The Effect of Expanded Antiretroviral Treatment Strategies on the HIV Epidemic among Men Who Have Sex with Men in San Francisco

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Modeling of expanding antiretroviral treatment to all HIV-infected adults already in care in San Francisco predicts reductions in new HIV infection at 5 years of 59% among men who have sex with men. Addition of annual HIV testing for men who have sex with men to universal treatment decreases new infections by 76%.

A model of annual testing and immediate initiation of antiretroviral therapy (ART) in South Africa predicted a dramatic reduction in incidence of HIV infection [1]. In response, critics highlighted the practical applicability of such an approach in South Africa, and the debate about the optimum timing of ART initiation continues. In San Francisco, which has a generalized epidemic among men who have sex with men (MSM; 24% prevalence), challenges exist but are far less significant than those in South Africa. More than 72% of MSM report annual testing, and >85% of MSM are aware of their HIV status. Linkage to primary care is high (88%) even among individuals who receive a diagnosis at a public health clinic [2]. Of most significance, the San Francisco Department of Public Health estimates that 78% of all known HIV-infected persons were receiving care in 2008 [3]. With the public health resources and political will to support wide availability of antiretroviral medications, including Healthy San Francisco, a city-wide public health insurance safety net, high population-level rates of virologic suppression are achievable. In the context of this setting and early 2009 guidelines for starting ART at CD4 cell counts <350, we sought to determine the potential impact on incident HIV infection in the MSM population of offering ART to all patients in care—a strategy that maximizes the individual and public health benefit for those already receiving care without requiring additional investment in outreach and expanded HIV testing.

METHODS

We developed an ordinary differential equation simulation model for HIV testing and treatment among MSM in San Francisco extending previous models [1, 4, 5]. We tested 3 ART expansion strategies: (1) treatment of all individuals currently receiving HIV care with CD4 cell counts <500 cells/mm^3; (2) treatment of all individuals receiving care; and (3) intensified annual HIV testing combined with treatment of all HIV-infected persons (the full test-and-treat strategy). Inputs to the model were based on comprehensive surveillance information on prevalence and incidence of HIV infection, testing rates, and treatment outcomes data available for San Francisco from the local health department and electronic patient databases of the San Francisco General Hospital outpatient HIV treatment clinics that contain information on 95% of individuals known to be HIV infected in San Francisco [6]. We stratified the population of MSM according to risk groups, HIV status, CD4 cell count group, and treatment, as follows. We classified individuals as either uninfected or infected. Infected men, in turn, are classified according to the untreated nadir CD4 cell count into 1 of 4 stages: CD4 cell count >500 cells/mm^3, CD4 cell count of 350–500 cells/mm^3, CD4 cell count of 200–350 cells/mm^3, and CD4 cell count <200 cells/mm^3. Individuals in the model may (1) have unknown serostatus and not be receiving treatment; (2) have known HIV infection but not receiving ART; (3) be receiving ART but not yet achieved suppression; or (4) be receiving long-term antiretroviral therapy. Eighty percent of individuals receiving long-term therapy were assumed to have achieved durable virological suppression. Untreated

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individuals progress forward through successive HIV stages according to rates estimated from previous studies [7]. Individuals who have achieved virologic suppression proceed through nadir CD4 cell count stages at a slower rate (zero in the baseline scenario). Individuals in either the short-term incomplete suppression classes have ongoing HIV progression through stages at a rate intermediate between the untreated and completely suppressed groups. The mean time between initiation of therapy and achievement of full suppression was 3 months.

Individuals with complete or incomplete suppression may stop therapy at rates estimated from observed fractions of therapy (mean of ~1% per year). The rate of starting therapy (or restarting therapy) depends on the HIV stage. Individuals with a CD4 cell count <200 are assumed to start therapy with a mean waiting time of 3 months. The time to initiation of therapy for individuals in other stages is assumed to be 3 months when a test-and-treat program has been initiated and is longer otherwise. The rate of stopping therapy was higher for individuals with incomplete suppression than for individuals with complete virological suppression. Finally, individuals undergo HIV testing at a rate of 1 test per 3 years in the absence of a treatment program (and, thus, transition from unknown status to known status) at this rate.

