Supplementary material

Detailed description of modelling methods

To estimate the HIV prevention impact of OST in Kenya, we developed a model of injecting and sexual HIV transmission amongst PWID similar to a previous model published by the authors [1]. The model schematic is shown in figure 1 in the main text, whereas the model equations and parameter values are given below. The model divides the population into low and high risk PWID and non-PWID. Each of these is then divided into different HIV infection states as shown in Figure 1 and described later in this section – in the technical model description. PWID can either be infected by other PWID due to sexual or injection related HIV transmission, or by non-PWID due to sexual related HIV transmission. A certain proportion of PWID are assumed to be high risk and have heightened injection related risk behaviour whereas all PWID are assumed to have sexual risk. A proportion of sexual contacts are assumed to occur amongst PWID and the remainder amongst non-PWID. The non-PWID model component is not modelled explicitly but just as a prevalence of HIV and coverage of ART that varies over time.

One crucial but uncertain aspect when modelling the impact of OST in this setting is determining the likely degree to which HIV transmission among PWID is sexually driven. We estimated the extent of sexual HIV transmission occurring before PWID start injecting and assumed this same level of sexual risk throughout their injecting career. The current yearly HIV incidence due to sexual HIV transmission amongst PWID was estimated by calibrating a constant force of infection model to the possible HIV prevalence amongst newly initiated PWID, while assuming sexual debut at 17 years and initiation into injecting at 26 years [2-3]. A high HIV prevalence was assumed for new PWID in 2012, with the model assuming double the 4% HIV prevalence observed amongst individuals of similar age (25-29 years) in Nairobi at that time[2]. This heightened sexual risk amongst PWID is supported by data among PWID from Tanzania suggesting sexual risk behaviour is a strong predictor of a PWID's HIV infection [4], as well as data from Nairobi and Tanzania showing that being female is a strong predictor of PWID being HIV infected [4]. The same average incidence of sexual HIV transmission was assumed to continue throughout a PWID's injecting career, with the model's probability of sexual HIV transmission being calibrated to give this sexual related HIV incidence amongst PWID in 2012 when no injecting related HIV transmission is occurring within the model. The HIV prevalence assumed for PWID when they start injecting was also used to estimate the HIV prevalence among new initiates to injecting for recent years.

However, because HIV prevalence estimates in Kenya have been higher in the past, we also assumed new initiates to injecting had higher HIV prevalence in the past [2, 5]. Using data from three general population surveys [2], HIV prevalence trends from the UNAIDS *Epidemic* Projections Package [5] were firstly adjusted to give estimates for Nairobi by weighting them by the changing ratio difference between the HIV prevalence in Nairobi and the whole of Kenya [2], and secondly adjusted for the skewed gender distribution of PWID (17% of PWID are female and 83% male [3]) and HIV prevalence in Kenya [2]. These earlier HIV prevalence trends (shown in Supplementary figure 1) were not further increased to account for PWID possibly having higher sexual risk due to the relative agreement between these trends and the estimated HIV prevalence amongst non-injecting drug users (13%) in 2003 [6]. As well as informing HIV prevalence estimates amongst new initiates to injecting, these HIV prevalence trends were also used to give yearly specific sexual HIV incidence

estimates that were used to determine if the sexual HIV transmission probability for PWID had to be increased in previous years.

The modelled HIV epidemic amongst PWID was initiated in 1999 [7] with an initial cohort of PWID with 15% HIV prevalence to mimic the adjusted HIV prevalence of individuals aged 30-34 years in Nairobi at that time [2, 5, 8]. The sexual transmission component of the model assumes that 5.4% of PWID sexual partners are also PWID with the remainder being non-PWID [3]. The PWID sexual partners that are PWID are assumed to be randomly selected from the PWID population with some being HIV infected and on ART as defined by the model, whilst a proportion of the non-PWID sexual partners are also assumed to be HIV infected and a proportion on ART, both of which vary over time as current data suggest [5, 8] and shown in supplementary figure 1. The sexual HIV transmission probability is then calibrated as described above. The injecting HIV transmission probability was then varied to give a 20% HIV prevalence amongst PWID in 2014, as found in recent respondent driven sampling (RDS) surveys in Nairobi [3]. Little data currently exists on the level of injecting transmission risk heterogeneity amongst the PWID population in Nairobi, but because it has been shown to be important in previous model analyses [9] it was incorporated here with 25% of PWID having 3 fold higher transmission risk as found amongst PWID having insecure housing in a recent PWID survey from Tanzania [4]. However, this should be seen as exploratory and will need to be amended once Kenya specific data becomes available. The duration of injecting was assumed to be 6 years; consistent with data on the duration of current injecting in recent cross sectional surveys [3].

