Modelling the impact of opioid substitution therapy on the prevention benefit of antiretroviral therapy amongst people who inject drugs

Short title: Impact of OST on ART benefit for HIV prevention

Authors: Christinah MUKANDAVIRE[1], Andrea LOW[1], Gitau MBURU[2,3], Adam TRICKEY[1], Margaret T. MAY[1], Nicky WELTON[1], Charlotte F. DAVIES[1], Clare E. FRENCH[1], Katy TURNER[4], Katharine J. LOOKER[1], Hannah CHRISTENSEN[1], Susie MCLEAN[2], Tim RHODES[5], Lucy PLATT[5], Andy GUISE[5], Matthew HICKMAN[1], Peter VICKERMAN[1]

Affiliations:
[1]School of Social and Community Medicine, University of Bristol, Bristol, UK
[2]International HIV/AIDS Alliance, Brighton, UK
[3]Division of Health Research, Lancaster University, UK
[4]School of Clinical and Veterinary Sciences, University of Bristol, Bristol, UK
[5]London School of Hygiene and Tropical Medicine, London, UK

Address of corresponding author
Peter Vickerman
School of Social Community Medicine
University of Bristol
Bristol BS8 2BN
UK
Telephone +44 7821196359
Email: Peter.Vickerman@bristol.ac.uk

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Abstract
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Objective: A recent systematic review suggested that opioid substitution therapy (OST) increased uptake of anti-retroviral treatment (ART) and HIV viral suppression. We modelled whether OST could improve the prevention benefit achieved by ART amongst people who inject drugs (PWID).

Methods: Findings from the systematic review were used to model how introducing OST improves ART coverage and HIV viral suppression across a PWID population for different baseline ART coverage levels. Changes in the level of viral suppression across the population were used to estimate the relative reduction in HIV transmission risk achieved by ART, with or without OST, compared to if there was no ART - defined as the prevention effectiveness of ART. In relative terms, we estimated how OST improved the prevention effectiveness of ART.

Results: Compared to not being on OST, the average prevention effectiveness of ART for PWID on OST is heightened relatively by 44% or 20% for a low (20%) or high (60%) baseline ART coverage, respectively. Similar improvements in the prevention effectiveness of ART can also be achieved at the population-level (across those on and off OST) when compared to if OST was not introduced. For instance, if OST is introduced at 40% coverage, the population-level prevention effectiveness of ART increases relatively by 37% or 19% for a low (20%) or high (60%) baseline ART coverage, respectively. Improvements in ART prevention effectiveness decrease for lower OST coverage levels.

Conclusions: OST could substantially improve the prevention benefit of ART; supporting strategies to concurrently scale-up OST with ART.

Keywords: antiretroviral therapy, opiate substitution therapy, HIV, viral suppression, Injecting drug use, treatment as prevention

Introduction

Injecting drug use is an important driver of HIV transmission in Eastern Europe, North America, and parts of Asia[1, 2] and is increasing in East Africa[3]. Although HIV transmission is decreasing in many settings, transmission amongst people who inject drugs (PWID) is still increasing in many settings[4, 5], and many of these epidemics are now expanding beyond these risk groups[6, 7].

While the use of antiretroviral treatment (ART) has improved the health and lives of those infected with HIV[8-12] and can dramatically reduce HIV transmission[13], access to treatment and treatment outcomes are frequently inferior amongst PWID due to a range of social and structural factors [14-16]. This could hinder the worldwide goal of achieving high coverage of HIV treatment and viral suppression, and in-turn prevent virtual elimination of global HIV transmission and morbidity[17].

Existing evidence suggests opioid substitution therapy (OST) can reduce the frequency of injecting drug use[18, 19], halve the risk of HIV and HCV acquisition among PWID[20, 21], and reduce drug-related mortality[22]. Within a range of potential structural and social interventions[23], evidence is also emerging that concurrent OST use can improve ART outcomes such as X, X, and X among PWID, as confirmed by a recent systematic review and meta-analysis[24]. Besides possibly improving the morbidity benefits for PWID in care[24], it is probable that combining the use of OST and ART amongst PWID could also improve the degree to which ART reduces the level of HIV transmission in this population through improving the proportion of PWID on ART and the level of viral suppression amongst these PWID.

We used modelling to estimate the possible impact of OST on improving the HIV prevention benefit of ART among PWID with different baseline coverage levels of ART before OST was introduced. We fist compared the average HIV prevention benefit achieved by ART among PWID on OST to that among PWID not on OST. We then compared the average prevention benefit achieved by ART at the population-level with and without OST. Projections were made with and without accounting for the possible dynamic effect of OST on increasing ART coverage.

