIV diagnoses are through partner notification, are only reduced by 1–2% (Table 2, Fig 2). The full monetary benefits of partner notification by preventing new HIV infections become more apparent over time.

**Sensitivity analysis**

One-way sensitivity analyses (Fig 3) highlighted the five key input parameters of our model. If the yearly cost discounting is assumed to be 0%, or the number needed to test increases to 60 per 1 HIV diagnosis, then the cost per QALY gained of partner notification increases to €47,953 (IQR €46,833–€48,680) and €49,727 (IQR €48,606–€50,585) respectively. Yearly QALY discounting reduced to 0%, the number needed to test decreases to 20 per 1 HIV diagnosis, or the cost of ART or HIV testing is decreased by 50%, partner notification becomes even more cost-effective. Decreasing the cost of ART is the parameter that results in the largest change in cost per QALY, with a median decrease of 34.2% in cost per QALY gained to €27,447 (IQR €26,864–€27,941).

**Discussion**

Partner notification supported by an online partner notification tool is an approach to get individuals at high risk for HIV transmission to test for HIV. Partner notification was increasingly cost-effective over time, even in Scenario 1 in which only 5% of patients are diagnosed through partner notification. More infections could be diagnosed in a timely manner if partner notification is improved. Identifying patients earlier is more likely to reduce the epidemic as the acute stage has a higher infectivity[33]. If acutely infected patients are identified and notify their partners who may also have been acutely infected, whole transmission clusters could be prevented. Not only can patients who test earlier initiate treatment earlier, but they may also reduce their risk behavior, preventing additional infections [34]. Therefore, ways in which to prioritize and improve HIV partner notification to get patients to test earlier, with a focus on recent infections, should be explored.

In this study, we have modeled the effectiveness of an existing partner notification process. As such, the utilized data includes all of the pitfalls of implementing this process in practice.
While the efficacy of partner notification could be higher, we have chosen to model this real-world scenario. We have shown, however, that even if the process becomes more effective and the number needed to test to diagnose one HIV patient decreases to 20, the cost-effectiveness
Table 2. Incremental cost-effectiveness of partner notification (Scenario 1 in which 5% are diagnosed via online partner notification, and Scenario 2 in which 20% of patients are diagnosed via online partner notification, and worst case scenario): at 5, 10, 15 and 20 years. All values listed are the median of all model simulations and interquartile range of simulations.

