Evaluating HIV prevention strategies for populations in key affected groups: The example of Cabo Verde

International Journal of Public Health

João Filipe G. Monteiro[a,b], Sandro Galea[c], Timothy Flanigan[b], Maria de Lourdes Monteiro[d], Samuel R. Friedman[e], Brandon DL Marshall[a]

a. Department of Epidemiology, Brown University School of Public Health, 121 South Main Street, Box G-S-121-2, Providence, RI, 02912, USA.

b. Division of Infectious Diseases, The Miriam Hospital, 1125 North Main Street, Providence, RI, 02906, USA.

c. Department of Epidemiology, Columbia University Mailman School of Public Health, 722 West 168th Street, Room 1508, New York, NY, 10032 USA.

d. Ministério da Saúde, Palácio do Governo, Praia, Ilha de Santiago, C.P. 47, Cabo Verde.

e. The Institute for Infectious Disease Research, National Development and Research Institutes, Inc., 71 West 23rd Street, 8th Floor, New York, NY, 10010, USA.

Email address of the corresponding author: filipemuks@gmail.com

HIV conceptual network model

The conceptual framework (Figure S1) shows the interdependent pathways of action among the simulated interventions, which we hypothesize act synergistically to decrease HIV incidence in the agent population. As shown in Figure S1, eligible HIV-infected agents who access VCT can initiate antiretroviral therapy (ART). Studies have indicated that early initiation of ART can effectively eliminate HIV transmission between serodiscordant partners by suppressing viral load (Cohen et al. 2011; Donnell et al. 2010; Montaner et al. 2010). HIV-positive agents who initiate ART are also less likely to progress to AIDS (Egger et al. 2002; Marks et al. 2005; Mocroft et al. 2003). Additionally, drug-using agents can enroll in substance abuse treatment, which increases the probability of initiating ART (Sorensen and Copeland 2000).

Between 1986 and 2010, 3,328 cases of HIV were reported to the PNLS and CCS-SIDA, of which 1,339 progressed to AIDS diagnosis, resulting in 787 recorded deaths. Modern highly ART was first introduced in Cabo Verde in December 1, 2004, and in 2010 the ART coverage (i.e., the percentage of known HIV-positive patients eligible for therapy that were reported to have received ART) was estimated to be 71.9% (UNAIDS 2012). The DOHCV guarantees universal and free access to ART to all eligible HIV-positive patients. Patients are considered eligible to initiate treatment according with the following DOHCV guidelines: (1) ART is recommended for all HIV-infected individuals who present with AIDS symptoms; or (2), asymptomatic HIV patients recommendations vary by pretreatment CD4 T lymphocyte (CD4) cell count and plasma HIV RNA (ribonucleic acid) viral load, as follows: treat all patient with CD4 <200 cells/mm^3, and considerer treatment based on patient motivation if CD4 is greater than 200 cells/mm^3 and less than 350 cells/mm^3. Finally, patients with CD4>350 cells/mm^3 should be treated if the plasma RNA levels are greater than 30,000 copies/mL, otherwise treatment should be delayed.

Table S2 shows the relationship between adherence to ART, the per-partnership annualized probability of HIV transmission between serodiscordant agents, and progression to AIDS. Based on a study by Bangsberg et al. (2000), which showed a highly correlated and approximately linear relationship between adherence to HIV therapy and $\log_{10}$ viral load, we modeled the effect of ART on probability of HIV disease transmission at the individual level (i.e., accounting for the relationship among adherence, viral load, and per-event HIV transmission).

Partnership formation

The model assumes that the status (e.g., HIV disease stage) of each agent i, $i = 1, \cdots, N$ is updated on an annual time-step t, $t = 1, \cdots T$, following pre-programmed rules and interactions with other agents, $1, \cdots, i-1, i+1, \cdots, N$. In the network, given an agent i, the number of (sexual and/or drug using) partnerships with other agents at time-step t (i.e., $k_{i,t}$), follows a negative binomial (NB) distribution for all agents per time step, $k_{i,t} \sim NB(p, r)$, where partners are acquired with probability p until r suitable partners are found (see Tables 2 and 3). This model for partnership formation and resulting partner distributions reflect empirical behavior and data observed in previously conducted sexual and drug-using network studies (Friedman et al. 1999; Latkin et al. 2003).

Partnership formation occurs when two agents are both drug users or if they are from opposite gender. The assortative mixing (i.e. sexual and/or drug using partnerships among people with similar risk for acquiring HIV), has been incorporated by weighting the probability of each contact to favor the formation of links between agents with similar characteristics. For PWUD, 58% are connected solely with PWUD.