Methods

Definition of ART prevention effectiveness

For all analyses in this study, we evaluate the prevention benefit of ART for a PWID sub-population (whether on or off ART) by estimating the degree to which the coverage of ART in that sub-population decreases the overall average transmission risk across all HIV-infected PWID whether on or off ART. We denote this as the **prevention effectiveness** of ART for that sub-population, which depends on both the coverage of ART amongst those PWID and the degree to which ART decreases the transmission risk or infectivity of those PWID on ART, as determined by their decrease in viral load after initiating ART[25].

Static estimation of benefits of OST

Assuming a certain coverage of ART amongst those not on OST, and level of viral suppression amongst those on ART, synthesised effect estimates from our recent systematic review[24] were used to estimate the increased coverage of ART amongst those currently on OST and increased proportion virally suppressed amongst those on OST and ART. This did not incorporate the dynamic effect of OST on ART recruitment or retention from the systematic review[24], but only its effect on ART coverage. For those on ART that are virally suppressed or unsuppressed, estimates of their log difference in viral load compared to PWID not on ART were used to estimate the relative decrease in HIV infectivity achieved through ART by these PWID. These calculations utilised existing observed associations between levels of plasma viral load (PVL) and HIV infectivity[25, 26]. Estimates of the

relative decrease in HIV infectivity for virally suppressed or unsuppressed PWID on ART were then averaged across the proportion virally suppressed or not for different intervention combinations, and used to estimate the prevention effectiveness of ART for PWID on and off OST, and at the population-level for specified OST coverage levels as well as if OST had not been introduced. The relative increase in the prevention effectiveness of ART for PWID on OST compared to PWID off OST was calculated, as was the relative increase in the overall prevention effectiveness of ART for different OST coverage levels compared to if OST had not been introduced. See supplementary materials for more methodological details.

Dynamic estimation of benefits of OST

A dynamic model of OST and ART recruitment and retention amongst HIV-infected PWID was developed to determine whether PWID transitioning on and off OST might affect the impact of OST on increasing ART coverage, and so the overall prevention effectiveness of ART. The model assumed PWID on OST have improved ART recruitment and retention, and through PWID transitioning on and off OST allowed improvements in ART coverage amongst PWID on OST to improve ART coverage levels amongst PWID not on OST. This contrasts with the static model, which just assumed a heightened ART coverage amongst PWID on OST, and did not model any movement on and off OST. The dynamic model was used to re-evaluate the increase in ART coverage that could occur due to introducing OST, and so the overall prevention effectiveness of ART for different OST coverage levels compared to if OST had not been introduced.

The model stratifies HIV-infected PWID by ART (never, currently or previously on ART) and OST (not on OST, short- or long-term OST) status. PWID leave the model due to non-HIV death or injecting cessation. ART-naïve HIV-infected PWID experience HIV-related mortality, or can be recruited onto ART. When on ART, HIV-related mortality is reduced, but PWID can discontinue HIV treatment. PWID discontinuing ART can recruit back on to ART, but at a lower rate than ART-naïve PWID. Recruitment into the HIV-infected compartment is set to maintain a constant population before ART was introduced. Recruitment onto OST occurs independently of ART status. When initiated on to OST, PWID enter short-term OST, from which they either leave OST or transition to long-term OST. PWID leave long-term OST at a reduced rate. When on OST, recruitment onto ART is increased and attrition is reduced. The schematic for the dynamic model is shown in Figure 1 and parameters defined in Table 1, with model equations shown in the supplementary materials.

Model parameterisation

The models were parameterized using data from various sources (Table 1). Firstly, the systematic review[24] gave estimates for how being on OST improved the coverage of ART (static model), the rates of recruitment onto and retention on ART (dynamic model), and the proportion on ART that are virally suppressed (both models). Odds ratios (Table 1) were converted to probabilities as described in the supplementary materials. The estimated baseline PVL amongst PWID off ART was obtained from the Antiretroviral Therapy Cohort Collaboration study [27] carried out among 5761 PWID in Europe and North America who initiated ART between 1996 and 2013. The same study gave estimates for the decrease in PVL from baseline for PWID on ART who were not virally suppressed at 12 months after initiating ART.