| Intervention | Total Cost (Millions Euros) | QALYs Gained | Infections Averted | Incremental Cost-Effectiveness Ratio |
|--------------|------------------------------|---------------|-------------------|-----------------------------------|
| Treat at CD4 cell count <500 cells/μl |                             |               |                   |                                   |
| **5 years**  |                              |               |                   |                                   |
| Scenario 1*  | €1,644,473 (€1,322,401–€1,977,121) | 39 (31–50) | 18 (13–24) | €41,736 (€40,791–€42,397) |
| Scenario 2** | €6,433,290 (€5,175,973–€7,731,741) | 155 (122–196) | 69 (51–93) | €41,476 (€40,529–€42,147) |
| **10 years** |                              |               |                   |                                   |
| Scenario 1*  | €4,264,124 (€3,451,544–€5,250,083) | 262 (204–335) | 73 (50–98) | €18,193 (€15,627–€16,926) |
| Scenario 2** | €16,376,219 (€13,289,756–€20,168,533) | 1,019 (792–1,300) | 282 (193–377) | €16,044 (€15,456–€16,784) |
| **15 years** |                              |               |                   |                                   |
| Scenario 1*  | €6,580,279 (€5,276,477–€8,335,685) | 756 (553–941) | 144 (94–195) | €9,057 (€8,561–€9,777) |
| Scenario 2** | €25,114,652 (€20,123,588–€31,731,638) | 2,903 (2,126–3,612) | 549 (359–741) | €8,944 (€8,454–€9,679) |
| **20 years** |                              |               |                   |                                   |
| Scenario 1*  | €8,499,662 (€6,783,954–€10,817,655) | 1,519 (1,081–1,890) | 221 (140–299) | €5,887 (€5,411–€6,552) |
| Scenario 2** | €32,005,785 (€25,472,626–€40,567,125) | 5,773 (4,134–7,196) | 830 (530–1,127) | €5,773 (€4,134–€7,196) |
| Immediate Treatment |                             |               |                   |                                   |
| **5 years**  |                              |               |                   |                                   |
| Scenario 1*  | €1,713,341 (€1,387,291–€2,114,998) | 41 (34–54) | 19 (14–26) | €41,065 (€39,261–€42,134) |
| Scenario 2** | €6,727,578 (€5,407,791–€8,101,635) | 165 (131–210) | 76 (56–102) | €40,739 (€39,659–€41,521) |
| **10 years** |                              |               |                   |                                   |
| Scenario 1*  | €4,327,315 (€3,515,059–€5,287,711) | 275 (214–359) | 76 (53–104) | €15,735 (€15,155–€16,551) |
| Scenario 2** | €16,511,947 (€13,510,976–€20,413,643) | 1,063 (828–1,365) | 298 (204–399) | €15,595 (€15,074–€16,364) |
| **15 years** |                              |               |                   |                                   |
| Scenario 1*  | €6,603,666 (€5,258,305–€8,243,750) | 757 (569–979) | 149 (97–201) | €8,793 (€8,221–€9,450) |
| Scenario 2** | €25,140,754 (€20,032,146–€31,254,688) | 2,993 (2,190–3,721) | 565 (371–760) | €8,663 (€8,092–€9,381) |
| **20 years** |                              |               |                   |                                   |
| Scenario 1*  | €8,363,538 (€6,582,787–€10,501,999) | 1,517 (1,120–1,939) | 222 (140–304) | €5,719 (€5,113–€6,339) |
| Scenario 2** | €31,372,511 (€24,810,117–€39,483,106) | 5,830 (4,244–7,291) | 832 (537–1,135) | €5,616 (€5,028–€6,266) |

*5% of patients diagnosed via partner notification
**20% of patients diagnosed via partner notification

doi:10.1371/journal.pone.0142576.t002

ratio only decreases by 21%. As shown in our sensitivity analysis, decreasing the price of antiretroviral drugs can be even more successful at reducing the cost per QALY gained. This is because partner notification gets patients into care sooner, and therefore potential earlier initiation of costly ART. In the Netherlands, tenofovir-containing drugs, including combination tenofovir-emtricitabine and combination tenofovir-emtricitabine-efavirenz, were the 2nd and 3rd most expensive outpatient drug per patient in 2013 [35]. As generics come onto the market, ART price reduction will become a straightforward method of reducing costs for partner notification [36]. Costs due to additional HIV testing and counseling may be overestimated as notified individuals may eventually have accessed testing without being notified. Our analysis is therefore a worst-case scenario in which we assume the HIV tests and counseling resulting from partner notification are all additional costs. This overestimation of costs may be offset slightly by the initial unknown costs of a partner notification program, such as personnel training.

The effectiveness of the modeled partner notification is similar to other partner notification systems among MSM in similar settings [37]. Some studies have, however, shown a greater
effectiveness of partner notification in identifying previously unknown HIV-infected persons in concentrated epidemics [12, 13, 38] As we have shown in our sensitivity analysis, an increased effectiveness would only make partner notification more cost-effective.