We assumed 2 risk groups (high and low) distinguished by more unprotected contacts per unit time. The transmission probability per uninfected contact was assumed to be 0.1[8]. Eighty percent of the population was assumed to be in the low-risk group. The transmission probability was assumed to be lower if the infected person was receiving treatment; we assumed 20% relative transmission for infected persons with incomplete virological suppression and 1% for persons with complete virological suppression [9]. We assumed nonrandom mixing between the high- and low-risk groups, with a mixing parameter of 0.6 (0 for completely random mixing to 1 for completely positive assortative [like only with like] mixing). The number of contacts per unit time and the mixing parameter were chosen to give a prevalence of 0.24 in 2007, in agreement with data. Finally, the total population at risk was assumed to be 67,000 and the mean sexually active residence time to be 30 years [4].

We performed sensitivity analyses on key variable inputs to assess model results variability by repeating model runs with inflated and deflated inputs for single variables chosen from the range of likely values as estimated from the literature and clinic databases. Change in model results were evaluated by calculating percent change in reduction in new HIV infections.

RESULTS

All 3 expanded ART strategies resulted in reduction of predicted prevalence of HIV infection and new HIV infections, compared with the 2008–2009 standard of care of starting ART for HIV-infected persons with CD4 cell counts <350 cells/mm^3 (see Table 1). Significant reductions in new HIV infections were predicted in as early as 5 years from the implementation of expanded ART for all 3 strategies. The test-and-treat all strategy had the largest effect of the 3 expanded ART strategies, eventually doubling the number of new HIV infections averted, compared with the least ambitious strategy. However, significant gains in averting new HIV infections were seen for both of the expanded ART strategies (<500 and treat all) that involved changing ART initiation practices without implementing additional HIV testing and linkage to care programs. The model does not predict elimination of the HIV epidemic among MSM in San Francisco (reduction of prevalence and incidence of HIV infection to negligible or zero levels). However, at 20 years, the test-and-treat strategy predicts reduction in prevalence of HIV infection among MSM in San Francisco from 26.2% to 12.8%, greater than reducing the prevalence of HIV infection by half in the absence of changes in 2008–2009 ART practices.

The model was most sensitive to assumptions of the effectiveness of ART in reducing HIV transmission probabilities. A reduction in the effectiveness of ART in reducing HIV transmission from 99% to 90% resulted in a >30% reduction in the percentage of new HIV infections averted over 20 years. The model was less sensitive to changes in the proportion of individuals who are able to achieve virological suppression, with a 10% decrease in the proportion achieving suppression resulting in a <10% decrease in the percentage of new infections averted. Other model input parameters evaluated in sensitivity analyses (treatment cessation rates, mortality rates, infectiousness with incomplete viral suppression, testing rates, and the proportion in the high-risk group) demonstrated similar relative effects between the strategies over the range of likely values.

DISCUSSION

San Francisco is one of the original epicenters of the HIV epidemic and remains the site of one of the largest concentrated epidemics of HIV infection in the United States, with a 24% prevalence among MSM, exceeding levels reported in other concentrated epidemics, such as MSM in New York City and African-American men in Washington, DC [10]. Despite advancements in treatment and expanded outreach efforts, ~600 incident HIV infections occurred in San Francisco in 2008 [11]. New strategies of combination prevention that include both behavioral and biomedical interventions are thus needed [12].