The dynamic model required additional data to parameterise the dynamics of OST and ART retention and mortality, with all parameter estimates given in Table 1. A wide range was used for the combined rate of injecting cessation and HIV-unrelated mortality (5-25% per year) because of uncertainty in the injecting duration across settings[22, 28-30]. HIV-related mortality[31, 32] was assumed to reduce by 66-80% if on ART[33-37]. Estimates for the baseline rate of ART retention for PWID were derived from a prospective pan-European study[38], whereas ART recruitment rates were calibrated to give different baseline ART coverage levels, as described in the next section.

Data for long-term attrition from OST are limited, with most studies only considering OST retention over 6-12 months[39]. To model attrition from OST over longer time periods, we combined five international datasets which captured OST retention for over a year ([40-43] and Matthew Hickman personal communication). These data were used to give a range of possible trajectories (and corresponding OST retention rates) for the long-term retention of PWID on OST (Figure S2 and S3), which were sampled for subsequent model runs (supplementary materials for details). Ranges obtained for the parameters are given in Table 1. Lastly, recruitment rates onto OST were calibrated to give different OST coverage scenarios, as described in the next section.

Model analyses – Static model

To incorporate uncertainty, 1000 parameter sets were randomly sampled from the static model parameter distributions given in Table 1. For each sampled parameter set, and a wide range of baseline ART coverage levels (10-90% when no OST), the model projected the absolute and relative increase in the prevention effectiveness of ART for someone on OST compared to someone not on OST. The model was then used to consider how the prevention effectiveness of ART at the population-level increases when OST is introduced at different coverage levels (20, 40, 60 and 80%) for different baseline ART coverage levels (10-90%).

Model analyses – Dynamic model

For the dynamic model, all additional model parameters with uncertainty distributions in Table 1 were randomly sampled to give 1000 parameter sets. For each parameter set, the recruitment rate onto ART was firstly calibrated to give a range of steady baseline ART coverage scenarios (10-90% coverage). Then, for each ART scenario, OST was introduced once ART had reached steady coverage, with different OST recruitment rates being used to give a range of OST coverage levels 10 years after introduction (20, 40, 60, and 80% coverage).

For each OST and ART coverage scenario, we projected the degree to which OST increased the overall coverage of ART 10 years after OST was introduced, and ART coverage among PWID on OST compared to PWID off OST. These latter projections were compared to the systematic review estimate for the increased odds of being on ART for PWID on OST compared to PWID off ART, as used in the static model. In addition, the odds of being on ART for PWID on OST compared to the baseline ART coverage was estimated to better evaluate for the degree to which OST elevates ART coverage.

Lastly, the projected ART coverage estimates for PWID on and off OST from the dynamic model were combined with the sampled parameter sets for the static model (other than the ART coverage parameters) to re-estimate the degree to which OST increases the population-level prevention effectiveness of ART for different coverage levels of OST and ART.

Uncertainty analysis

A linear regression analysis of covariance (ANCOVA)[44] was undertaken to determine which parameter uncertainties contribute most to variability in the dynamic model's projections of the relative increase in population-level prevention effectiveness of ART for an OST coverage of 40% and baseline ART coverage of 40%. The proportion of the model's outcome sum-of-squares contributed by each parameter was calculated to estimate the importance of individual parameters to the overall uncertainty.

Results

Static model projections

Compared to not being on OST, the static model suggests that being on OST could increase the absolute prevention effectiveness of ART by a median of 6.5% (2.5th to 97.5th percentile range: 2.8-11.8%), 9.4% (4.2-15.5%) and 9.3% (4.3-14.4%), for a baseline ART coverage of 20, 40 or 60%, respectively (Figure 2(a)). This means that for a baseline ART coverage of 40%, being on OST (instead of not) increases the prevention effectiveness of ART (or average decrease in HIV transmission risk due to ART) from 31.8% (19.1-37.4%) to 40.7% (27.0-51.0%), i.e. ART results in a 31.8% decrease in HIV transmission risk without OST, and 40.7% decrease in transmission risk with OST. This is not affected by the underlying coverage of OST. These increases translate to a 43.8% (17.0-78.8%), 31.0% (12.7-56.6%) and 19.9% (8.6-39.9%) relative increase in the prevention effectiveness of ART amongst PWID on OST for a baseline ART coverage of 20, 40 or 60%, respectively (Figure 2(b)).

At the population-level, the static model suggests that high OST coverage (60%) could improve the prevention effectiveness of ART relatively by 26.3% (10.2-47.3%), 18.6% (7.6-34.0%) and 11.9% (5.2-23.9%) for a baseline ART coverage of 20, 40 and 60%, respectively (Figure 3(a)). This reduces to 17.5% (6.8-31.5%), 12.4% (5.1-22.6%) and 8.0% (3.5-15.9%) for the same baseline ART coverage levels, if OST coverage is 40% instead of 60%. Although less relative effect is achieved by OST at higher ART coverage levels due to the increases in ART coverage being less in relative terms, the absolute effects are similar or increase as presented in the previous paragraph.