Many mathematical modeling studies have been performed in recent years that investigate the preventative effect of earlier ART initiation in resource rich settings [23, 39–43]. Models agree that earlier treatment initiation can reduce costs and will avert incident HIV infections over time. Studies have yet to explicitly model how to logistically get patients to test earlier, and just one model was based on a European MSM epidemic [43]. Our study addresses this by modeling a method that can get patients to test earlier. We find, however, a relatively limited impact of partner notification given the fact that a large proportion of sexual contacts are anonymous and cannot be notified [44]. Our model adds to the previous literature on mathematical modelling of partner notification by of the addition of dynamic HIV transmission and parameterization to real partner notification data within the model[45]. While modeling very different settings and partner notification programs and including dynamic HIV transmission directly into our model, we find a nearly identical cost per infection averted between our long-term analysis and the primary analysis conducted by Varghese et al. ($32,000 per infection averted

Fig 2. Cost per quality adjusted life year (QALY) gained over time in 5 year increments. Scenario 1 in which 5% of patients are diagnosed through partner notification (Graph A when treatment is started a CD4 cell count <500 cells/μl, Graph C when treatment is initiated immediately). Scenario 2 in which 20% of patients are diagnosed through partner notification. Graph A is when treatment is initiated at a CD4 cell count <500 cells/μl. Graph B is when treatment is initiated immediately (Graph B when treatment is started a CD4 cell count <500 cells/μl, Graph D when treatment is initiated immediately).

doi:10.1371/journal.pone.0142576.g002
in Varghese et al., and approximately €38,000 per infection averted in our 20 year analysis [45].

Other ways to get patients into care early should be further investigated and modeled. Mobile testing units have had successes in a broad variety of settings [46–49], and is currently implemented in the Rotterdam region. Increasing awareness among general practitioners, along with physicians from other specialties, and efforts to normalize HIV testing can also be of importance, particular in resource-rich settings with low general HIV prevalence [50–52]. Many patients who were diagnosed late in infection had visited their general practitioner in the years before diagnosis with symptoms that could suggest an HIV infection. General practitioners that do more frequent HIV testing, especially among known at-risk populations such as MSM, can help to identify HIV. As such, increased HIV testing by general practitioners can lead to a reduction in the number of infected individuals who are diagnosed late [51, 52]. Finally, it has been shown that a large proportion of high sexual risk behavior MSM do not get tested regularly [53]. Therefore, efforts to increase awareness and testing among high-risk MSM may be a cost-effective strategy to get patients tested and into care earlier in infection.

Our mathematical model has several strengths. First, to our knowledge this is the first study to model and predict the long-term effectiveness of HIV partner notification. While previous models have focused on the effect of getting people into care sooner [23, 39–43], models have
not been created to determine how to implement this. Second, we have access to complete and accurate data of the Dutch HIV epidemic and were able to successfully calibrate our model to that data. Finally, we modeled the effectiveness of a program using real programmatic data. This allows us to make accurate and practical predictions on the effectiveness of the partner notification process.

This study has some potential limitations. First, it is unknown what proportion of new infections can be diagnosed through partner notification when scaled up. To address this we have looked at both 5% and 20% of new diagnoses being identified via partner notification. While the preventative impact of partner notification was predicted to be higher if more individuals come in through partner notification, the cost-effectiveness is virtually identical regardless of the percentage of patients identified through partner notification. Second, there are limitations of the partner notification process itself. Just 46% of the partners of HIV-infected MSM were identifiable [44]. Of the partners that were identifiable however, nearly all were notified [44]. The partner notification in the Netherlands was shown to be similarly effective as a comparable process in the United States [44, 54]. While notifying anonymous partners appears difficult, it may be possible to notify a network of people that may have had contact with an infected individual, i.e. contacting individuals that visit the same sex club or dating website [55]. Cost-effectiveness may be increased and additional infections could be averted if these other techniques are implemented simultaneously. We have chosen to model the existing partner notification process, as predictions based on real data can be made with greater confidence. Third, we did not model a change in risk behavior after an HIV diagnosis or after ART initiation, as we did not have reliable data on this for our setting and we wanted to model a worst-case scenario. Other research shows that risk behavior can decrease after a positive test and ART initiation [34, 56]. If we had included a decrease in risk behavior in our model, we would expect the preventative impact of partner notification to be larger, and that partner notification would be more cost-effective. Finally given the ongoing and unresolved debate surrounding cost-effectiveness thresholds, we have chosen to not compare our costs per QALY gained to a threshold in this analysis [57, 58].