PWID infected with HIV are stratified into different stages, with new infections initially entering the acute high viraemia phase of infection, then progressing to the latent phase of infection, where they become eligible for ART, and then progressing to the pre-AIDS high viraemia phase of infection. Individuals in this or the previous stage of infection can be recruited on to ART where they have reduced infectivity and disease progression [10]. Conversely, the acute and pre-AIDS high viraemia stages are both associated with increased infectivity [11]. The recruitment rate of PWID onto ART was calibrated to qualitatively fit with the proportion of HIV infected PWID on ART, as estimated in current research undertaken among the co-authors of 8% in 2012, 16% in 2013, and 29% in 2014 [3]. Because the level of viral suppression amongst these PWID was low (1/25) [3], we assumed a relatively low efficacy of ART for reducing HIV infectivity of 58% as noted by a recent systematic review of observation cohorts [12], and ART extending life by 15 years [13-15]. This parameter does not affect our projections since our model assumes that PWIDs only inject for 6 years [3].

The baseline model assumes no coverage of OST, which is the national situation at the time of writing. The model was used to consider the impact of OST scaling up over 2015 to 10%, 20% or 40% of the PWID population, with OST assuming to reduce the risk of injecting related HIV transmission by 50% as found in recent systematic review [16]. We estimate the impact of this scale-up in OST on reducing HIV prevalence and incidence over 5, 10 and 20 years for both sexual HIV transmission scenarios.

Technical model description

The model stratifies the PWID population into those that are susceptible to HIV infection (stage x) and those that are HIV infected. The HIV infected population can either be in the initial high viraemia

phase of infection (stage h with average duration 1/ν), longer latent stage of low viraemia (stage y with average duration 1/γ), a short late phase of high viraemia pre-AIDS (stage a with average duration 1/η), or on ART (stage τ with average duration 1/Δ). PWID enter the population at a rate Ω(t) that is set to maintain a constant population size before ART is initiated, with a proportion p_0 of these new injectors being HIV infected. Because these individuals are quite young and few PWID were on ART before 2012[3] it was assumed that none of the incoming HIV infected injectors were on ART. PWID can be recruited onto ART (at a rate r) once they enter the long latent phase of HIV, upon which they have reduced infectivity (cofactor ω). Those in the initial and late phases of high viraemia have heightened transmission (cofactors δ and θ respectively) compared to the injection and sexual related infection rate of those in the latent phase of HIV (β_{inj} and β_{sex}). OST is assumed to have specific coverage level o(t) that varies and reduces injection related HIV transmission by cofactor ψ_o. OST is not modelled explicitly because PWID move in and out of OST and so incorporating them as average coverage levels is a reasonable approximation. The model also stratifies the PWID into those with low and high injecting risk (denoted by the subscript j=0 for low risk and 1 for high risk, with H_i being the initial proportion of PWID in each), with the injection related risk of HIV transmission among susceptible PWID in the high-risk strata being a factor (m) greater than amongst the low risk PWID. The model assumes a proportion (ε) of the transmission events of PWID in a specific injecting risk state are with PWID from that same risk state (like-with-like mixing), and then the remaining transmission events are spread across PWID from any injecting risk state proportional to the overall relative frequency of transmission events for PWID in that state. Sexual HIV transmission amongst PWID is modelled simply with a proportion of sexual contacts being with PWID randomly assigned to all PWID, and the remaining ones being amongst non-PWID. The HIV prevalence amongst the non-PWID is a time varying function with a a time varying proportion being on ART. The model equations are included below:

$$\frac{dx_0}{dt} = \Omega(t)H_0(1-p_0) - \left[\Phi(t)\lambda_{inj}^0 + \lambda_{sex}\right]x_0 - \mu x_0$$

$$\frac{dh_0}{dt} = \left[\Phi(t)\lambda_{inj}^0 + \lambda_{sex}\right]x_0 - h_0(\nu+\mu)$$