Dynamic model projections

In comparison to the static model (Figure 4), the dynamic model projects over double the increase in ART coverage due to OST for any specific baseline ART and OST coverage. For instance, with a 20, 40 or 60% baseline ART coverage and an OST coverage of 40%, the static model predicts a 15.0% (5.6-26.6%), 10.3% (4.1-17.2%), 6.3% (2.6-10.0%) relative increase in overall ART coverage from baseline levels, whereas the dynamic model predicts a 34.6% (20.3-49.4%), 27.3% (16.2-40.1%) and 17.3% (10.0-26.0%) relative increase. This means that for a baseline ART coverage of 40% before OST introduction, the static model predicts ART coverage would increase to 44.1% (41.6-46.9%) following OST scales-up to 40% coverage, whereas the dynamic model predicts ART coverage would increase to 50.9% (46.5-56.3%).

Without being calibrated to the data, the dynamic model projections agree well with the systematic review's findings (used by static model) of how being on OST increases ART coverage[24]. Irrespective of OST and ART coverage, the dynamic model projects a ~50% increased odds (OR=1.46 (1.18-2.64) for 40% OST coverage) of being on ART if a PWID is on OST compared to if they are not on OST (Figure S4). This, however, does not portray the full benefits of OST in increasing ART coverage because ART coverage also increases among PWID not currently on OST. Indeed, projections (Figure S5) from the dynamic model suggest that being on OST increases the odds of being on ART by 50 to 130% (median OR varies from 1.5-2.3 depending on OST and ART coverage) compared to the baseline coverage of ART before OST was introduced.

These greater increases in ART coverage due to OST result in the dynamic model predicting that OST scale-up will result in greater increases in the population-level prevention effectiveness of ART (Figure 3(b)) than those from the static model. For instance, the dynamic model projects that scaling-up OST to 40% coverage results in the population-level prevention effectiveness of ART increasing by 36.8% (22.1-53.7%), 29.6% (17.9-42.9%) and 18.8% (11.2-29.5%) for a baseline ART coverage of 20, 40 and 60%, respectively (Table S1). These estimated increases in ART prevention effectiveness are over twice what was projected by the static model.

Uncertainty analysis

There is uncertainty associated with our model projections. ANCOVA analyses suggest that most of the variability in the dynamic model's projections of the relative increase in population-level prevention effectiveness of ART (OST coverage of 40% and baseline ART coverage of 40%) is due to

the factor increase in the ART recruitment rate amongst PWID on OST compared to PWID off OST (accounts for 76.2% of variability), the log decrease in viral load among unsuppressed PWID on ART compared to baseline (8.0%), the combined rate of injecting cessation and non-HIV death (4.2%), and the factor decrease in the ART attrition rate amongst PWID on OST compared to PWID off OST (4.6%). Parameters that contribute more that 1% variability in the model projections are shown in supplementary Figure S6.

Discussion

Our findings suggest that being on OST could dramatically increase the relative prevention effectiveness of ART for reducing the infectivity of PWID, by nearly half (44%) for a low baseline coverage of ART (20%), and by a fifth (20%) for a high baseline coverage of ART (60%). At the population-level, considerable impact could also be achieved if OST is scaled-up, with moderate OST coverage (40%) increasing the prevention effectiveness of ART by nearly a third if the baseline ART coverage is moderate (40%). This beneficial effect is mainly due to OST increasing the coverage of ART amongst those on OST, which can also markedly increase the coverage of ART amongst those not on OST because PWID transition on and off OST.

Limitations

There are limitations to our projections. Firstly, there was uncertainty around many of the model parameters, such as the long-term loss to follow up from OST, or the effect of OST use on ART recruitment and coverage. However, our modelling results were generally robust to these uncertainties, with only uncertainty in the factor increase in ART recruitment for PWID on OST compared to PWID off OST resulting in sizeable uncertainty in our model projections. Improved data on this parameter would reduce our uncertainty in how OST could improve the prevention impact of ART.