Not only can infections be averted using partner notification, but there is additional clinical and monetary benefit of the early identification of HIV in the short and long-term. Thus, while partner notification will not lead to end of the HIV epidemic, it does prevent new infections and have increasing cost-effectiveness over time. As such, it should be considered for implementation throughout the Netherlands and countries with similar epidemics.

**Supporting Information**

**S1 Fig. Model schematic.**

(DOCX)

**S2 Fig. Calibration to number of newly diagnosed MSM patients: modeled data in green (median and interquartile range), and Dutch data in purple.**

(DOCX)

**S3 Fig. Recursive partitioning analysis.** Higher epsilon value (greater than 0.61) was the strongest predictor for a reduction in new infections. A higher epsilon value means a higher rate of assortative mixing, or people who are highly sexually active are more likely to have sex with people who also are highly sexually active. The next strongest predictor for a reduction in new infections, among those simulations with a high epsilon value, is the number of HIV diagnosed among MSM in 2012. The simulations that had >730 new diagnoses also had the largest
number of infections averted.

S1 Table. Variables used to calibrate and accept simulations using the Monte Carlo filtering technique.

S2 Table. Assumed utility weightings for QALYs.

S1 Text. Full model description and equations.

Acknowledgments

Aids Fonds Netherlands (2010–035); European Union: FP7 CHAIN (No. 223131), FP7 Dyna-Nets (No. 233847).

Author Contributions

Conceived and designed the experiments: BN HG EvG AV CR CB DvdV. Performed the experiments: BN HG DvdV. Analyzed the data: BN DvdV. Contributed reagents/materials/analysis tools: HG. Wrote the paper: BN HG EvG AV CR CB DvdV.

References

1. Beyrer C, Baral SD, van Griensven F, Goodreau SM, Charuvala SK, Wirtz AL, et al. Global epidemiology of HIV infection in men who have sex with men. Lancet. 2012; 380(9839):367–77. Epub 2012/07/24. doi:10.1016/S0140-6736(12)60821-6 PMID: 22819660; PubMed Central PMCID: PMC3805037.
2. The Gap Report. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS), 2014.
3. van Sighem A, Gras L, Smit C, Stolte I, Reiss P. Monitoring Report 2014: Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Amsterdam: Stichting HIV Monitoring (SHM), 2014.
4. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011; 365(6):493–505. Epub 2011/07/20. doi:10.1056/NEJMoa1105243 PMID: 21767103.
5. Eaton JW, Menzies NA, Stover J, Cambiano V, Chindelevitch L, Cori A, et al. How should HIV programmes respond to evidence for the benefit of earlier treatment initiation? A combined analysis of twelve mathematical models. Lancet Global Health. 2014; 2:e23–34. Epub 10 December 2013. doi:10.1016/S2214-109X(13)70172-4 PMID: 25104632.
6. Muessig KE, Smith MK, Powers KA, Lo YR, Burns DN, Grulich AE, et al. Does ART prevent HIV transmission among MSM? Aids. 2012; 26(18):2267–73. Epub 2012/05/10. doi:10.1097/QAD.0b013e328355713d PMID: 22569019; PubMed Central PMCID: PMC3499670.
7. Collaboration H-C, Cain LE, Logan R, Robins JM, Sterne JA, Sabin C, et al. When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: an observational study. Ann Intern Med. 2011; 154(8):509–15. Epub 2011/04/20. doi:154/8/509 [pii] doi:10.7326/0003-4819-154-8-201104190-00001 PMID: 21502648; PubMed Central PMCID: PMC3610527.
8. Mocroft A, Lundgren JD, Sabin ML, Monforte A, Brockmeyer N, Casabona J, et al. Risk factors and outcomes for late presentation for HIV-positive persons in Europe: results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE). PLoS Med. 2013; 10(9):e1001510. Epub 2013/10/19. doi:10.1371/journal.pmed.1001510 PMID: 24137108; PubMed Central PMCID: PMC3796947.
9. Hall HI, Holtgrave DR, Maulsby C. HIV transmission rates from persons living with HIV who are aware and unaware of their infection. Aids. 2012; 26(7):893–6. Epub 2012/02/09. doi:10.1097/QAD.0b013e328351f73f PMID: 22313960.
10. Gotz HM, van Rooljen MS, Vriens P, Op de Coul E, Hamers M, Heijman T, et al. Initial evaluation of use of an online partner notification tool for STI, called ‘suggest a test’: a cross sectional pilot study. Sex
Brown LB, Miller WC, Kamanga G, Nyirenda N, Mmodzi P, Pettifor A, et al. HIV partner notification is effective and feasible in sub-Saharan Africa: opportunities for HIV treatment and prevention. J Acquir Immune Defic Syndr. 2011; 56(5):437–42. Epub 2011/11/03. PMID: 22046601; PubMed Central PMCID: PMC3207356.

