An Examination of Diagnosis Strategies to Maximize the Preventive Potential of Post-Diagnosis Behavior Change: Insights from Southern California

Abstract

We use network models to compare diagnosis strategies to reduce HIV incidence among men who have sex with men (MSM). We extend prior models, parameterized from the behavioral sub-study of the Southern California Acute Infection and Early Disease Program (and other published biological and demographic data), that demonstrated the population-level effects of post-diagnosis behavior change (presented at PAA 2013).

The diagnosis strategies we model here involve tests with shorter detection windows, more frequent testing, and other individualized testing regimens. We simulate these strategies over a 10 year period and our primary outcome is the number of new infections. We find that individualized testing (IT) strategies (i.e. testing every 3 partners or 3 months, or every 6 partners or 6 months) are significantly more effective than realistic models of other diagnosis strategies. This work highlights the potential importance of individualized strategies for new public health policies in HIV prevention.

1 Introduction

Men who have Sex with Men (MSM) continue to be the group most affected by HIV in the United States [1]. In recent studies, MSM have been estimated to account for 61% of all new infections in the United States [1]. There is evidence that a large proportion of infections in this population either go undiagnosed [1, 2], or are diagnosed late [3]. There are at least two public health benefits to early diagnosis: timely enrollment in treatment [4, 5], and change in behavior through seroadaptive behaviors (some examples include partner reduction, serosorting, increased condom use) [6, 7, 8]. Increasing diagnoses among HIV-positive men who have sex with men (MSM) has been a major component of public health interventions. Different strategies for achieving this goal

have been suggested. Our objective here is to examine how we can utilize the preventive potential of post-diagnosis behavior change (PDBC) to reduce the number of incident HIV infections in MSM.

Acute HIV infection is one reason why early diagnosis may be crucial. An HIV infected individual is most infectious during the first 6 to 12 weeks of infection [9, 10, 11, 12, 13, 14, 15]. While the precise estimates for number of onward transmission events directly attributable to acute infection vary [16], it is accepted that early detection of HIV during this phase is critical for infection management [17].

Early diagnosis depends on the "detection window" (minimum time between onset of infection and positive test result) of the test that is used for diagnosis, and the testing behavior of individuals at risk of infection. HIV tests with shorter detection windows continue to be developed, and third and fourth generation enzyme immunoassays (EIA's) have detection windows of 20-30 days and 15-20 days respectively [18]. The fourth generation EIA is widely used in industrialized economies [16, 19, 20]. Other combination methods that combine antigen and antibody testing (for example the Combo RT) are available; however, one study showed that the antigen portion of the test is not successful at detecting acute infection, but the antibody test is [21].

An alternative is adoption of the rapid nucleic acid amplification tests (NAATs) and antigen tests that can detect HIV as early as 10 to 15 days after infection [22, 18]. Since the HIV NAATs detect the presence of HIV RNA they do not rely on the presence of antibodies to diagnose HIV infection [23]. However, HIV RNA tests are much more costly than the antibody tests [24]. Current recommendation on tests in high-incidence populations include pooled NAAT or fourth-generation assays [25].

Testing behavior is the other piece of the early diagnosis puzzle. Current estimates suggest that MSM tend to test on average about once a year [26], but other data show a high proportion of MSM with undiagnosed infection [2]. A variety of techniques to improve access to testing having been developed; in particular, recent developments in point-of-care testing [27], home-based counseling and testing [28] and understanding the problems in and improving access to care [29, 30] reflect the urgency to develop

adequate strategies to diagnose infected individuals early.

Currently, the CDC recommends that all MSM get tested for HIV every year, and sexually active MSM get tested every 3 to 6 months [31]. There is interest in exploring more individually tailored testing testing strategies. For example, King, Pierce and Snohomish counties in Washington State have recently implemented the "Find Your Frequency" program that encourages MSM to evaluate their risk based on the status of partners, number of partners, type of sex, drug use and history of sexually transmitted diseases. The website has a simple module that anyone can go through and makes a recommendation to test every 3 months or every 12 months [32]. The California Department of Public Health is interested in individualized testing (IT) strategies (colloquially known as "oil change") that propose MSM test after a certain number of partners, or a certain period of time (Dan Wohlfeiler, personal communication). Two particular forms of this strategy are the "3/3 IT" (where men test every 3 months or every 3 partners) and the "6/6 IT" (where men test every 6 months or every 6 partners). These IT strategies are different from strategies implemented in the Find Your Frequency program, in that the latter MSM evaluate their risk, while in the former, MSM may update their assessments of their risk more dynamically.