$$\frac{dy_0}{dt} = \Omega(t)H_0 p_0 + \nu h_0 - y_0(\mu+\gamma+r)$$

$$\frac{da_0}{dt} = \gamma y_0 - a_0(\mu+\eta+r)$$

$$\frac{d\tau_0}{dt} = r(a_0+y_0) - \tau_0(\mu+\Delta)$$

$$\frac{dx_1}{dt} = \Omega(t)H_1(1-p_0) - \left[\Phi(t)\lambda_{inj}^1 + \lambda_{sex}\right]x_1 - \mu x_1$$

$$\frac{dh_1}{dt} = \left[\Phi(t)\lambda_{inj}^1 + \lambda_{sex}\right]x_1 - h_1(\nu+\mu)$$

$$\frac{dy_1}{dt} = \Omega(t)H_1 p_0 + \nu h_1 - y_1(\mu+\gamma+r)$$

$$\frac{da_1}{dt} = \gamma y_1 - a_1(\mu+\eta+r)$$

$$\frac{d\tau_1}{dt} = r(a_1+y_1) - \tau_1(\mu+\Delta)$$

Where Φ (t) is the protective effect of OST and has the following form where the coverage of OST is o and varies over time:

$$\Phi(t) = (1-o) + o\,\psi_o ,$$

And λ_{sex} and λ_{inj} are the sexual and injecting force of infection for HIV transmission which have the following form:

$$\lambda_{sex} = \frac{\beta_{sex}}{N}\left[(1-\rho)p_1((1-T)+\omega T) + \rho\sum_{i=0,1}(h_i\delta + y_i + \theta a_i + \omega\tau_i)\right]$$

$$\lambda^0_{inj} = \beta_{inj}\left[\left(\varepsilon + (1-\varepsilon)\frac{N_0}{N_0 + mN_1}\right)(h_0\delta + y_0 + \theta a_0 + \omega\tau_0)/N_0 + \left((1-\varepsilon)\frac{mN_1}{N_0 + mN_1}\right)(h_1\delta + y_1 + \theta a_1 + \omega\tau_1)/N_1\right]$$

$$\lambda^1_{inj} = \beta_{inj}\left[\left((1-\varepsilon)\frac{N_0}{N_0 + mN_1}\right)(h_0\delta + y_0 + \theta a_0 + \omega\tau_0)/N_0 + \left(\varepsilon + (1-\varepsilon)\frac{mN_1}{N_0 + mN_1}\right)(h_1\delta + y_1 + \theta a_1 + \omega\tau_1)/N_1\right]$$

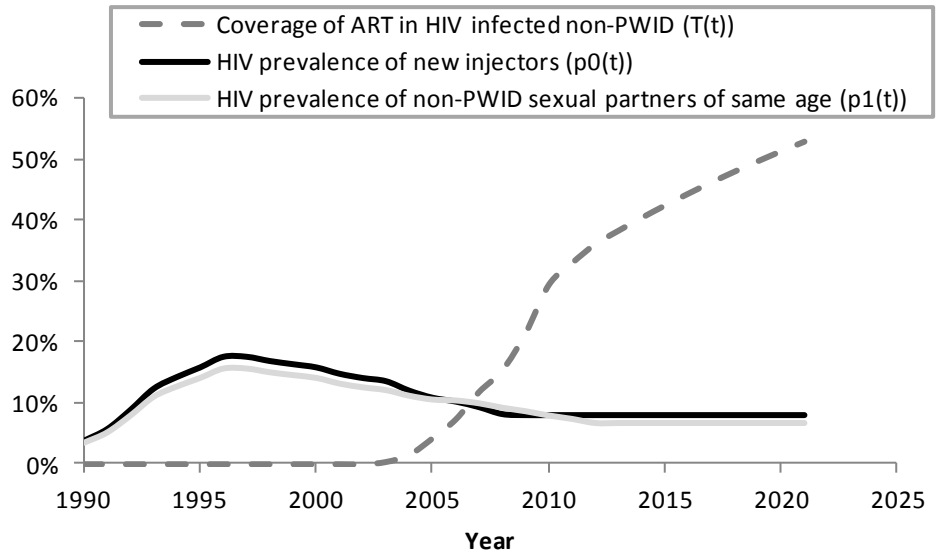
Where N is the total PWID population size (N=x+h+y+a+τ), N_0 and N_1 are the population sizes of the low and high risk groups, and ε is the degree to which PWID have injection related transmission events with PWID of the same risk strata. The inflow into the PWID population (Ω(t)) is defined as below where *a* is the number that would be in the AIDS state if no ART were present:

$$\Omega(t) = \mu N + \eta a$$

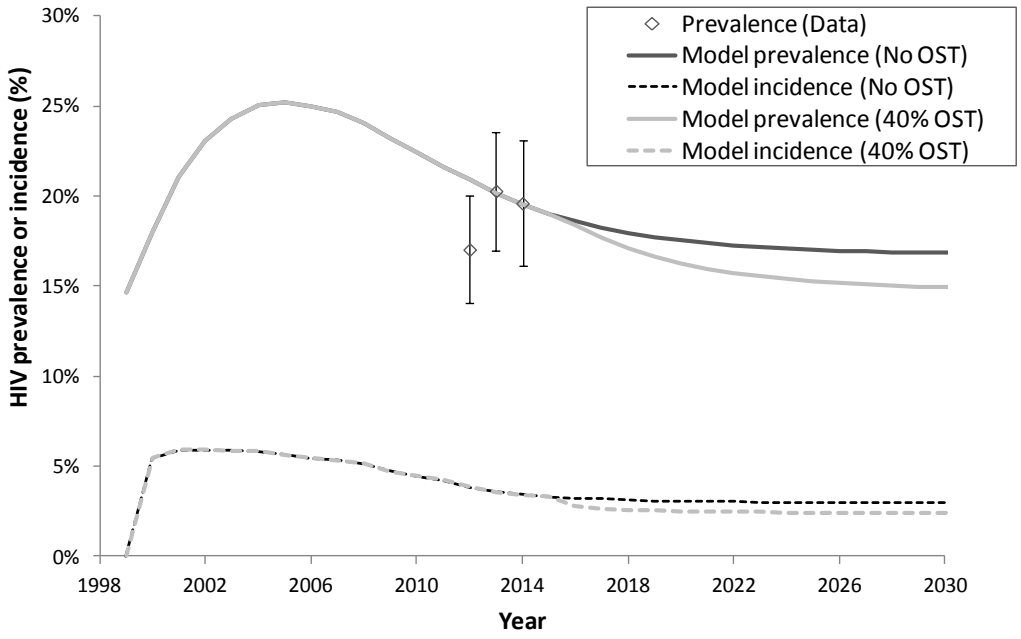
Supplementary table 1: Model parameters

Model parameter	Value used	Data source
Behavioural and epidemiological parameters for PWID		
Average duration inject in years ($1/\mu$)	6	TLC data gives about 5 years amongst current injectors[3]
Proportion of sexual contacts with PWID (ρ)	5.4%	[3]
Percentage of PWID defined as high-risk (H_1)	25%	[4]
Factor increase in injection related HIV transmission risk if high-risk (m)	3	[4]
Proportion of PWID that mix like-with-like to form injecting partnerships (ε)	0.5	No data but given relatively high value to be conservative [17]
Year injecting drug use started in Nairobi	1999	[7]
Seed HIV prevalence in 1996 (γ_0)	15%	HIV prevalence in 1999 [5] weighted for Nairobi and PWID gender ratio [18]
HIV prevalence amongst new injectors ($p_0(t)$)	See Figure below (8% in 2012)	Set to be double HIV prevalence amongst individuals of that age range (25-29 years) [18]
Parameters for non-PWID		
HIV prevalence in non-PWID sexual contacts ($p_1(t)$)	See Figure below	[5, 8]
Proportion of HIV infected non-PWID sexual contacts on ART (T(t))		[5, 8]
HIV 'biological' model parameters		
Injection related infection rate per month in latent phase of HIV (β_{inj})	0.0025	Varied to give 20% HIV prevalence amongst PWID in 2014 after sexual HIV transmission is calibrated
Sexual related infection rate per month in latent phase of HIV (β_{sex})	0.0164	Varied to give same incidence amongst PWID in 2012 (when no injecting risk) as gives 8% HIV prevalence after 9 years of sexual activity from age 17 to 26 when start injecting drug use [3]
Cofactor increase in HIV transmission probability during:		
Initial acute phase of high viraemia (δ)	26	[11]
Pre-AIDS phase of high viraemia (θ)	7	[11]
Duration of initial acute phase of high viraemia in years ($1/\delta$)	0.25	[11]
Duration of pre-AIDS phase of high viraemia in years ($1/\eta$)	0.75	[11]
Duration of latent phase in years ($1/\gamma$)	9.4	[19]
Model intervention effectiveness parameters		
Relative HIV infection rate while on ART compared to latent phase transmission probability (ω)	0.42	No data for PWID – Low efficacy assumed [12] because of low level of viral suppression [12, 20-26];
Average survival time with HAART in years ($1/\Delta$)	15	PWID have lower survival on ART than non-PWID [13-15, 27]
Relative infection rate if susceptible IDU is currently on OST (Ψ_o)	0.5	[16]