Other simplifying assumptions include assuming that the rate of non-HIV death and/or injecting cessation is the same for PWID on and off OST. Studies generally show that being on OST improves drug-related mortality[22], although mortality can be raised in the initial periods on and off OST[45, 46], but evidence that OST increases injecting cessation is conflicting[47, 48]. Although important effects, it is unlikely that they will affect our results, as suggested by our uncertainty analysis and previously published analyses[49]. Additionally, the dynamic model assumed that OST and ART attrition occurred independently of each other, which resulted in the model projecting increased ART coverage amongst PWID not on OST. However, it is possible that both events could be linked, maybe due to both treatments being dispensed alongside each other, or a common disabling social or structural factor or event hindering further use of both services, for example arrest or incarceration. If this was the case, then the results of the static model could be closer to reality, which predicts a smaller but still important impact. There is also uncertainty around the efficacy of ART for reducing injecting HIV transmission. Although it is likely that ART will reduce the risk of injection-related HIV transmission, due to large reductions in viral load, the actual efficacy is uncertain. While this would affect the absolute magnitude of our results in terms of the prevention benefit of ART, it should not affect the relative degree to which OST improves the prevention effectiveness of ART, as shown by our uncertainty analysis.

The model used in this analysis only considered the short-term benefits of OST in increasing the individual and population-level prevention effectiveness of ART for decreasing HIV transmission risk. Over time, any differences in transmission risk between two intervention scenarios are likely to become amplified, and so the degree to which OST improves the effectiveness of ART over the long-term may be greater than we estimated. The projections of this model were primarily based on findings from a recent systematic review that synthesised evidence on the effects of OST use on

different ART outcomes[24]. Although this should be considered a strength of the model analysis, weaknesses in the synthesised datasets, including the reliance on observational cohorts and the preponderance of data from the US and Europe does raise concerns which could only be reduced through further data collection from other settings. However, future studies will still likely rely on observational cohorts, with their inherent weaknesses, because the other proven benefits of OST[20, 22, 45, 46] restrict the ability to randomise PWID onto OST or not.

Comparison with other studies

A recent systematic review found that OST can halve the risk of HIV acquisition among PWID[20], and numerous modelling analyses have suggested that scaling up OST and/or ART amongst PWID could dramatically reduce HIV transmission[50-52], and be cost-effective[53-55]. However, to our knowledge this is the first study to estimate the degree to which OST may improve the effectiveness of ART for reducing HIV transmission amongst PWID, suggesting it could have large benefits especially in settings with low to moderate ART coverage.

Implications and Conclusions

Accumulating evidence suggests that OST could dramatically improve the cascade-of-care amongst HIV-infected PWID[24, 37, 56], with modelling in this paper further suggesting that these improvements could lead to significant improvements in the effectiveness of ART in reducing HIV transmission. These findings add to the evidence base for the multiple benefits of OST amongst PWID[57-60], and support strategies to integrate OST with HIV services to optimise the benefits achieved. Unfortunately, many countries have low coverage of OST, or even forbid its provision[61, 62], and PWID frequently have sub-optimal coverage of ART[33]. Many of these countries have significant on-going HIV epidemics or have experienced new HIV outbreaks, such as Russia[63], other countries in Eastern Europe[4, 64], Central Asia[4], Pakistan[65, 66], rural USA[67], and Greece[68, 69]. In these settings, the joint scale-up of OST with ART could have a substantial effect on HIV transmission, and is likely to be highly cost-effective or even cost saving[70-72] due to the multiple health and social benefits of OST and the large prevention benefit that can be afforded by ART and OST in these settings. Despite these benefits, the coverage of OST is highly inequitable, and is illegal in some countries (ref). To achieve optimal impact of OST a number of structural and policy barriers will have to be overcome to increase the uptake of OST and/or ART among PWID, including reducing the stigmatisation of PWID in health settings and the criminalisation of drug use[23].

Tables

Table 1. Parameter values and ranges used in models.