In order to avoid overestimation of the partnership turnover or underestimation of the

partnership duration that may result from randomly re-assigning all (*k*) links at each new time step, we developed the following algorithm that describe the process of partnership formation and dissolution: at each subsequent time step, partners are added or removed from the index agent's network according to the difference between the total number of partners in the previous time step and the new time step. For instance, if an agent *i* had *k*=2 partners in time step *t=1* and *k*=4 partners are drawn for the agent at the beginning of time step *t=2*, then agent i adds two new agents to the four she/he is already connected to. On the other hand, if only *k*=1 partner is drawn for the index agent at time step *t=2*, then the agent looses one of the two links in its network at random. This process continues sequentially through the list of agents so that the population's degree distribution is updated iteratively.

The people who use drugs' and female sex workers' risk network

The principal illicit drugs consumed in Cabo Verde are marijuana, followed by crack, and hashish. In general, the drugs are smoked, snorted or chewed, although a small proportion reported injection drug use. According to a recent survey, injecting drug users represented only 1.7% of the PWUD population in Cabo Verde, and only 2 cases of HIV infection were attributed to injection drug use in 2010 (Monteiro and Sylva 2011). Therefore, we did not include a separate class of agents that are injecting drug users. In recent years, with growing tourism and immigration from the Economic Community Of West African States (ECOWAS), the FSW population in Cabo Verde has increased substantially (Monteiro and Sylva 2011). In Cabo Verde, PWUD receive support from local non-profit organizations and from the Department of Health of Cabo Verde, through universal healthcare system care centers that provide referrals to substance abuse treatment centers (Monteiro and Sylva 2011). The centers follow the Minnesota model (Cook 1988) to treat substance abuse.

This approach has abstinence as the principal objective, and is typically characterized by a thorough and ongoing assessment of all aspects of the patient and of multimodal therapeutic approaches, which includes a multidisciplinary team of professionals (e.g., counselors, psychologists, nurses). In Cabo Verde, this treatment is employed on a 9-month inpatient and 3-month outpatient basis.

Figure S2 shows the simulated Cabo Verde HIV population network structure at model initialization, for a random subsample of 1,000 agents; stratified by drug use, HIV status, sex and female sex workers (FSW) activity. We observed a large number of dendritic (linear chains of connections between nodes) and cyclic (multiple pathways between network members) microstructures, which are common characteristics of drug-using networks (as seen among PWUD in New York city by Friedman et al. (1999) and in Colorado Potterat et al. (2002)), and sexual networks in west Africa (INE et al. 2008; Sawers and Stillwaggon 2010). Moreover, a major component, with a cluster of PWUD and FSW, is seen in the individual-based model risk network, which includes agents who act as a "bridge" between smaller components and the central core.

Sensitivity analyses

The individual-based model was coded in PYTHON™ (version 2.7.2), an open-source programming language (van Rossum and Drake 2001), and all analyses were conducted using a Beowulf supercomputing cluster. The simulation's performance among non-drug users and PWUD was tested in the following three scenarios:

a) per-contact rate of HIV transmission during unprotected intercourse was increased by 25% and 50%, and decreased by 25% among all agents;

b) annual probability of progression to AIDS among HIV-positive agents naïve to therapy and on ART (across all adherence strata) is increased by 25% and 50%, and decreased by 25% among all agents;

c) annual probability of sexual risk behavior is not increased/decreased among all HIV-positive agents, 25% increase among HIV-positive agents, and decreased by 25% among all agents.

Figure S3 shows a series of tests in which different sets of parameter values were varied and their influence on the simulated HIV transmission dynamics among Cabo Verde population described. Overall, the individual-based model produced reasonable results for the three test scenarios and demonstrated analogous changes for the non-drug users population and PWUD agents. The model was more sensitive when the per-contact rate of HIV transmission during unprotected intercourse was scaled up by 50% among agents, with gain of 57% and 51% for HIV incidence among non-drug users and PWUD respectively, when compared with the *status quo*. The individual-based model was least sensitive in test scenario showed in Panel b), with maximum gain in HIV incidence of 3% (among non-drug users) and 5% (among PWUD).

We performed additional sensitivity analyses in transmission probabilities during the acute phase assuming higher and lower acute stage infectivity (30 and 3 times higher than the latent stage, respectively). The results in HIV incidence showed that the individual-based model is sensitive in the difference between transmission probabilities in acute and latent phases. Therefore, the effect of changing acute phase probabilities does not influence which sets of interventions performed best, and consequently the interpretation of the results.