12. Marcus JL, Bernstein KT, Klausner JD. Updated outcomes of partner notification for human immunodeficiency virus, San Francisco, 2004–2008. AIDS. 2009; 23(8):1024–6. Epub 2009/03/19. doi: 10.1097/QAD.0b013e32832921a7 PMID: 19293685.

13. Garcia de Olalla P, Molas E, Barbera MJ, Martin S, Arellano E, Gosch M, et al. Effectiveness of a pilot partner notification program for new HIV cases in Barcelona, Spain. Plos One. 2015; 10(4):e0121536. Epub 2015/04/08. doi: 10.1371/journal.pone.0121536 PONE-D-14-36586 [pii]. 25849451; PubMed Central PMCID: PMC4388637.

14. Hogben M, McNally T, McPheeters M, Hutchinson AB. The effectiveness of HIV partner counseling and referral services in increasing identification of HIV-positive individuals a systematic review. American journal of preventive medicine. 2007; 33(2 Suppl):S89–100. doi: 10.1016/j.amepre.2007.04.015 PMID: 17657019.

15. Nichols BE, Boucher CA, van Dijk JH, Thuma PE, Nouwen JL, Baltussen R, et al. Cost-effectiveness of Pre-Exposure Prophylaxis (PrEP) in preventing HIV-1 infections in rural Zambia: a modeling study. Plos One. 2013.

16. Nichols BE, Sigaloff KC, Kityo C, Mandaliya K, Hamers RL, Bertagnolio S, et al. Averted HIV infections due to expanded antiretroviral treatment eligibility offsets risk of transmitted drug resistance: a modeling study. Aids. 2014; 28(1):73–83. Epub 2013/08/08. doi: 10.1097/01.aids.0000433239.01611.52 PMID: 23921620.

17. Marcus U, Hickson F, Weatherburn P, Schmidt AJ, Network E. Estimating the size of the MSM populations for 38 European countries by calculating the survey-surveillance discrepancies (SSD) between self-reported new HIV diagnoses from the European MSM internet survey (EMIS) and surveillance-reported HIV diagnoses among MSM in 2009. Bmc Public Health. 2013; 13:919. Epub 2013/10/04. doi: 1471-2458-13-919 [pii] doi:10.1186/1471-2458-13-919 PMID: 24088198; PubMed Central PMCID: PMC3850943.

18. The World Bank. Netherlands: World Development Indicators 2014 [cited 2014 7 October]. Available from: http://data.worldbank.org/country/netherlands.