Variable or parameter	Symbol	Value (range used)	Source and comments
Parameters for static model			
ART coverage at baseline without effect of OST	x	0 - 100%	Varied for different ART scenarios
OST coverage	y	0 - 100%	Varied for different OST scenarios
Odds ratio for OST use increasing ART coverage (used in static model only)	r_a	1.54 (95%CI: 1.17-2.03)	[24]
Odds ratio for OST use increasing viral suppression on ART	r_s	1.45 (95%CI: 1.21-1.73)	[24]
Baseline plasma viral load when not on ART	v_b	4.79 (IQR: 4.11-5.27) log 10 copies/ml	[14, 27]
Plasma viral load among virally suppressed PWID on ART	v_s	1.7 log 10 copies/ml	Assume 50 copies/mL as limit of detection – translates to 92% decrease in HIV infectivity similar to trial[13]
Log difference in plasma viral load among unsuppressed PWID on ART compared to before they initiated ART	Δ_u	-0.81 (IQR: -2.27-0.00) log 10 copies/ml	Median (25 and 75% IQR) difference in plasma viral load 1 year after initiating ART compared to before ART[14, 27]
Factor difference in HIV transmission risk for each log increment in plasma viral load	r_t	2.45 (95%CI: 1.85-3.26)	[25]
Proportion virally suppressed among PWID on ART if not on OST	p_s	0.56 (0.35-0.86)	Median (2.5-97.5% range) for 9 studies from systematic review [24]
Additional parameters for dynamic model			
Baseline mortality and cessation			
HIV mortality rate in the latent stage of HIV per year	δ	1/10.5-1/8.5	[31, 32]
Injecting cessation and non-HIV death rate per year	ν	5-25%	[48, 73-75]
OST parameters			
Recruitment rate onto OST per year	ε	To fit: 0-100%	Varied to fit different OST coverage scenarios
Rate of leaving short stay OST per year	κ	0.2-1.6	Estimated through fitting a split exponential function to OST retention data – see supplementary materials
Rate of leaving long stay OST per year	π	0.083-0.87	
Rate of moving from short to long stay OST per year	a	0.25-1.48	
ART parameters			
Baseline recruitment rate onto ART when not on OST per year	ω	To fit: 0-100%	Varied to fit different ART coverage scenarios
Cofactor difference in ART recruitment rate after having discontinued ART compared to when initiating ART	χ	0.5 - 1.0	No data so sampled in range
Cofactor difference in HIV mortality rate while on ART compared to latent stage	φ	1/5-1/3	[35-37]
Rate at which PWID on ART discontinue treatment per year	σ	2.99-9.84%	Estimated using data from [38] - see methods and supplementary materials
Effect of OST on ART outcomes			
Odds ratio for OST use increasing the rate of ART recruitment	b	1.87 (95%CI: 1.50-2.33)	[24]
Odds ratio for OST use decreasing the rate of ART attrition	d	0.77 (95%CI: 0.63-0.95)	[24]

Figures

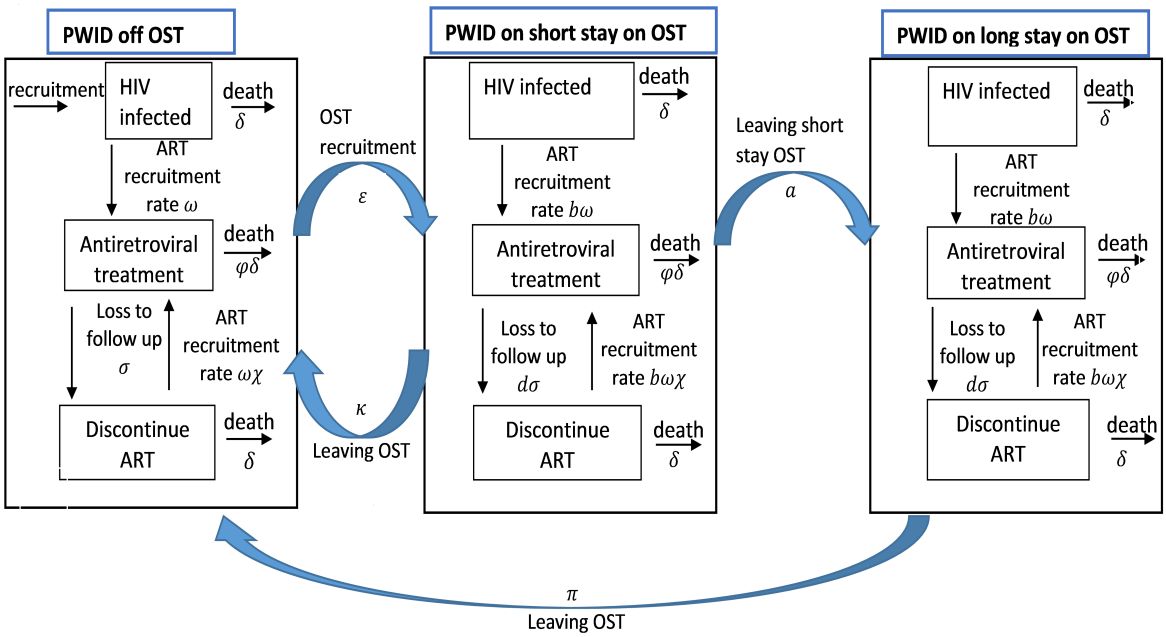
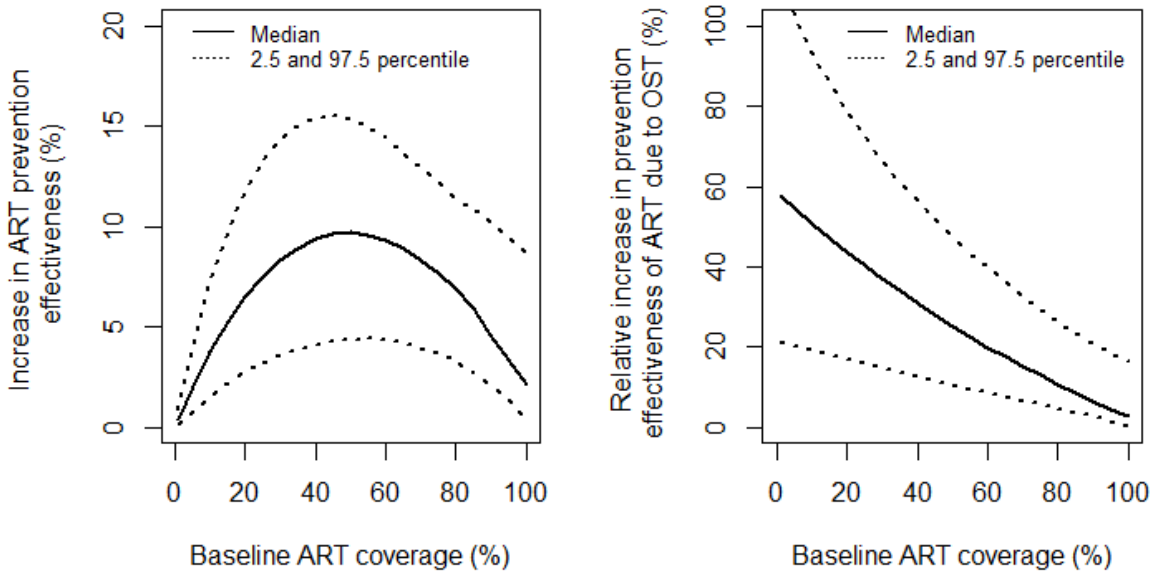