The preventive potential of diagnosis-induced behavior change depends on the timing and magnitude of such behavior change, and the contexts in which such behavior change does or does not occur. Such post-diagnosis behavior change in Southern California MSM was documented in the behavioral sub-study of the Southern California Acute Infection and Early Disease Research Program (AIEDRP) [7, 8]. The public health impact of such behavior change, however, remains largely unknown. These benefits of early diagnosis are recognized, [33], and have started to receive more attention in modeling studies [34]. Much focus in modeling studies has been placed on early initiation of treatment to control new infections [35, 36, 37, 38]; our focus here is on recommending strategies to maximize the preventive potential of diagnosis induced behavior change (PDBC). In previous work, we showed the population-level impact of PBDC on overall HIV prevalence in men who have sex with men (MSM). We extend

these existing models to examine the effectiveness of strategies that maximize the preventive potential of PDBC – both by instituting tests with shorter detection windows, and increasing the frequency of testing, in a general and individualized manner.

2 Methods

2.1 Overview

Our models follow the same basic structure as in a previous study [39]. We extend network models based on exponential-family random graph models (ERGMs). These models incorporate key demographic (birth, death, and aging), epidemiological (testing behavior, treatment, meth use, circumcision), behavioral (partnership types, activity levels, multiple concurrent partnerships in the various types, sero-adaptive behaviors) and biological (viral load trajectories, infectivity) variables.

The behavioral data are primarily from the Southern California substudy of AIEDRP [7, 8], and supplemented with biological and demographic data from other published studies (details in [39]). Newly diagnosed HIV-positive men completed AIEDRP questionnaires at baseline. Follow-up information was collected by offering interviews every 3 months after initial enrollment. At baseline, respondents provided detailed information on their three most recent partners, and at follow-up, on the most recent partner, in addition to reports on their total number number of partners at baseline and followup [8]. The types of partnerships MSM engage in are complex [40], but we dichotomize these partnerships as "main" partnerships, and "non-main" partnerships for simplicity [39]. We assumed a 22-day detection window for tests in our baseline models, in accordance with third and fourth generation EIA's and consistent with other modeling work [41].

The mechanisms of PDBC we model are:

1. Reduction in total number of non-main partnerships.
2. Selection of non-main partners by diagnosis status.

3. UAI in Main Partnerships.

Our baseline models are built around a mean inter-test interval of 351 days in accordance with Goodreau et al. [41] (as derived from data by Helms et al. [26]). We consider an alternate baseline testing frequency of one test every two years for consistency with a separate modeling study by Cassels et al. [6]. We call this the testing frequency (TF) scenario, and we label a mean inter-test interval of 351 days as "TF1" and a mean inter-test interval of two years as "TF2."

Due to the possible incompatibility between data on reported rates of frequency of testing and the level of awareness of infection – we examined a separate scenario that matched the level of awareness of infection [39] (Details on this incompatibility are discussed in [39]). These level-of-awareness (LOA) models are set to match CDC data of 55-60% diagnosis of infected MSM; we assumed memoryless testing at a mean inter-test interval of 4000 days (approximately 10.9 years) to achieve this level of awareness of infection [39]. We examine various strategies for diagnosis interventions under each of these scenarios. The three main scenarios we consider are summarized in Table 1.

Table 1: Scenarios of Interest

Scenario	Feature of Interest	Data Source to Match	Notation
Testing Frequency	Mean inter-test interval of 351 days	Helms et al. (2009) [26]	TF1
	Mean inter-test interval of	Cassels et al. (2009) [6]	TF2
Level of Awareness	55-60% of Infected Diagnosed	NHBS (2008) [1, 2]	LOA
	Match 55-60% awareness of infection		

Our previous modeling work provides a baseline for current patterns in HIV testing among MSM [39]. We simulated these models until stable equilibrium prevalence in the three scenarios of interest: TF1, TF2 and LOA. (Simulating from a baseline of equilibrium prevalence helps model transmission dynamics in a late-stage epidemic.) With these baseline models as the starting point, we then simulate the baseline condition in each scenario, and the diagnosis interventions of interest in each scenario. We

evolve our models in daily time steps, and each intervention we test is over 10 years. We perform 10 repetitions of each experiment. Our primary outcome variable is the number of new infections over the simulation period of each model repetition in each intervention. We compute 95% theoretical confidence intervals around the mean number of new infections. Other outcome metrics we consider are reduction in the number of new infections achieved through intervention relative to baseline, and relative to the maximum possible, where maximum possible is defined as the difference in the mean number of infections obtained in baseline with the hypothetical best case models in each of TF1, TF2 and LOA. We perform two-sample t-tests to compare consecutive strategies interventions ordered by an apriori hypothesized ordering of effectiveness.