Table S1 Hypothetical HIV prevention strategies evaluated using the Cabo Verde individual-based model, in Cabo Verde at year 2010

Strategy	Rate of HIV testing	Rate of condom usage	Rate of initiating SA treatment	Rate of discontinuing SA treatment	Rate of initiating ART	Likelihood of achieving ≥90% ART adherence	Rate of discontinuing ART
***Status quo* (1)**	% of population tested per year: 15.0% of non-drug users 14.0% of PWUD 27.0% of FSW	% of condom usage per year: 59.0% of non-drug users 55.6% of PWUD 55.3% of FSW	9.2% of PWUD population initiates SA treatment per year	14.6 % of PWUD in SA treatment discontinue treatment per year	% of HIV^+ population initiates ART per year: 40.0% of non-drug users 8.0% of PWUD (14.0% among those in SA treatment) 30.0% of FSW	% of HIV^+ on ART achieve ≥90% adherence: 73.5% of non-drug users 50.0% of PWUD (73.5% among those in SA treatment) 50.0% of FSW	% of HIV^+ on ART discontinue therapy per year: 17.8% of non-drug users 25.0% of PWUD (15.0% among those in SA treatment) 25.0% of FSW
Increase HIV testing (2)	% of population tested per year: 30.0% of non-drug users 28.0% of PWUD 54.0% of FSW	Same as *status quo* strategy	Same as *status quo* strategy	Same as *status quo* strategy	Same as *status quo* strategy	Same as *status quo* strategy	Same as *status quo* strategy
Increase condom distribution (3)	Same as *status quo* strategy	% of condom usage per year: 78.5% of non-drug users 74.0% of PWUD 73.8% of FSW	Same as *status quo* strategy	Same as *status quo* strategy	Same as *status quo* strategy	Same as *status quo* strategy	Same as *status quo* strategy
Increase SA treatment (4)	Same as *status quo* strategy	Same as *status quo* strategy	18.4% of PWUD population initiates SA treatment per year	7.3% of PWUD in SA treatment discontinue treatment per year	Same as *status quo* strategy	Same as *status quo* strategy	Same as *status quo* strategy
Scale-up early HIV treatment and optimization of care (5)	Same as *status quo* strategy	Same as *status quo* strategy	Same as *status quo* strategy	Same as *status quo* strategy	% of HIV^+ population initiates ART per year: 80.0% of non-drug users 16.0% of PWUD (28.0% among those in SA treatment) 60.0% of FSW	% of HIV^+ on ART achieve ≥90% adherence: 97.8% of non-drug users 66.5% of PWUD (97.8% among those in SA treatment) 66.5% of FSW	% of HIV^+ on ART discontinue therapy per year: 8.9% of non-drug users 12.5% of PWUD (7.5% among those in SA treatment) 12.5% of FSW
Combination prevention (6)	Same as increase HIV testing strategy	Same as increase condom distribution	Same as increase SA treatment strategy	Same as increase SA treatment strategy	Same as improve ART strategy	Same as improve ART strategy	Same as improve ART strategy

Abbreviations: ART – antiretroviral therapy; PWUD – people who use drugs; SA – substance abuse; FSW – female sex workers

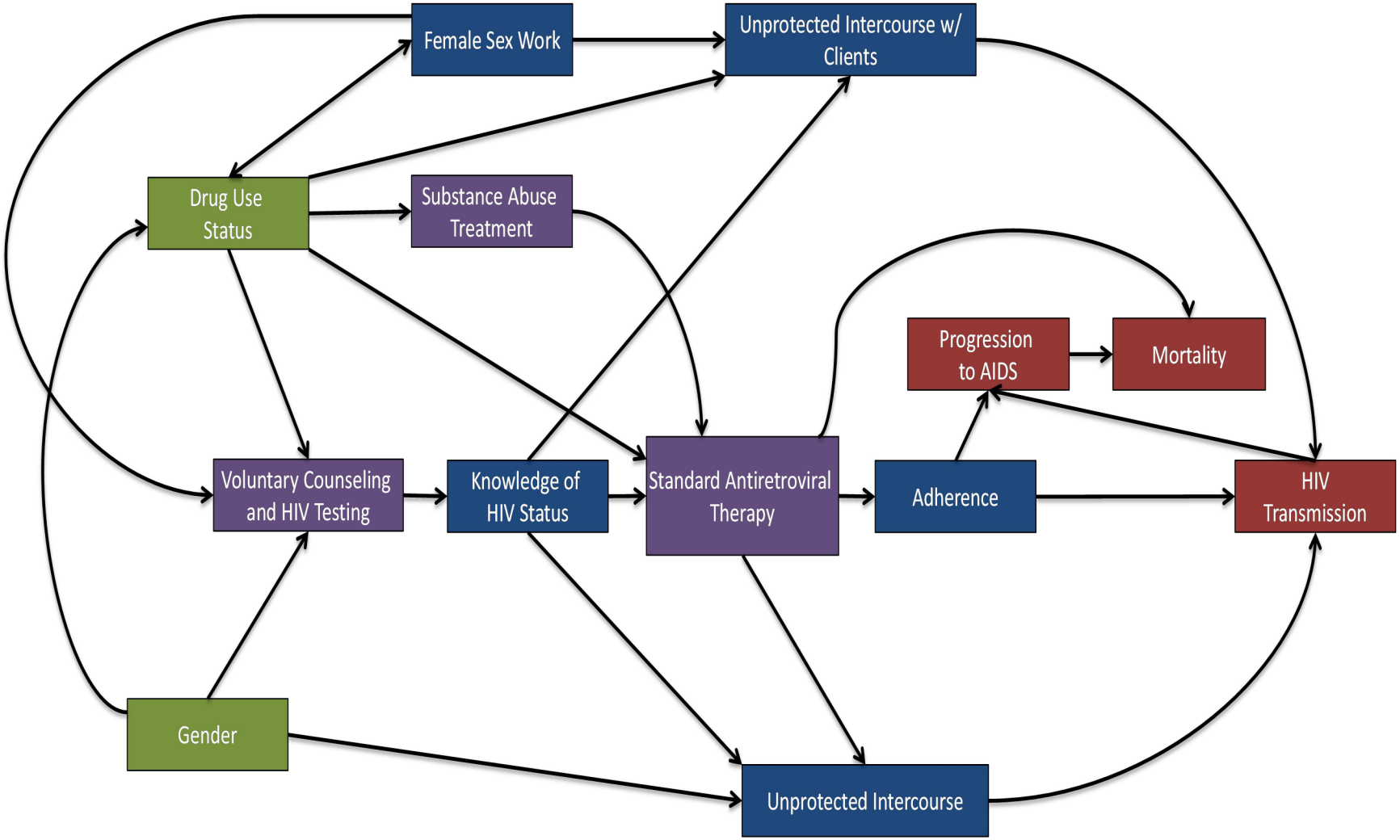
Table S2 Relationship between adherence to ART, per-act risk of HIV transmission between serodiscordant agents (heterosexual male, heterosexual female, female sex workers), and progression to AIDS, in Cabo Verde at year 2010