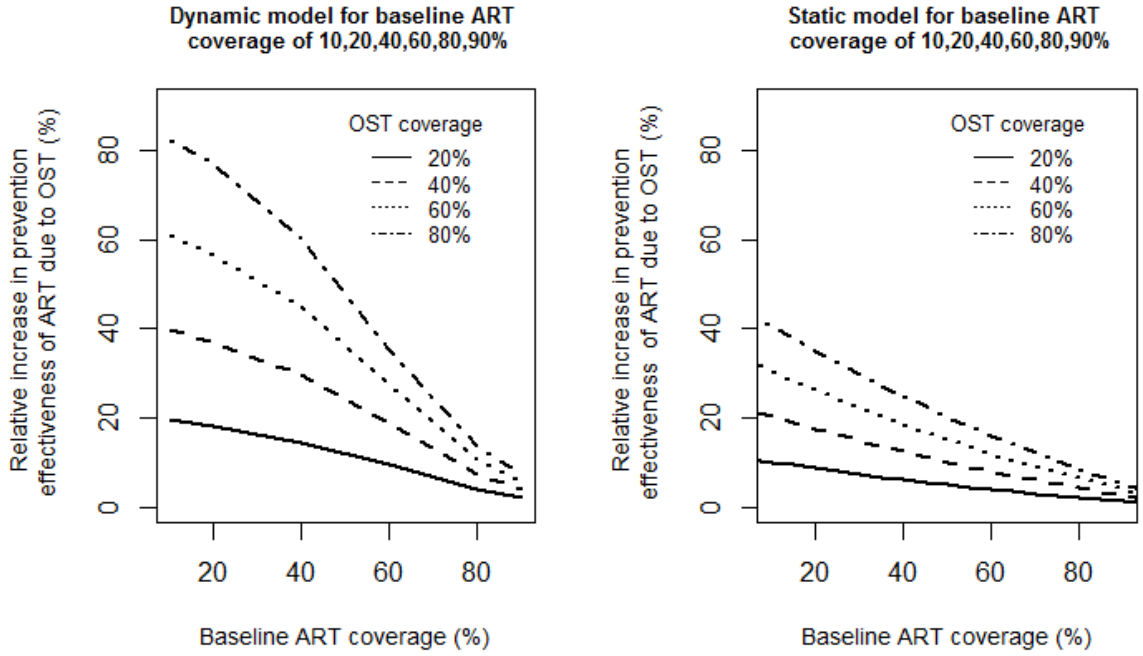
Figure 1. Model schematic showing dynamics of ART and OST recruitment and attrition amongst a population of HIV-infected PWID. Arrows show possible transitions from one state to the other and are labelled by the flow rates. New PWID enter the model in the HIV infected off OST compartment at a rate Θ and leave all compartments due to non-HIV death and injecting cessation at a rate ν. Modelled PWID not on anti-retroviral treatment (ART) also experience HIV-related death at a rate δ, and are recruited onto ART at a rate ω if not on OST and $b\omega$ if on OST. PWID on ART discontinue treatment at a rate σ if not on OST, and at a decreased rate $d\sigma$ if on OST. Those who discontinue ART can be recruited back onto ART at a rate $\omega\chi$. PWID are recruited onto OST at a rate ε and either have a short stay on OST for an average duration of $1/\kappa$ or move into the OST class for a long stay at a rate a. PWID remain in the long stay OST for an average duration of $1/\pi$.