19. W.H.O. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization, 2013.

20. NVHB. 2.1. Wanneer beginnen?: NVHB; 2014 [cited 2014 17 December]. Available from: http://www.nvhb.nl/richtlijnvib/index.php/2.1._Wanneer_beginnen%3F.

21. Pilcher CD, Joasi G, Hoffman IF, Martinson FE, Mapanje C, Stewart PW, et al. Amplified transmission of HIV-1: comparison of HIV-1 concentrations in semen and blood during acute and chronic infection. Aids. 2007; 21(13):1723–30. Epub 2007/08/11. doi: 10.1097/QAD.0b013e3281532c82 0002030-200708200-00007 [pii]. PMID: 17690570; PubMed Central PMCID: PMC2673564.

22. Lodi S, Phillips A, Touloumi G, Geskus R, Meyer L, Thiebaut R, et al. Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 Cells/mm 3: assessment of need following changes in treatment guidelines. Clin Infect Dis. 2011; 53(8):817–25. Epub 2011/09/17. doi: cir494 [pii] doi:10.1093/cid/cir494 PMID: 21921225.

23. Sood N, Wagner Z, Jaycoks A, Drabo E, Vardavas R. Test-and-treat in Los Angeles: a mathematical model of the effects of test-and-treat for the population of men who have sex with men in Los Angeles County. Clin Infect Dis. 2013; 56(12):1789–96. Epub 2013/03/15. doi: cit158 [pii] doi:10.1093/cid/cit158 PMID: 23487387; PubMed Central PMCID: PMC3658365.

24. Nakagawa F, Lodwick RK, Smith CJ, Smith R, Cambiano V, Lundgren JD, et al. Projected life expectancy of people with HIV according to timing of diagnosis. Aids. 2012; 26(3):335–43. Epub 2011/11/18. doi: 10.1097/QAD.0b013e32834ddec9 PMID: 22089374.

25. Brinkhof MW, Boule A, Weigel R, Messou E, Mathers C, Orrell C, et al. Mortality of HIV-infected patients starting antiretroviral therapy in sub-Saharan Africa: comparison with HIV-unrelated mortality. PLoS medicine. 2009; 6(4):e1000066. PMID: 19399157. doi: 10.1371/journal.pmed.1000066

26. W.H.O. Global Health Observatory Data Repository: Life expectancy Geneva2014 [cited 2014 27 October]. Available from: http://apps.who.int/gho/data/node.main.688?lang=en.
28. Tan SS, Bouwmans CA, Rutten FF, Hakkaart-van Roijen L. Update of the Dutch Manual for Costing in Economic Evaluations. Int J Technol Assess Health Care. 2012; 28(2):152–8. Epub 2012/05/09. doi: 10.1017/S0266462312000062 [pii] doi: 10.1371/journal.pone.0142576

29. Rose KA, Smith E, Gardner R, Bremker A, Bartell S. Parameter sensitivities, Monte Carlo Filtering, and model forecasting under uncertainty. J Forecast. 1991; 10:117–33.

30. Insurance FhI. Guidelines for pharmacoeconomic research, updated version. The Netherlands: Col-

lege voor zorgverzekerings, Diemen; 2006 [cited 2014 17 October 2014]. Available from: http://www.
isp.or/peguidelines/source/HTAGuidelinesNLupdated2006.pdf.

31. Therneau TM, Atkinson EJ. An introduction to recursive partitioning using the RPART routines. Mayo Foundation, 1997.

32. Venables WN, Ripley BD. Chapter 9: Tree-Based Methods. In: Venables WN, Ripley BD, editors. Modern Applied Statistics with S. Statistics and Computing. 4 ed. New York: Springer; 2002.

33. Bellan SE, Dushoff J, Galvani AP, Meyers LA. Reassessment of HIV-1 acute phase infectivity: account-

ing for heterogeneity and study design with simulated cohorts. PLoS Med. 2015; 12(3):e1001801. Epub 2015/03/18. doi: 10.1371/journal.pmed.1001801 PMEDICINE-D-14-01583 [pii] PMID: 25781323; PubMed Central PMCID: PMC4363602.