2.2 Models for Diagnosis Interventions

We model each of the conditions we consider under each of the three scenarios of interest: TF1, TF2 and LOA. First, we consider an HIV test that has a detection window of 1 day. We then model testing every 3 months and 6 months, under the baseline assumptions that apply to the specific scenario. We consider individualized testing testing strategies (IT) where MSM test every 6 months (180 days) or 6 non-main partners whichever comes first (the 6/6 IT intervention), or every 3 months or 3 non-main partners – whichever comes first (the 3/3 IT strategy). As a hypothetical scenario, we model a "best case" scenario where every undiagnosed individual tests every day and the test can detect positive serostatus one day after transmission. This set of simulations helps us analyze the limits of these interventions (given our models).

To compare the effectiveness of these diagnosis interventions, we hypothesize their effectiveness in the following sequence (in increasing order of effectiveness): baseline models, detection window of 1 day, 6-monthly and 3-monthly testing, followed by the 6/6 and 3/3 IT interventions, and finally the hypothetical best case. We perform two-sample t-tests to compare consecutive strategies interventions this sequence and assess significance at the 0.05 level. As separate measures of effectiveness, we present the number of infections averted relative to baseline, and, the number of infections

averted in each strategy relative to the maximum possible, where maximum possible is as defined above.

3 Results

We summarize the number of infections over 10 simulations in TF1, TF2 and LOA in Table 2. We summarize the number of infections prevented in each strategies, relative to baseline (Table 3) and relative to the maximum possible (Table 4), where maximum possible is defined as the difference in the number of infections in the baseline and best case.

Table 2: Number of new infections produced with different intervention strategies in each scenario. The number of new infections are over 10 repetitions of each model. The 95% confidence interval about the mean is computed using the t-distribution.

Model	Detection Window	Testing Pattern	TF1	TF2	LOA
Baseline	22	DPT	738.9 ± 20.1	790.2 ± 22.9	955.3 ± 21.1
	1	Mean inter-test interval of 351 days	738.0 ± 10.2	804.9 ± 22.3	944.1 ± 25.7
Testing Behavior	22	6 monthly	734.4 ± 3.4	764.9 ± 8.6	881.8 ± 18.5
	22	3 monthly	730.1 ± 11.6	736.2 ± 12.3	866.6 ± 10.3
6/6 IT	22	Every 6 months or 6 partners	696.5 ± 10.9	739.2 ± 14.3	618.2 ± 35.5
3/3 IT	22	Every 3 months or 3 partners	704.9 ± 21.3	705.8 ± 16.7	553.6 ± 15.2
Best Case	1	1	689.9 ± 10.1	654.8 ± 6.6	517.9 ± 10.8

NB It is counter-intuitive that the 6/6 IT strategy produces slightly fewer infections than the 3/3 IT strategy. But it is important to note that this difference is not statistically significant (p-value=0.53) and this slight difference can be attributed to the stochastic nature of these models.

Table 3: Proportion of cases prevented by each strategy (relative to the baseline) in the three scenario scenario. Maximum possible is defined as the difference between the number of new infections in the baseline and best-case scenarios.

Strategy	Scenario TF1	Scenario TF2	LOA
Detection Window 1 day	1.8%	-10.9%	2.1%
Half-Yearly Testing	9.2%	18.7%	16.4%
Quarterly Testing	17.9%	39.9%	19.9%
6/6 IT	86.5%	37.7%	76.9%
3/3 IT	69.3%	66.1%	91.8%

Table 4: Proportion of cases prevented by each strategy (relative to maximum possible) in the three scenario scenario. Maximum possible is defined as the difference between the number of new infections in the baseline and best-case scenarios.

Strategy	Scenario TF1	Scenario TF2	LOA
Detection Window 1 day	1.8%	-10.9%	2.1%
Half-Yearly Testing	9.2%	18.7%	16.4%
Quarterly Testing	17.9%	39.9%	19.9%
6/6 IT	86.5	37.7%	76.9%
3/3 IT	69.4	62.3%	96.1%

We present results from two-sample t-tests of sequential comparison of the number of new infections between the testing strategies in Table 5. We note that simply instituting a test with the shortest possible detection window does not significantly reduce the number of new infections over a 10-year period in any baseline scenario we consider. Testing every 3 months and 6 months significantly reduces the number of infections over 10 years in TF2 only; thus the effectiveness of these strategies appears contingent upon the baseline assumptions we make. In the TF1 and LOA scenarios, the 6/6 IT strategy performs significantly better than more frequent testing but there is no

significant difference between the 3/3 IT strategy and the 6/6 IT strategy). In the TF2 scenario, the 3/3 IT strategy performs significantly better than the 6/6 IT strategy. Thus, the two IT strategies appear most effective in terms of incidence reduction in the three models we consider.