(2a) Absolute increase

(2b) Relative increase

Figure 2. Absolute (2a) and relative (2b) increase in the prevention effectiveness of ART for PWID on OST compared to PWID off OST. These projections hold irrespective of the level of OST coverage. Bold line shows the median and dotted lines show the 2.5th and 97.5th percentiles from 1000 sampled parameter sets.



(a) Static model projections (b) Dynamic model projections

Figure 3. Static (3a) and dynamic (3b) model projections of the relative increase in the population-level prevention effectiveness of ART for different OST coverages and baseline ART coverages (ART coverage before OST introduced), compared to before OST was introduced. The graph shows the median plots from the 1000 sampled parameter sets.

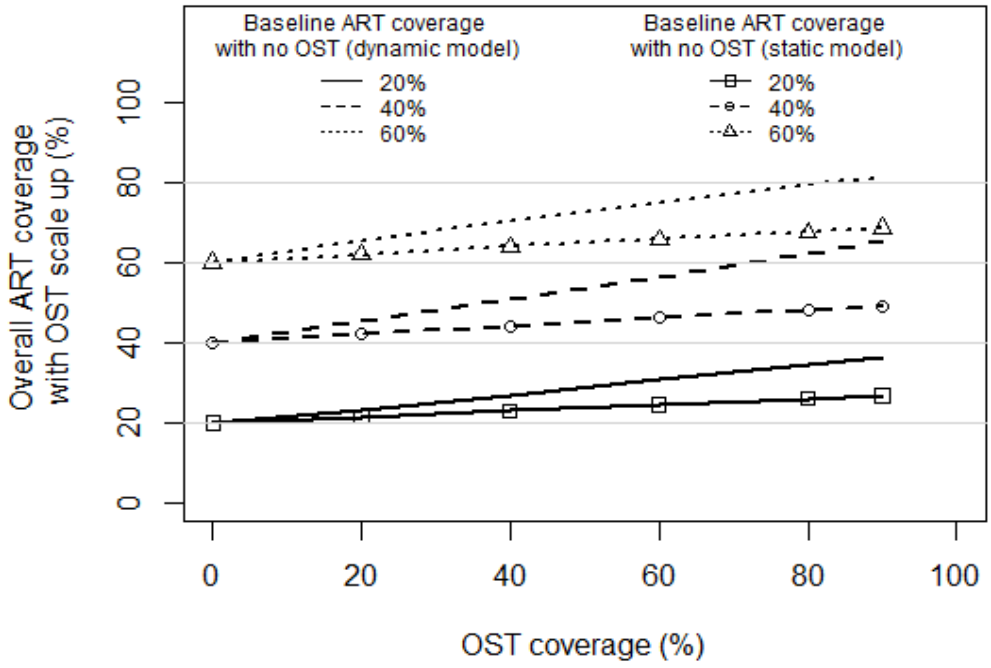


Figure 4. Overall increase in ART coverage as OST coverage increases for the dynamic and static models for baseline ART coverage of 20, 40 and 60%.

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PV and GM conceived of the study. PV and CM provided overall leadership for the study design, analysis and interpretation of the findings. CM developed model and performed all model analyses. AT and MM undertook additional analyses of the Antiretroviral Therapy Cohort Collaboration study dataset. CM wrote the first draft with PV. All authors have contributed to interpreting the results, and to writing subsequent versions of the manuscript.

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