34. Colfax GN, Buchbinder SP, Cornelisse PG, Vittinghoff E, Mayer K, Celum C. Sexual risk behaviors and implications for secondary HIV transmission during and after HIV seroconversion. Aids. 2002; 16 (11):1529–35. Epub 2002/07/20. PMID: 12131911.

35. Zorghinstituut Nederland. GIPeiligen 2013: Ontwikkelingen genees- en hulpmededelengebruik en het Neder-

lands: Zorghinstituut Nederland; 2014 [cited 2014 23 October]. 35:[Available from: http://www.
zorghinstituutnederland.nl/binary/content/documents/zin-www/documenten/publicaties/gipeiligen/ 1410-gipeiligen-2013/GIPeiligen+2012.pdf.

36. Walensky RP, Sax PE, Nakamura YM, Weinstein MC, Pei PP, Freedberg KA, et al. Economic savings versus health losses: the cost-effectiveness of generic antiretroviral therapy in the United States. Ann Intern Med. 2013; 158(2):84–92. Epub 2013/01/16. doi: 1556848 [pii] doi: 10.7326/0003-4819-158-2-201301150-00002 PMID: 23318310; PubMed Central PMCID: PMC3664029.

37. Golden MR, Hogben M, Potterat JJ, Handsfield HH. HIV partner notification in the United States: a national survey of program coverage and outcomes. Sex Transm Dis. 2004; 31(12):709–12. Epub 2004/12/21. doi: 00007435-200412000-00003 [pii] PMID: 15608584.

38. Ahrens K, Kent CK, Kohn RP, Nieri G, Reynolds A, Philip S, et al. HIV partner notification outcomes for HIV-infected patients by duration of infection, San Francisco, 2004 to 2006. J Acquir Immune Defic Syndr. 2007; 46(4):749–84. Epub 2007/12/14. PMID: 18077837.

39. Lima VD, Johnston K, Hogg RS, Levy AR, Harrigan PR, Anema A, et al. Expanded access to highly active antiretroviral therapy: a potentially powerful strategy to curb the growth of the HIV epidemic. J Infect Dis. 2008; 198(1):59–67. Epub 2008/05/24. doi: 10.1086/586573 PMID: 18498241.

40. Long EF, Brandaule ML, Owens DK. The cost-effectiveness and population outcomes of expanded HIV screening and antiretroviral treatment in the United States. Ann Intern Med. 2010; 153(12):778–89. Epub 2010/12/22. doi: 153/12/778 [pii] doi: 10.7326/0003-4819-153-12-201012210-00004 PMID: 21173412; PubMed Central PMCID: PMC3173812.

41. Walensky RP, Palliel AD, Losina E, Morris BL, Scott CA, Rhode ER, et al. Test and treat DC: forecasting the impact of a comprehensive HIV strategy in Washington DC. Clin Infect Dis. 2010; 51(4):392–400. Epub 2010/07/14. doi: 10.1086/655130 PMID: 20617921; PubMed Central PMCID: PMC2906630.

42. Sorensen SW, Sanson SL, Brooks JT, Marks G, Begier EM, Buchacz K, et al. A mathematical model of comprehensive test-and-treat services and HIV incidence among men who have sex with men in the United States. Plos One. 2012; 7(2):e29098. Epub 2012/02/22. doi: 10.1371/journal.pone.0029098 PONE-D-11-13033 [pii] PMID: 22347991; PubMed Central PMCID: PMC3277596.

43. van Sighem A, Vidondo B, Glass TR, Bucher HC, Vennarza P, Gebhardt M, et al. Resurgence of HIV infection among men who have sex with men in Switzerland: mathematical modelling study. Plos One. 2012; 7(9):e44819. Epub 2012/10/02. doi: 10.1371/journal.pone.0044819 PONE-D-12-04314 [pii] PMID: 23024766; PubMed Central PMCID: PMC3443082.