Our model demonstrates that expansion of ART to those already in care with CD4 cell counts <500 cells/mm^3 or at any

Table 1. Model Results

Year	Prevalence of HIV infection, %			
	Baseline CD4 cell count <350 cells/mm^3	ART initiation, CD4 cell count <500 cells/mm^3	Treat all in care	Test-and-treat all
2009	24.7	24.7	24.7	24.7
2014	25.1	22.9	21.9	20.9
2019	25.5	21.7	19.4	17.5
2029	26.2	21.8	17.1	12.8
New HIV infections since 2009	Baseline (CD4<350)	ART start CD4<500	Treat all in care	Test-and-treat all
2014	3703	2149	1534	893
2019	7446	4344	2896	1406
2029	14,960	10,020	6739	2771
HIV Infections Averted*		ART start CD4<500	Treat all in care	Test-and-treat all
2014	Reference	1554	2169	2810
2019	Reference	3102	4550	6040
2029	Reference	4940	8221	12,189
Percent reduction in new HIV infections[a]	Reference	ART start CD4<500	Treat all in care	Test-and-treat all
2014	Reference	42	59	76
2019	Reference	42	61	81
2029	Reference	33	55	81

[a] HIV infections averted and percent reduction in new infections are relative to 2009 model estimates. Expansion of ART treatment strategies are assumed to start in 2009.

CD4 cell count is likely to significantly reduce the number of future HIV infections. Further reductions could be gained by the addition of routine annual testing and linkage to care. These findings extend other models of San Francisco and Vancouver by anchoring the analysis to empirical data regarding engagement in care and the new Department of Health & Human Services (DHHS) guidelines for ART initiation [13].

It is instructive to contrast our findings to those of a recent modeling analysis of the HIV epidemic in Washington, DC. Our model predicts greater reductions in new HIV infections, compared with analysis from Washington, DC. Although the deterministic model with its inherent limitations differed from the stochastic simulation model used by Walensky et al may have contributed to these differences, the critical difference is that only 50% of persons in the DC model are linked to care after a positive HIV test result [14]. Indeed, these authors and other modeling reports from South Africa emphasize the importance of linkage to care as a limiting factor in ART expansion strategies reducing incident HIV infections [15]. When the DC model includes nearly complete linkage to care, results of the models converge. Testing and linkage to care are appropriately one of the highest public health priorities in populations with high prevalence worldwide. In San Francisco, with the high rates of HIV testing and linkage to care, we have the opportunity to reduce HIV transmission by expanding ART to those already receiving care while we determine the most cost-effective approaches to further expand testing.

Of importance, realization of the prevention benefits of expanded ART strategies depend on a number of components. Retention in care and expanded financial, clinical, social, and structural adherence and support measures for treatment, including specific support for psychiatric and substance use comorbid conditions, and addressing homelessness and marginal housing all need to be components of the strategy in a city such as San Francisco. Also of concern is the potential for changes in behavior among MSM leading to increased transmission risk, thereby offsetting any potential gains and the specter of drug-resistant strains of HIV. However, these obstacles are not insurmountable, as evidenced by the recent public health commitment and movement to universal ART and a comprehensive, multi-level HIV prevention strategy in San Francisco [16]. It is possible that such strategies are comparatively cost-effective and should be evaluated as data become available. Of note, there is little observed evidence of significant increases in HIV transmission risk behavior [9], and contrary to recent modeling exercises, transmitted drug resistant HIV strains have remained stable or even decreased in San Francisco and in similar cities, such as Vancouver, where ART has rapidly expanded [17–19].

Modeling of complex phenomena, such as a local HIV epidemic and making cogent predictions about the future, are subject to numerous limitations. In essence, modeling is

a thought experiment, informed by data, but subject to the validity and completeness of the model's internal structures. The model presented here while able to recapitulate the observed HIV epidemic in San Francisco from its beginning with high fidelity does not specifically model the impact of acutely HIV-infected persons, which may be a significant driver of new HIV infections or account for perturbations arising from HIV drug resistance which may affect virological suppression rates; however, the sensitivity analyses performed indirectly address these issues by varying the reach of HIV testing and ART effectiveness in producing viral suppression.