Variable	Base Estimate	Source
Progression to AIDS (annual probability)		(Bangsberg et al. 2001; CASCADE Collaboration 2003)
Not on ART	0·100	
0% – 29% adherent to ART	0·100	
30% – 49% adherent to ART	0·082	
50% – 69% adherent to ART	0·064	
70% – 89% adherent to ART	0·046	
≥90% adherent to ART	0·010	
Risk of infection per sex act (latent phase)		(Bangsberg et al. 2000; Gray et al. 2001; Quinn et al. 2000)
Not on HAART	0.0196	
0% – 29% adherent to HAART	0.0196	
30% – 49% adherent to HAART	0.0158	
50% – 69% adherent to HAART	0.0079	
70% – 89% adherent to HAART	0.0040	
≥90% adherent to HAART	0.0004	(Hughes et al. 2012)
Increase in per-act risk of infection during acute phase[a]	4·3	

Abbreviations: AIDS – acquired immunodeficiency syndrome; ART – antiretroviral therapy; HIV – human immunodeficiency

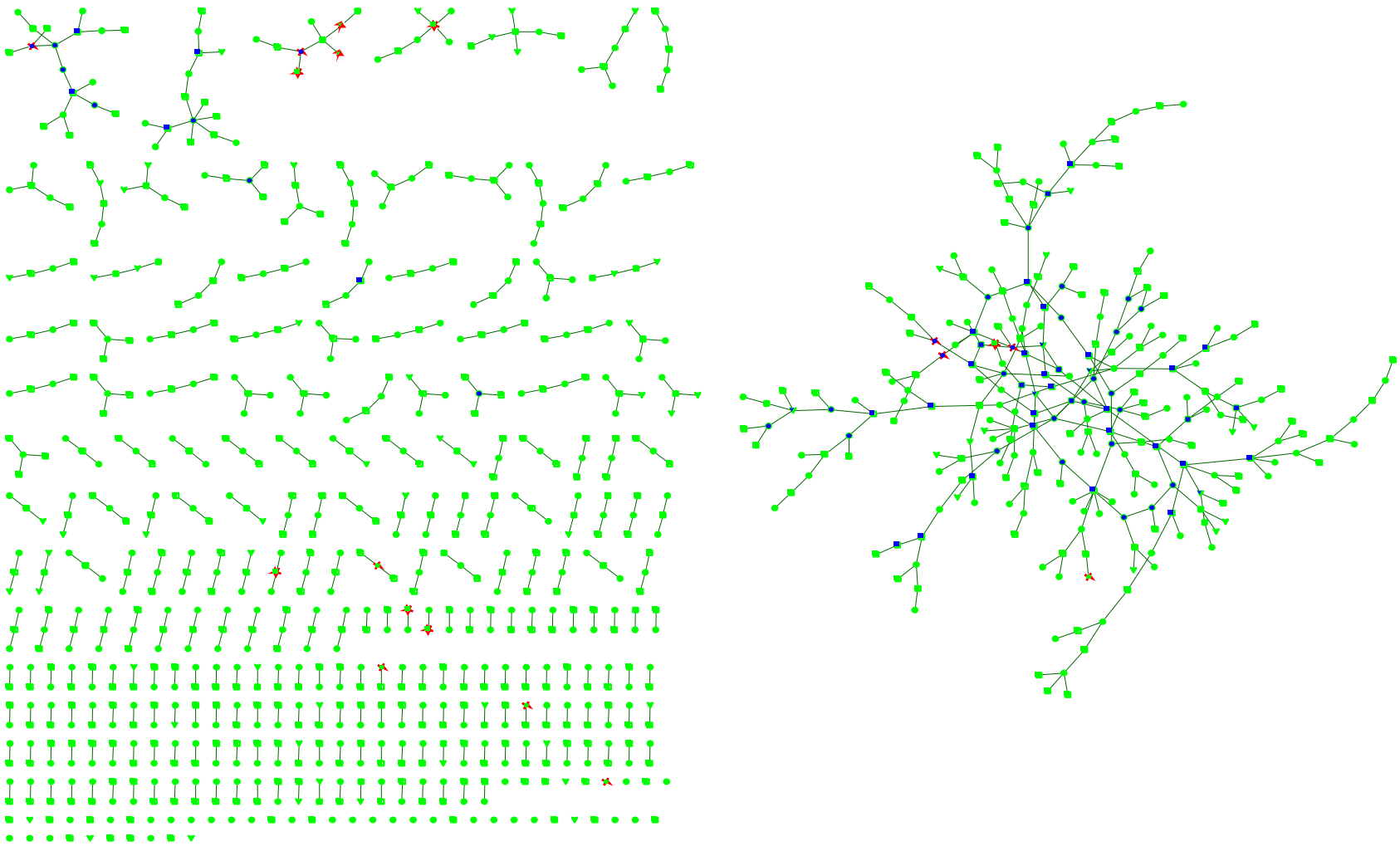
Notes: a – acute phase defined as the first year following seroconversion