44. van Aar F, van Weert Y, Spijker R, Gotz H, de Coul EO, for the Partner Notification G. Partner notifica-

tion among men who have sex with men and heterosexuals with STI/HIV: different outcomes and chal-

lenges. Int J STD AIDS. 2014. Epub 2014/08/22. doi: 0956462414547398 PMID: 25141854.

45. Varghese B, Peterman TA, Hoftgrave DR. Cost-effectiveness of counseling and testing and partner notification: a decision analysis. Aids. 1999; 13(13):1745–51. Epub 1999/10/06. PMID: 10509577.

46. de la Fuente L, Delgado J, Hoyos J, Belza MJ, Alvarez J, Gutierrez J, et al. Increasing early diagnosis of HIV through rapid testing in a street outreach program in Spain. Aids Patient Care STDS. 2009; 23
47. Lipsitz MC, Segura ER, Castro JL, Smith E, Medrano C, Clark JL, et al. Bringing testing to the people—benefits of mobile unit HIV/syphilis testing in Lima, Peru, 2007–2009. Int J STD AIDS. 2014; 25(5):325–31. Epub 2013/10/11. doi: 10.1177/0956462413507443 PMID: 24108451; PubMed Central PMCID: PMC4110635.

48. Govindasamy D, Kranzer K, van Schaik N, Noubary F, Wood R, Walensky RP, et al. Linkage to HIV, TB and non-communicable disease care from a mobile testing unit in Cape Town, South Africa. Plos One. 2013; 8(11):e80017. Epub 2013/11/16. doi: 10.1371/journal.pone.0080017 PONE-D-13-23672 [pii]. PMID: 24236170; PubMed Central PMCID: PMC3827432.

49. Mabuto T, Latka MH, Kuwane B, Churchyard GJ, Charalambous S, Hoffman CJ. Four models of HIV counseling and testing: utilization and test results in South Africa. Plos One. 2014; 9(7):e102267. Epub 2014/07/12. doi: 10.1371/journal.pone.0102267 PONE-D-13-54692 [pii]. PMID: 25013938; PubMed Central PMCID: PMC4094499.

50. Donker G, Dorsman S, Spreeuwenberg P, van den Broek I, van Bergen J. Twenty-two years of HIV-related consultations in Dutch general practice: a dynamic cohort study. BMJ Open. 2013; 3(4). Epub 2013/04/30. doi: bmjopen-2012-001834 [pii] doi:10.1136/bmjopen-2012-001834 PMID: 23641499.

51. van Bergen JE. Normalizing HIV testing in primary care. Commentary on: Late HIV diagnoses in Europe: a call for increased testing and awareness among general practitioners. Eur J Gen Pract. 2012; 18(3):133–5. Epub 2012/09/08. doi: 10.3109/13814788.2012.704361 PMID: 22954191.

52. Champenois K, Le Gall JM, Jacquemin C, Jean S, Martin C, Rios L, et al. ANRS-COMTEST: description of a community-based HIV testing intervention in non-medical settings for men who have sex with men. BMJ Open. 2012; 2(2):e000693. Epub 2012/04/03. doi: bmjopen-2011-000693 [pii] doi:10.1136/bmjopen-2011-000693 PMID: 23466158; PubMed Central PMCID: PMC3323802.

53. Edelman EJ, Gordon KS, Fagerlin A, Hagan H, Luft C, McKee M, et al. Sexual risk behaviour and viral suppression among HIV-infected adults receiving medical care in the United States. J Acquir Immune Defic Syndr. 2014; 66(3):309–17. Epub 2014/03/14. doi: 10.1097/QAI.0b013e3182b9c02e PMID: 24629300; PubMed Central PMCID: PMC3960779.