In conclusion, our projections suggest that ensuring HIV-infected patients in San Francisco already receiving care are offered ART would significantly reduce the incidence of HIV infection in San Francisco. These predictions are supported by recent surveillance data from San Francisco and Vancouver that show decreasing rates of new HIV infections that correlate with ART expansion and lower community viral load [20, 21]. With new national and San Francisco Health Department ART guidelines supporting treatment for most HIV-infected persons for their individual health, secondary benefits of reducing HIV transmission could be realized if adequate support for care delivery are in place.

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References

1. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet **2009**; 373:48–57.
2. Zetola NM, Bernstein K, Ahrens K, et al. Using surveillance data to monitor entry into care of newly diagnosed HIV-infected persons: San Francisco, 2006–2007. BMC Public Health **2009**; 9:17.
3. HIV/AIDS Statistics and Epidemiology Section. HIV/AIDS Epidemiology Annual Report 2008. San Francisco: San Francisco Department of Public Health, 2009.
4. Blower SM, Gershengorn HB, Grant RM. A tale of two futures: HIV and antiretroviral therapy in San Francisco. Science **2000**; 287:650–4.
5. Dodd PJ, Garnett GP, Hallett TB. Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings. AIDS **2010**; 24:729–35.
6. HIV/AIDS Statistics and Epidemiology Section. HIV/AIDS Epidemiology Annual Report 2008. San Francisco: San Francisco Department of Public Health, 2009.
7. Schechter MT, Le N, Craib KJ, Le TN, O'Shaughnessy MV, Montaner JS. Use of the Markov model to estimate the waiting times in a modified WHO staging system for HIV infection. J Acquir Immune Defic Syndr Hum Retrovirol **1995**; 8:474–9.
8. Grant RM, Wiley JA, Winkelstein W. Infectivity of the human immunodeficiency virus: estimates from a prospective study of homosexual men. J Infect Dis **1987**; 156:189–93.
9. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. Lancet **2010**; 375:2092–8.
10. El-Sadr WM, Mayer KH, Hodder SL. AIDS in America–forgotten but not gone. N Engl J Med **2010**; 362:967–70.
11. Scheer S, Chin CS, Buckman A, McFarland W. Estimation of HIV incidence in San Francisco. AIDS **2009**; 23:533–4.
12. Coates TJ, Richter L, Caceres C. Behavioural strategies to reduce HIV transmission: how to make them work better. Lancet **2008**; 372:669–84.
13. Department of Health & Human Services (DHHS). Panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 2010:1–161.
14. Walensky RP, Paltiel AD, Losina E, et al. Test and Treat DC: Forecasting the Impact of a Comprehensive HIV Strategy in Washington DC. Clin Infect Dis **2010**; 51:392–400.
15. Charlebois ED, Havlir DV. "A bird in the hand": a commentary on the test and treat approach for HIV. Arch Intern Med **2010**; 170:1354–6.
16. Okie S. Fighting H.I.V., a community at a time. New York Times, 2009. October 26 2009.
17. Blower S, Volberding P. What can modeling tell us about the threat of antiviral drug resistance? Curr Opin Infect Dis **2002**; 15:609–14.
18. Jain V, Pilcher C, Deeks S, et al. Increasing prevalence of NNRTI-associated drug-resistance mutations in patients with acute, early HIV in San Francisco. 16th Conference on Retroviruses and Opportunistic infections. Boston: Massachusetts, 2009.
19. Gill VS, Lima VD, Zhang W, et al. Improved virological outcomes in British Columbia concomitant with decreasing incidence of HIV type 1 drug resistance detection. Clin Infect Dis **2010**; 50:98–105.
20. Das M, Chu PL, Santos GM, et al. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. PLoS One **2010**; 5:e11068.
21. Montaner JS, Lima VD, Barrios R, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. Lancet **2010**; 376:532–9.