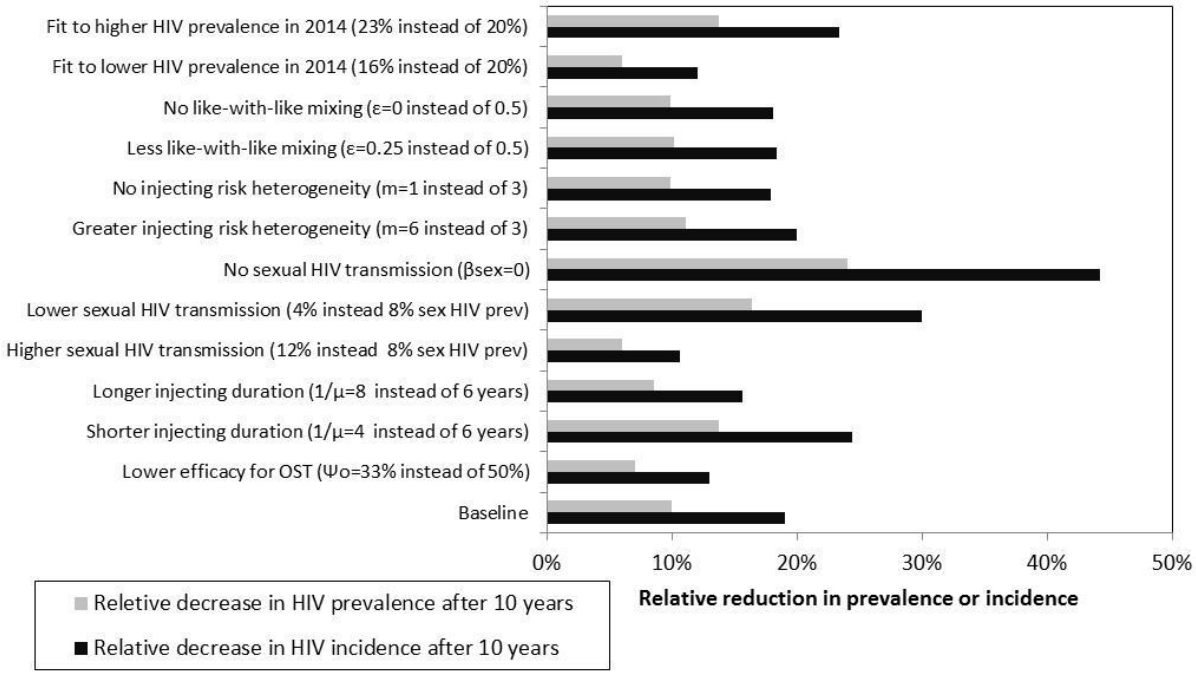
Supplementary Figure 1: Time varying functions for HIV prevalence amongst new PWID ($p_0(t)$) or non-PWID sexual contacts of the same age ($p_1(t)$) and coverage of ART in HIV infected non-PWID (T(t))



Supplementary Figure 2: Model fit to available HIV prevalence data and projected impact of 40% coverage of OST on HIV prevalence and incidence over time.



Supplementary figure 3: Sensitivity analysis on the projected relative decrease in HIV prevalence and incidence after 10 years due to scaling up OST in Nairobi to 40% of PWID. Parameter assumptions are described in the figure (with parameters defined in Supplementary Table 1) and main text methods section.