Table 5: P-values from two-sample t-tests of sequential comparison of number of new infections between the testing strategies we consider. The sequence is in increasing order of effectiveness as we hypothesized apriori. TF1 and TF2 are the testing frequency models with annual and two-yearly testing respectively, LOA is the level-of-awareness scenario. The strategy DW1 is a test with a detection window of 1 day, 6m and 3m are half-yearly and quarterly testing respectively, 6/6 and 3/3 IT are the individualized strategies with testing 6 months or 6 partners and 3 months or 3 partners respectively.

Strategy	TF1	TF2	LOA
Baseline vs DW1	0.94	0.41	0.62
DW1 vs 6m	0.52	**0.007**	**0.002**
6m vs 3m	0.54	**0.002**	0.21
3m vs 6/6 IT	**0.001**	0.77	**less than 0.001**
6/6IT vs 3/3 IT	0.53	**0.01**	0.009
3/3 IT vs Best Case	0.26	**less than 0.0001**	0.002

4 Discussion

Our comparison of the various strategies suggests that amongst the realistic strategies we consider, both the IT strategies appear to be most effective in terms of preventing more new infections over a 10 year period. In all cases we consider, instituting a test with a short detection window does not make a significant difference in the number of new infections. The effectiveness of quarterly or half-yearly testing depends on the baseline assumptions we make.

In our presentation of the number of new infections obtained under the various

strategies in the three scenarios we study, we notice a counter-intuitive result – that the 6/6 IT strategy averts more infections (relative to the maximum possible) than the 3/3 IT strategy in TF1. However, these differences presumably result from stochastic variation, are not statistically significant (as we see in Table 5). However, this difference appears magnified when we compare this measure to the maximum possible number of preventions.

The three baseline models we considered were based on different assumptions about testing behavior. The TF1 scenario assumed annual testing on average (and resulted in approximately 95% of infections diagnosed at equilibrium), while the LOA scenario was set to match 55-60% of diagnoses among those infected at equilibrium. The truth is likely somewhere between these two extremes, and investigating these distinct baseline conditions gives us a bound around our assessment of the interventions we consider.

We also observed that the question of the optimal strategy between 3/3 IT and 6/6 IT is still open; the TF1 scenario showed no significant difference between the two IT strategies, while the TF2 scenario shows 3/3 IT is significantly better than 3/3 IT. The 6/6 IT strategy would presumably cost considerably less to implement, and experience fewer barriers to implementation and uptake than the 3/3 IT strategy. However, which strategy will work better in any given population likely depends on the average frequency of testing in that population.

The IT strategies are both being considered by the California Department of Health (Dan Wohlfeiler, personal communication). Our work suggests that these IT interventions have much prevention potential, and they should be utilized. Currently, the "Find Your Frequency" campaign in Washington state allows MSM to sign up for 3-monthly or 12-monthly reminders (via text messages) to test for HIV. Yet, this intervention is different from the IT interventions we consider because they require risk assessment (and consequent testing) to dynamically occur. The success of these IT interventions is contingent upon such continual risk assessment, and adherence to the testing regimen.

Our study has several important limitations. We did not conduct a formal cost-benefit analysis to compare these strategies; our analysis is clearly more focused on

the benefits than the costs. As we mentioned above, one potential "cost" of the IT strategies may be lower adherence since it is easier to count the number of days since the last test (especially with a periodic reminder) than the number of partners. Similarly, we do not know (through this work) what the above testing strategies will demand in terms of money, human capital and other public-health resources.

To simplify computation, in our models for IT we only counted the number of non-main partners. The preventive potential of these strategies may exceed our estimates if recommendations include counting main partners as well. A related limitation is that under the individualized testing strategies, people can potentially test an unlimited number of times (if they have a high enough number of non-main partners in a given period of time). In practice, it is likely that men may suffer from "testing fatigue" and not test more than a certain number of times in a given time period. We also did not consider dependence between risk behavior and testing behavior there is some evidence that that men may be more likely to test after an episode of risky sex.

We reiterate that the focus of this work does is not on HIV prevention via early treatment initiation (though treatment is an important component of our models, more details are in [39]. Our focus is on prevention via behavior change and we demonstrate here that knowledge of infection status may result in averting a significant number of new infections via the mechanism of PDBC. Biomedical and behavioral prevention strategies have synergistic potential, which should be further explored.

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