Fig. S1 Conceptual framework of the HIV transmission individual-based model, in Cabo Verde at year 2010



Legend**:** Arrows represent causal effects between two phenomena in the model. For example, accessing voluntary counseling and HIV testing increases an agent's probability of HIV testing, which can result in both the knowledge of an HIV-positive status and initiation of antiretroviral therapy. **Green** boxes represent agent characteristics, **blue** boxes represent agent behaviors, and **purple** boxes represent interventions that influence these behaviors. **Red** boxes represent model outputs. Adapted from Marshall et al. (2012)

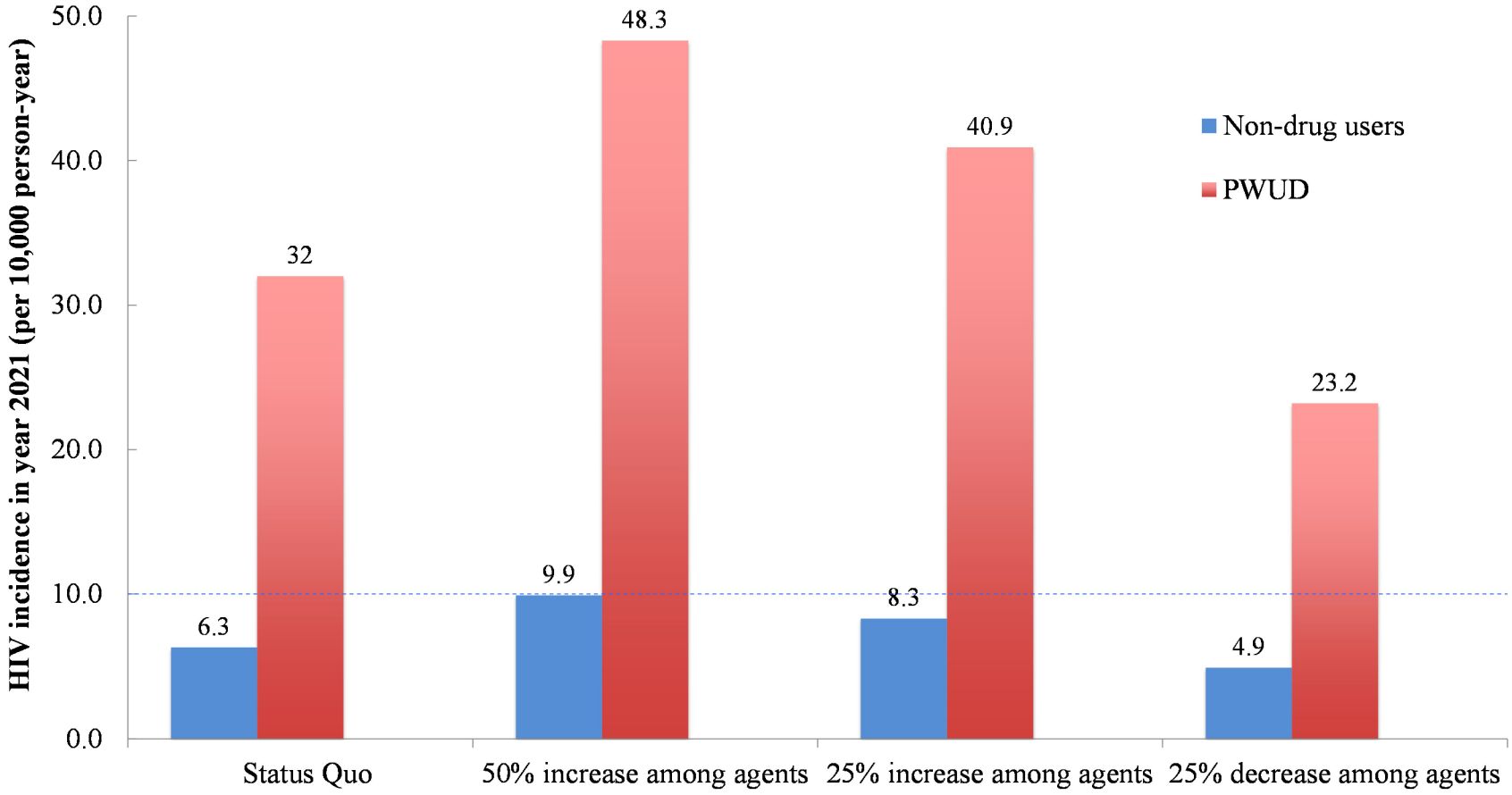
Fig. S2 Simulated Cabo Verde HIV population network structure at model initialization of a representative subsample of 1000 agents, stratified by drug use and HIV status (color) and gender (shape), in Cabo Verde