Reference

1. Vickerman, P., et al., *Is the HCV-HIV co-infection prevalence amongst injecting drug users a marker for the level of sexual and injection related HIV transmission?* Drug Alcohol Depend, 2013.
2. National AIDS and STI Control Programme (NASCOP), *Kenya AIDS Indicator Survey 2012: Final Report*. 2014: Nairobi, Kenya.
3. Kurth, A., *Personal communication linked to their 'Treatment linkage respondent driven sampling survey of people who inject drugs in Kenya' TLC-IDU study, funder NIDA R01 DA032080, Principal investigators A. Kurth and P. Cherutich*. 2014.
4. Williams, M.L., et al., *HIV seroprevalence in a sample of Tanzanian intravenous drug users.* AIDS Educ Prev, 2009. **21**(5): p. 474-83.
5. National AIDS Control Council of Kenya, *Kenya AIDS Response Progress Report 2014: Progress to Zero*. 2014.
6. Muasya, T., et al., *Prevalence of hepatitis c virus and its genotypes among a cohort of drug users in Kenya.* East African Medical Journal, 2003. **85**: p. 318-325.
7. Beckerleg, S., M. Telfer, and G.L. Hundt, *The rise of injecting drug use in East Africa: a case study from Kenya.* Harm Reduct J, 2005. **2**: p. 12.
8. National AIDS Control Council of Kenya, *Kenya AIDS Epidemic Update 2011*. 2012.
9. Vickerman, P., N.K. Martin, and M. Hickman, *Understanding the trends in HIV and hepatitis C prevalence amongst injecting drug users in different settings--implications for intervention impact.* Drug. Alcohol Depend., 2012. **123**(1-3): p. 122-31.
10. Cohen, M.S., et al., *Prevention of HIV-1 infection with early antiretroviral therapy.* N. Engl. J. Med., 2011. **365**(6): p. 493-505.
11. Hollingsworth, T.D., R.M. Anderson, and C. Fraser, *HIV-1 transmission, by stage of infection.* J. Infect. Dis., 2008. **198**(5): p. 687-93.
12. Anglemyer, A., T. Horvath, and G. Rutherford, *Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples.* JAMA, 2013. **310**(15): p. 1619-20.
13. Brinkhof, M.W., et al., *Mortality of HIV-infected patients starting antiretroviral therapy in sub-Saharan Africa: comparison with HIV-unrelated mortality.* PLoS Med, 2009. **6**(4): p. e1000066.
14. Johansson, K.A., B. Robberstad, and O.F. Norheim, *Further benefits by early start of HIV treatment in low income countries: survival estimates of early versus deferred antiretroviral therapy.* AIDS Res Ther, 2010. **7**(1): p. 3.
15. Mills, E.J., et al., *Mortality by baseline CD4 cell count among HIV patients initiating antiretroviral therapy: evidence from a large cohort in Uganda.* AIDS, 2011. **25**(6): p. 851-5.
16. MacArthur, G.J., et al., *Evidence for the effectiveness of opiate substitution treatment in relation to HIV transmission in people who inject drugs: a systematic review and meta-analysis.* BMJ, 2012. **345**(e5945): p. 1-16.
17. Vickerman, P., et al., *Can needle and syringe programmes and opiate substitution therapy achieve substantial reductions in HCV prevalence? Model projections for different epidemic settings.* Addiction, 2012. **107**: p. 1984-95.
18. National AIDS and STI Control Programme (NASCOP), *Kenya AIDS Indicator Survey 2012: Final Report*. 2104: Nairobi, Kenya.
19. Prins, M., et al., *Pre-AIDS mortality from natural causes associated with HIV disease progression: evidence from the European Seroconverter Study among injecting drug users.* AIDS, 1997. **11**(14): p. 1747-56.
20. Malta, M., et al., *Adherence to antiretroviral therapy among HIV-infected drug users: a meta-analysis.* AIDS Behav, 2010. **14**(4): p. 731-47.

21. Wood, E., et al., *Adherence and plasma HIV RNA responses to highly active antiretroviral therapy among HIV-1 infected injection drug users.* CMAJ, 2003. **169**(7): p. 656-61.
22. Nolan, S., et al., *Adherence and plasma HIV RNA response to antiretroviral therapy among HIV-seropositive injection drug users in a Canadian setting.* AIDS Care, 2011. **23**(8): p. 980-7.
23. Bangsberg, D.R., et al., *Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population.* AIDS, 2000. **14**(4): p. 357-66.
24. Petersen, M.L., et al., *Pillbox organizers are associated with improved adherence to HIV antiretroviral therapy and viral suppression: a marginal structural model analysis.* Clin Infect Dis, 2007. **45**(7): p. 908-15.
25. Gross, R., et al., *Effect of adherence to newly initiated antiretroviral therapy on plasma viral load.* AIDS, 2001. **15**(16): p. 2109-17.
26. Braithwaite, R.S., et al., *Adherence, virological and immunological outcomes for HIV-infected veterans starting combination antiretroviral therapies.* AIDS, 2007. **21**(12): p. 1579-89.
27. Carrico, A.W., *Substance use and HIV disease progression in the HAART era: implications for the primary prevention of HIV.* Life Sci, 2011. **88**(21-22): p. 940-7.