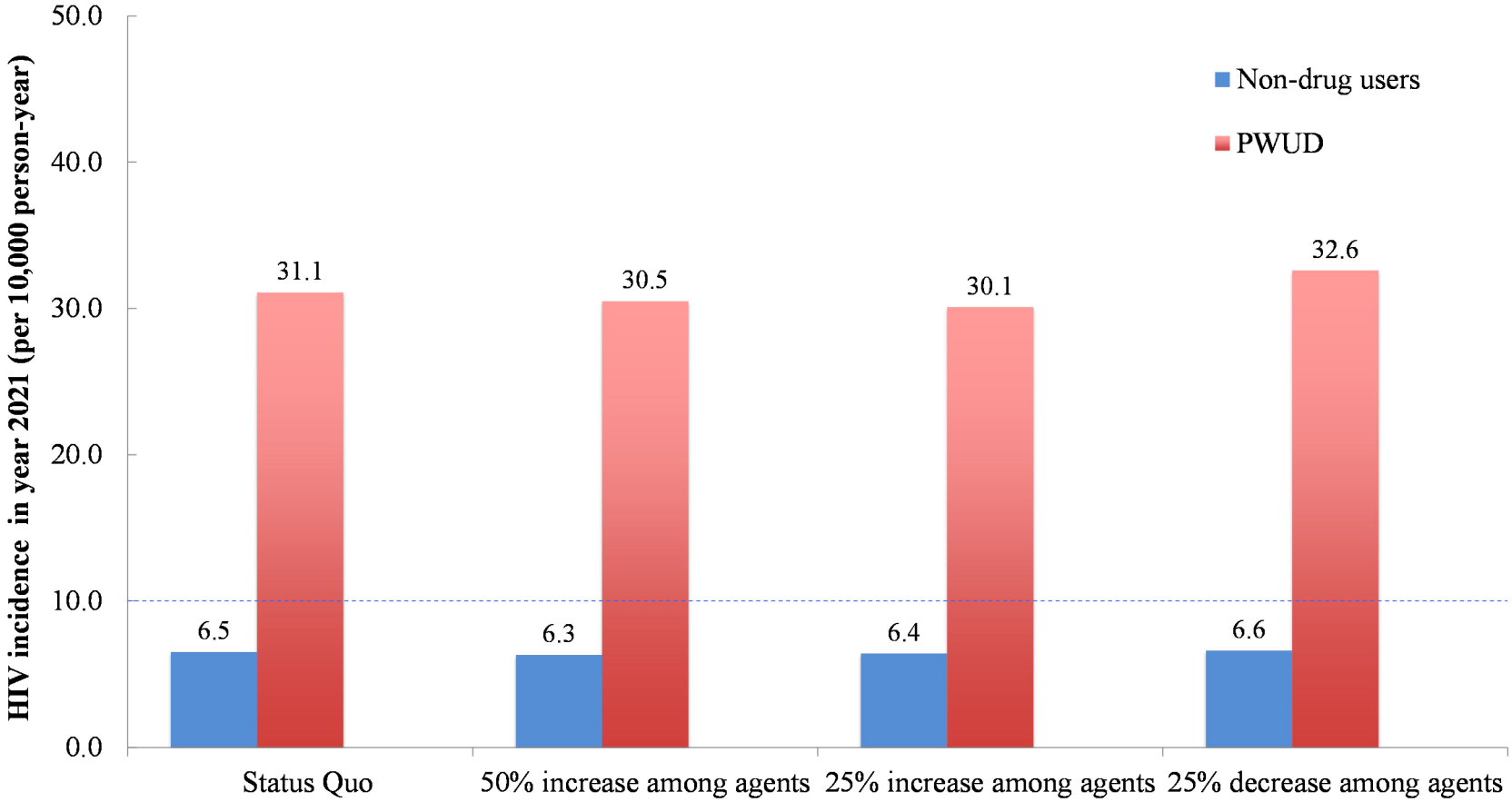
Legend: HIV-positive (red); people who use drugs (blue); non-drug users (green); heterosexual male (square); heterosexual female (circle); Female sex workers (inverted arrow). Links indicate heterosexual intercourse/drug usage activity between two agents.

Fig. S3 Sensitivity analysis of projected HIV incidence (per 10,000 person years) in 2021 among the non-drug users adult Cabo Verde population and the drug-using population, for various scenarios

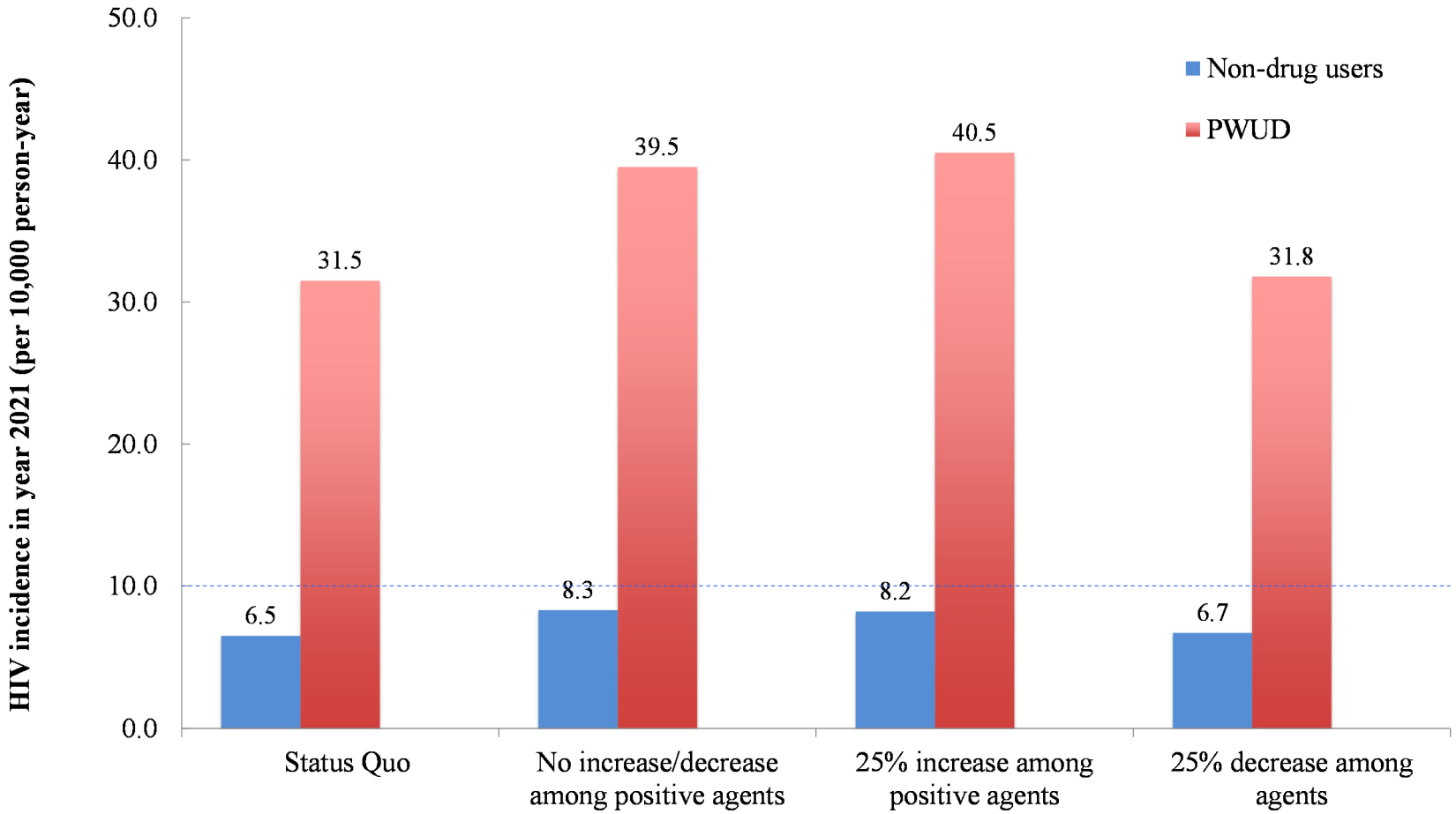
Panel a



Panel b


HIV incidence in year 2021 (per 10,000 person-year)
50.0
40.0
30.0
20.0
10.0
0.0
Non-drug users
PWUD
31.1
30.5
30.1
32.6
6.5
6.3
6.4
6.6
Status Quo
50% increase among agents
25% increase among agents
25% decrease among agents

Panel c



Note: a) Increase/decrease in the per-contact rate of HIV transmission during unprotected intercourse; b): Increase/decrease in the annual probability of progression to AIDS among HIV positive agents naive to therapy and on ART (across all adherence strata); c) Increase/decrease in the annual probability of sexual risk behavior

Abbreviations: AIDS – acquired immunodeficiency syndrome; ART – antiretroviral therapy; HIV – human immunodeficiency virus; Dashed line indicates "HIV elimination phase" (less than 10 cases per 10,000 per year), as defined by Granich et al. (2009)

REFERENCES

Bangsberg DR, Hecht FM, Charlebois ED, et al. (2000) Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. AIDS 14:357-366

Bangsberg DR, Perry S, Charlebois ED, et al. (2001) Bangsberg DR, Perry S, Charlebois ED, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. AIDS 15:1181-1183

CASCADE Collaboration (2003) Determinants of survival following HIV-1 seroconversion after the introduction of HAART. Lancet 362:1267-1274

Cohen MS, Chen YQ, McCauley M, et al. (2011) Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 365:493–505

Cook CCH (1988) The Minnesota Model in the management of drug and alcohol and drug dependency: miracle, method or myth? Part I. The Philosophy and the Programme. Br J Addict 83(7):735-748

Donnell D, Baeten JM, Kiarie J, et al. (2010) Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. Lancet 375:2092–2098

Egger M, May M, Chêne G, et al. (2002) Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet 360:119-129

Friedman SR, Curtis R, Neaigus A, Jose B, Des Jarlais DC (1999) Social Networks, Drug Injectors' Lives, and HIV/AIDS. Springer-Verlag, New York (NY)

Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG (2009) Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet 373(9657):48-57

Gray RH, Wawer MJ, Brookmeyer R, et al. (2001) Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. Lancet(357):1149-1153

Hughes JP, Baeten JM, Lingappa JR, et al. (2012) Determinants of per-coital-act HIV-1 infectivity among African HIV-1-serodiscordant couples. J Infect Dis 205:358–365

INE, Ministério da Saúde, Macro International (2008) Segundo Inquérito Demográfico e de Saúde Reprodutiva, Cabo Verde, IDSR-II, 2005 [Second Demographic and Reproductive Health Survey, Cabo Verde, IDSR-II, 2005]. Instituto Nacional de Estatística de Cabo Verde (INE) [National Statistics Institute of Cabo Verde], Calverton, Maryland, USA

Latkin CA, Forman V, Knowlton A, Sherman S (2003) Norms, social networks, and HIV-related risk behaviors among urban disadvantaged drug users. Soc Sci Med 56(3):465-476

Marks G, Crepaz N, Senterfitt JW, Janssen RS (2005) Meta-analysis of highrisk sexual behavior in persons aware and unaware they are infected with HIV in the United

States: implications for HIV prevention programs. J Acquir Immune Defic Syndr 39:446-453

Marshall BDL, Paczkowski MM, Seemann L, et al. (2012) A complex systems approach to evaluate HIV prevention in metropolitan areas: Preliminary implications for combination intervention strategies. PLoS ONE 7:e44833

Mocroft A, Ledergerber B, Katlama C, et al. (2003) Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet 362:22-29

Montaner JS, Lima VD, Barrios R, et al. (2010) Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. Lancet 376:532–539

Monteiro ML, Sylva RC (2011) Estudo Socio-comportamental e de seroprevalência do VIH/SIDA nos usários de droga/usários de drogas injectável [Socio-behavioral and seroprevalence study of HIV/AIDS in drug users tand injecting drug users]. Minstério da Saúde [Department of Health], Praia, República de Cabo Verde [Republic of Cape Verde]

Potterat J, Phillips-Plummer L, Muth S, et al. (2002) Risk network structure in the early epidemic phase of HIV transmission in Colorado Springs. Sex Transm Infect 78:i159-i163

Quinn TC, Wawer MJ, Sewankambo N, et al. (2000) Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med 342:921-929

Sawers L, Stillwaggon E (2010) Concurrent sexual partnerships do not explain the HIV epidemics in Africa: a systematic review of the evidence. J Int AIDS Soc 13(34)

Sorensen JL, Copeland AL (2000) Drug abuse treatment as an HIV prevention strategy: a review. Drug Alcohol Depend 59:17-31

UNAIDS (2012) Rapport d'activite sur la riposte au SIDA au Cap Vert [Progress report on the response to AIDS in Cabo Verde]. Comité de coordenação do combate à SIDA [Coordination Committee for the Fight Against AIDS], República de Cabo Verde [Republic of Cabo Verde]

van Rossum G, Drake FL (2001) Python Reference Manual. PythonLabs, VA